



Prospective Study

Gender differences in ghrelin, nociception genes, psychological factors and quality of life in functional dyspepsia

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Abstract

AIM

to evaluate gender differences in the aspect of ghrelin, nociception-related genes and psychological aspects and the quality of life (QoL) in Korean functional dyspepsia (FD) patients.

METHODS

Total of 191 persons were prospectively enrolled between March 2013 and May 2016 in Seoul National Bundang Hospital, and classified into control and FD group based

on ROME III criteria. Questionnaire included assessment for dyspepsia symptoms, QoL and anxiety or depression. Preproghrelin and nociception genes in the gastric mucosa and plasma acyl/des-acyl ghrelin were measured.

RESULTS

Lower level of plasma acyl ghrelin in FD patients compared to control was significant only in male (15.9 fmol/mL *vs* 10.4 fmol/mL, $P = 0.017$). Significantly higher mRNA expressions of nerve growth factor and transient receptor potential vanilloid receptor 1 were observed in male ($P = 0.002$ and $P = 0.014$, respectively) than in female. In contrast, female FD patients had a higher anxiety and depression score than male FD ($P = 0.029$), and anxiety score was correlated with epigastric pain only in female FD patients (female: Spearman rho = 0.420, $P = 0.037$). The impairment of overall QoL was more prominent in female FD patients than male patients (5.4 ± 0.3 *vs* 6.5 ± 0.3 , $P = 0.020$).

CONCLUSION

Gender differences of ghrelin and nociception-related genes in male and psychological factors in female underlie FD symptoms. More careful assessment of psychological or emotional status is required particularly for the female FD patients.

Key words: Functional dyspepsia; Gender differences; Quality of life

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Core tip: Gender-specific medicine has become a recently rising medical field in which differences between males and females are recognized and actively utilized in the clinical study, diagnosis and treatment. The lower level of plasma acyl ghrelin and higher expressions of nociception-related genes are associated with pathogenesis of functional dyspepsia (FD) in males, while female FD patients had more serious anxious and depressive mood. Underlying mechanism in FD could be different according to gender, and meticulous attention for psychological predisposition is required particularly in the treatment of female FD patients.

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INTRODUCTION

Functional dyspepsia (FD) is a heterogeneous disorder characterized by recurrent upper abdominal discomfort or pain. According to the main symptom, FD is further classified into postprandial distress syndrome (PDS)

and epigastric pain syndrome (EPS). FD is not life-threatening but imposes a socio-economic burden due to its high prevalence. Several factors could underlie this disorder including abnormal motor function^[1], visceral hypersensitivity^[2], genetic predisposition^[3] or psychosomatic feature^[4]. Interestingly, most functional gastrointestinal (GI) disorder (FGID), including FD, shows female predominance^[5].

Gender-specific medicine has become a recently rising medical field in which differences between males and females are recognized and actively utilized in the diagnosis and treatment. Gender is assumed to be a crucial factor in the pathogenesis, disease progression and even prognosis of certain diseases^[6-8]. However, there have been only a few reported gender differences in FGIDs, and attention has focused mostly on irritable bowel syndrome (IBS). Moreover, the topic of most studies were restricted to the prevalence of FGID^[9], specified GI symptoms^[10] or quality of life (QoL)^[11].

Ghrelin controls appetite^[12] and modulates gastric motility. A reduced acyl ghrelin level has been correlated with impaired gastric emptying^[13], leading to postprandial fullness or vomiting^[14]. Transient receptor potential vanilloid-1 (TRPV1) is believed to be an important integrator of the transmission and modulation of pain with nerve growth factor (NGF) or glial cell line-derived neurotrophic factor (GDNF). Previously, we demonstrated that the genes encoding these nociception-related proteins are involved in the pathogenesis of FD, particularly in the EPS type^[15]. Regarding the PDS type, we found an association of increased plasma acyl ghrelin levels with abatement of dyspepsia following *Helicobacter pylori* eradication^[16]. However, we have not evaluated the differences of expression of ghrelin or nociception-related genes regarding gender specific manner. Female predominance of FGIDs maybe related with extraintestinal conditions such as hysterectomy, which was reported to be 3-fold higher in women with IBS^[17]. However, its relationship with female FD has not been evaluated so far.

Against this background, we hypothesized that there might be a difference in the underlying mechanisms of FD which could cause a difference in QoL between males and females. To verify this hypothesis, we analyzed the possible etiological factors including ghrelin, nociception-related genes, psychological aspects and history of abdominal operation as well as basal characteristics, dyspepsia symptoms and QoL between male and female FD patients.

MATERIALS AND METHODS

Subjects

The subjects were enrolled prospectively at the Department of Gastroenterology of Seoul National University Bundang Hospital(SNUBH), between March 2013 and May 2016. All subjects were of Korean and received upper gastrointestinal endoscopies

and completed questionnaires about gastrointestinal symptoms including dyspepsia, emotional state and QoL under the supervision of a well-trained interviewer. History of abdominal operations including gynecological surgeries (*i.e.* hysterectomy, salpingoophorectomy or gynecologic surgery) was evaluated. Subjects were excluded if there was a history of gastrointestinal GI surgery, current duodenal/gastric ulcer and any history of malignancy. Users of non-steroid anti-inflammatory drugs/anticoagulants, patients with systemic diseases requiring chronic medication (except for hypertension and diabetes mellitus) were also excluded.

The subjects were classified into the FD or control group. FD was defined to be according to the Rome III criteria^[15,16]. FD patients were categorized into PDS, EPS and mixed subgroups on the basis of the Rome III criteria^[18]. Individuals without GI symptoms and any endoscopic lesion were assigned to the controls. The Institutional Review Board of SNUBH approved this study (B-1101/119-010), and written informed consent was obtained from all participants.

Dyspepsia symptom, emotional status and QoL assessment

The severities of epigastric pain/burning, postprandial fullness, early satiation and overall abdominal pain (not restricted to epigastric area) were scored using a five-point scale (0, none; 1, mild; 2, moderate; 3, severe; 4, very severe) using validated Korean version of Talley's bowel disease questionnaire^[19]. Stool consistency based on Bristol Stool Form Scale^[20] and the number of bowel habits was evaluated. In order to assess the anxiety and depression of participants, the hospital anxiety and depression scale (HADS) was used^[21]. It is subdivided into anxiety and depression subscales, both containing seven items. Each response is ranked on a 4 point (0-3) scale. Higher HADS score indicates that the subject is more depressive or anxious, with a score > 7 of each subscale indicating potential anxiety disorder or depression^[22]. History of abdominal operations including hysterectomy and gynecologic surgery were collected. World Health Organization quality of life scale field trial version (WHOQOL-BREF) was used to evaluate the QoL of each subject^[23]. It consists of questions about overall QoL and general health with four domains of physical health, psychological health, social relationship and environmental domains. Results are expressed as an overall score (range 0-100) and domain score (range 0-20). Higher scores denote higher QoL. These three questionnaires have been validated in Korea^[19,24,25].

Upper endoscopy and biopsy

During endoscopy, biopsy specimens were obtained from the antrum, body and fundus for histological studies. Specimens taken from the fundus were used to measure the mRNA of preproghrelin, TRPV1, GDNF and NGF^[16]. The baseline *H. pylori* infection status and histology using the updated Sydney scoring system^[26]

was evaluated (Supplementary document).

Measurement of preproghrelin and nociception-related gene expression

Preproghrelin- and nociception-related gene expression was measured based on previous studies^[15,16]. Detailed method was described in Supplementary document.

Measurement of plasma ghrelin level

Acyl/desacyl ghrelin was measured according to previous study (Supplementary document)^[13].

Statistical analysis

Categorical variables were analyzed by χ^2 test or Fisher's exact test. Continuous variables presented as mean or median were analyzed by Student *t*-test or Mann-Whitney test, respectively. Spearman correlation test was used to evaluate potential correlations between HADS score and dyspepsia symptoms. SPSS Statistics version 20.0 (IBM, Armonk, NY, United States) was used. All statistical tests were 2-sided, and $P < 0.05$ was considered to be statistically significant.

RESULTS

General characteristics

A total of 191 subjects were included in this study. Among them, 87 subjects and 104 patients were classified into the control and FD group, respectively. Demographic characteristics of study population are summarized in Table 1. The control group was older than the FD group. The proportions of males were not significantly different between the control and FD groups (43.7% vs 37.5%. $P = 0.386$). The mean body mass index (BMI), *H. pylori* infection positivity, glandular atrophy and intestinal metaplasia were not significantly different between FD and control groups. However, there were more smokers in the FD group than the control group. The proportion of alcohol consumers was not significantly different between the groups.

Female FD patients had a lower BMI than male FD patients. A higher proportion of men smoked and consumed alcohol than women in the both FD and control groups (all $P < 0.001$). There were no significant gender differences in *H. pylori* infection positivity, glandular atrophy, intestinal metaplasia and the proportion of FD subtypes. Regarding history of gynecological surgeries, 87.8% of female subjects in the control and 73.8% of female subjects in the FD group responded. FD patients were more likely to have undergone gynecological surgeries, but this was insignificant (52.1% vs 30.2%, $P = 0.171$).

Comparison of expression of ghrelin and nociception-related gene

We analyzed whether gender and dyspepsia symptoms were associated with levels of plasma acyl-/desacyl ghrelin and expression of preproghrelin, NGF, GDNF

Table 1 Characteristics of the subjects *n* (%)

Variables	Control (<i>n</i> = 87)			FD (<i>n</i> = 104)			<i>P</i> value		
	Total (<i>n</i> = 87)	Male (<i>n</i> = 38)	Female (<i>n</i> = 49)	Total (<i>n</i> = 104)	Male (<i>n</i> = 39)	Female (<i>n</i> = 65)	Control vs FD	Control ¹	FD ¹
Age (mean ± SD, yr)	54.9 ± 12.1	57.4 ± 12.1	52.9 ± 11.8	50.5 ± 11.3	49.6 ± 11.6	51.3 ± 11.1	0.010	0.084	0.536
Male	38 (43.7)	38 (100)	0	39 (37.5)	39 (100)	0	0.386	-	-
BMI (mean ± SD, kg/m ²)	23.1 ± 2.9	22.4 ± 2.9	22.9 ± 3.30	22.4 ± 3.0	23.3 ± 2.7	21.9 ± 3.4	0.140	0.482	0.039
<i>H. pylori</i>	58 (66.7)	23 (60.5)	35 (71.4)	60 (57.7)	21 (53.8)	39 (60.0)	0.204	0.360	0.547
AG antrum	33 (37.9)	15 (39.5)	18 (36.7)	28 (26.9)	9 (23.1)	19 (29.2)	0.104	0.794	0.493
AG body	13 (14.9)	5 (13.2)	8 (16.3)	11 (10.6)	4 (10.3)	7 (10.8)	0.365	0.681	0.999
IM antrum/body	22 (25.3)	12 (31.6)	10 (20.4)	18 (17.3)	6 (15.4)	12 (18.5)	0.177	0.234	0.688
Smoking	13 (14.9)	10 (26.3)	1 (2.0)	24 (23.1)	17 (43.6)	2 (3.1)	< 0.001	< 0.001	< 0.001
Alcohol	20 (23.0)	16 (42.1)	4 (8.2)	30 (28.8)	21 (53.8)	9 (13.8)	0.342	< 0.001	< 0.001
Gynecologic surgery ²	-	-	13/43 (30.2)	-	-	25/48 (52.1)	0.171	-	-
Subtype in FD	-	-	-	-	-	-	-	-	-
PDS	-	-	-	-	9 (23.1)	15 (23.1)	-	-	0.408
EPS	-	-	-	-	6 (15.4)	17 (26.2)	-	-	-
Mixed	-	-	-	-	24 (61.5)	33 (50.8)	-	-	-

¹Between males and females; ²Hysterectomy, salpingoophorectomy or cesarean section were included. Only some patients responded to this question. AG: Atrophic gastritis; BMI: Body mass index; EPS: Epigastric pain syndrome; mixed, postprandial distress syndrome and epigastric pain syndrome; FD: Functional dyspepsia; IM: Intestinal metaplasia; PDS: Postprandial distress syndrome; SD: Standard deviation; -: not available.

Table 2 Expression of plasma ghrelin, gastric ppepghrelin and nociception-related genes in the control and functional dyspepsia groups

Variables	Control (<i>n</i> = 87)			FD (<i>n</i> = 104)			<i>P</i> value ¹		
	Total (<i>n</i> = 87)	Male (<i>n</i> = 38)	Female (<i>n</i> = 49)	Total (<i>n</i> = 104)	Male (<i>n</i> = 39)	Female (<i>n</i> = 65)	Control vs FD	Control ²	FD ²
Plasma acyl ghrelin (fmol/mL, median [IQR])	14.1 (9.1-20.8)	15.9 (9.2-33.7)	12.2 (9.0-18.6)	11.2 (6.6-16.8)	10.4 (6.5-18.4)	11.4 (6.8-16.5)	0.018	0.204	0.388
Plasma des-acyl ghrelin (fmol/mL, median [IQR])	67.9 (37.5-162.5)	108 (31.8-212.9)	65.4 (38.2-111.0)	62.1 (32.2-110.6)	58.5 (28.8-134.3)	63.6 (32.2-108.0)	0.297	0.389	0.913
Ghrelin mRNA (median [IQR])	2.6 (0.7-4.9)	2.1 (0.5-4.2)	3.2 (1.0-6.1)	1.7 (0.4-5.4)	1.9 (0.4-9.0)	1.5 (0.3-4.7)	0.435	0.076	0.308
NGF mRNA (median [IQR])	1.1 (0.7-1.7)	1.2 (0.7-1.8)	0.9 (0.5-1.6)	1.6 (0.9-2.3)	1.8 (1.1-2.7)	1.4 (0.8-2.2)	0.006	0.056	0.129
GDNF mRNA (median [IQR])	1.0 (0.7-1.6)	1.2 (0.8-1.5)	0.9 (0.7-1.7)	1.8 (1.0-2.9)	1.6 (1.1-3.0)	1.9 (0.9-2.9)	< 0.001	0.404	0.992
TRPV1 mRNA (median [IQR])	1.0 (0.6-1.5)	1.1 (0.8-1.6)	0.9 (0.6-1.2)	1.4 (0.9-2.3)	1.4 (0.9-2.2)	1.4 (0.8-2.3)	0.006	0.102	0.584

¹Mann-Whitney test was used; ²Male vs female. FD: Functional dyspepsia; GDNF: Glial cell-line derived neurotrophic factor; IQR: Interquartile range; NGF: Nerve growth factor; PDS: Postprandial distress syndrome; TRPV1: Transient receptor potential vanilloid receptor 1.

and TRPV1 mRNA (Table 2). While the levels of plasma acyl ghrelin in the control group was higher than in the FD group, those of NGF, GDNF and TRPV1 mRNA expressions in the control group were lower than in the FD group (Table 2) (all *P* < 0.05). When the comparison was restricted to control subjects, female control subjects tended to show lower levels of plasma acyl/desacyl ghrelin and mRNA expression level of NGF, GDNF and TRPV1 than male subjects, with no statistical significances. Preproghrelin mRNA was higher in female control subjects than male individuals, but was not significantly different. Among the FD group, there were no significant gender differences in expressions of the aforementioned proteins or genes.

The lower level of plasma acyl ghrelin in FD patients compared to controls subjects was significant only in men (15.9 fmol/mL vs 10.4 fmol/mL, *P* = 0.017;

12.2 fmol/mL vs 11.4 fmol/mL, *P* = 0.348). Higher expressions of most nociception-related genes were more prominent in men than in women (Table 3).

Dyspepsia symptoms and bowel habit

Supplementary Table 1 shows the severity of dyspepsia symptom and bowel habit in FD patients according to gender. The score of epigastric burning of female patients was higher compared to male patients (3.5 ± 0.1 vs 2.7 ± 0.2, *P* = 0.047). On the other hand, overall abdominal pain, early satiation and postprandial fullness were slightly more severe in male patients compared to female patients, but there was no statistical significance (Table 4). In case of nausea, the score was higher in female without statistical significance. In addition, there were no significant differences in stool consistency and number of defecations.

Table 3 Expression of plasma ghrelin, gastric peptoghrelin and nociception-related genes in different gender

Variables	Male			Female		
	Control (<i>n</i> = 38)	FD (<i>n</i> = 39)	<i>P</i> value ¹	Control (<i>n</i> = 49)	FD (<i>n</i> = 65)	<i>P</i> value ¹
Plasma acylghrelin (fmol/mL, median [IQR])	15.9 (9.2-33.7)	10.4 (6.5-18.4)	0.017	12.2 (9.0-18.6)	11.4 (6.8-16.5)	0.348
Plasma des-acylghrelin (fmol/mL, median [IQR])	108.0 (31.8-212.9)	58.5 (28.9-134.3)	0.302	65.4 (38.2-111.0)	63.6 (32.2-108.0)	0.844
Ghrelin mRNA (median [IQR])	2.1 (0.5-4.2)	1.9 (0.4-9.1)	0.428	3.2 (1.0-6.1)	1.5 (0.3-4.7)	0.092
NGF mRNA (median [IQR])	1.2 (0.7-1.8)	1.8 (1.1-2.7)	0.002	0.9 (0.5-1.6)	1.4 (0.8-2.2)	0.119
GDNF mRNA (median [IQR])	1.2 (0.7-1.5)	1.6 (1.1-3.0)	0.003	0.9 (0.7-1.7)	1.9 (0.9-2.9)	0.018
TRPV1 mRNA (median [IQR])	1.1 (0.8-1.6)	1.4 (0.9-2.2)	0.014	0.9 (0.6-1.2)	1.4 (0.8-2.3)	0.089

¹ Mann-Whitney test was used. FD: Functional dyspepsia; GDNF: Glial cell-line derived neurotrophic factor; IQR: Interquartile range; NGF: Nerve growth factor; PDS: Postprandial distress syndrome; TRPV1: Transient receptor potential vanilloid receptor 1.

Table 4 Dyspepsia symptoms, stool consistency and bowel movement between males and females

Symptoms	Male FD (<i>n</i> = 39)	Female FD (<i>n</i> = 65)	<i>P</i> value ¹
Overall abdominal pain ² (mean ± SE)	3.4 ± 0.1	3.1 ± 0.2	0.195
Early satiation (mean ± SE)	2.8 ± 0.5	2.5 ± 0.3	0.434
Postprandial fullness (mean ± SE)	3.2 ± 0.3	3.1 ± 0.2	0.221
Epigastric burning/pain (mean ± SE)	2.7 ± 0.2	3.5 ± 0.1	0.047
Bloating (mean ± SE)	2.6 ± 0.3	2.2 ± 0.2	0.339
Nausea (mean ± SE)	1.5 ± 0.3	1.8 ± 0.2	0.327
Vomiting (mean ± SE)	0.5 ± 0.2	0.6 ± 0.1	0.203
BSFS (mean ± SE)	4.8 ± 0.2	4.4 ± 0.2	0.103
Number (per week) (mean ± SE)	4.8 ± 0.3	4.5 ± 0.2	0.532

¹ *t*-test was used; ² Pain not restricted to the epigastric area. BSFS: Bristol stool form score (from 1 = very hard to 7 = watery); FD: Functional dyspepsia.

Female FD patients were further classified according to the presence of history of gynecologic surgery. There were no answers from 17 patients. Twelve patients had received hysterectomy or salpingo-oophorectomy, and 13 patients underwent more than one Cesarean section. When patients with/without history of gynecologic surgery were compared, the patients who underwent these operations showed more frequent and severer overall abdominal pain and nausea compared to their counterparts (Supplementary Table 1).

Anxiety, depression and QoL

In order to evaluate the impact of mood and QoL on FD HADS scores and WHOQOL-BREF scores were analyzed between control and FD and between males and females.

When the FD and control groups were compared, FD patients showed higher mean HADS total score and higher mean HADS scores of both anxiety and depression than control subjects (Total, 15.8 ± 1.2 vs 11.0 ± 0.8; anxiety, 7.4 ± 0.7 vs 5.1 ± 0.4 and depression, 8.4 ± 0.6 vs 5.9 ± 0.4, all *P* < 0.05) (Table 5). In terms of quality of life with WHOQOL-BREF questionnaires, the scores of total, social domain and environmental domain was lower in the FD group than in the control group (Table 5).

In terms of gender, there were no significant differences in HADS score and every score of WHOQOL-BREF system between male and female in the control

group. In contrast, FD group showed very clear gender difference. That is, female patients showed higher mean HADS total, anxiety and depression scores compared to male patients (total, 18.6 ± 2.1 vs 13.2 ± 1.3; anxiety, 9.0 ± 1.3 vs 6.0 ± 0.7; depression, 9.7 ± 1.0 vs 7.2 ± 0.8, all *P* < 0.05) (Figure 1). Moreover, the severity of epigastric pain correlated with HADS anxiety score only in female FD patients (males: Spearman rho = 0.232, *P* = 0.128; females: Spearman rho = 0.420, *P* = 0.037) (Figure 2).

Similar to HADS score WHOQOL-BREF scoring system showed gender difference only in FD group. That is, female FD patients scored lower in every domain including the scores of total, overall QoL and general health, physical, psychological, social and environmental domains compared to male FD patients (Table 5). In particular, the scores of overall QoL and general health, and physical domain in females were significantly lower than males (*P* = 0.020 and 0.016, respectively) (Table 5).

DISCUSSION

We demonstrated that differences in plasma acyl ghrelin and the gastric expressions of most nociception-related gene between FD and control groups were significant only in men. In contrast, female FD patients had a more anxious and depressive mood, and showed a more apparent impaired QoL compared to male FD

Table 5 HADS and WHOQOL-BREF scores in the control and functional dyspepsia groups according to gender

Variables	Control			FD			<i>P</i> value ¹		
	Total	Male	Female	Total	Male	Female	Control vs FD	Control ²	FD ²
	(<i>n</i> = 87)	(<i>n</i> = 38)	(<i>n</i> = 49)	(<i>n</i> = 104)	(<i>n</i> = 39)	(<i>n</i> = 65)			
HADS score ³ (mean ± SE)									
Total	11.0 ± 0.8	10.8 ± 1.2	11.2 ± 1.1	15.8 ± 1.2	13.2 ± 1.3	18.6 ± 2.1	0.001	0.780	0.029
Anxiety	5.1 ± 0.4	4.9 ± 0.6	5.3 ± 0.6	7.4 ± 0.7	6.0 ± 0.7	9.0 ± 1.3	0.005	0.587	0.036
Depression	5.9 ± 0.4	5.9 ± 0.7	5.9 ± 0.6	8.4 ± 0.6	7.2 ± 0.8	9.7 ± 1.0	0.001	0.984	0.047
WHOQOL-BREF score ⁴ (mean ± SE)									
Total	59.5 ± 1.6	60.7 ± 2.7	58.0 ± 1.5	54.0 ± 1.9	57.5 ± 1.9	51.6 ± 2.1	0.027	0.417	0.074
Overall quality of life and general health	6.2 ± 0.2	6.6 ± 0.3	5.8 ± 0.3	5.9 ± 0.3	6.5 ± 0.3	5.4 ± 0.3	0.278	0.080	0.020
Physical domain	13.4 ± 0.4	13.6 ± 0.7	13.1 ± 0.4	12.6 ± 0.4	13.6 ± 0.5	11.6 ± 0.7	0.185	0.575	0.016
Psychological domain	12.8 ± 0.4	13.2 ± 0.7	12.4 ± 0.5	11.8 ± 0.4	12.4 ± 0.5	11.4 ± 0.7	0.092	0.410	0.278
Social domain	13.7 ± 0.4	14.0 ± 0.6	13.3 ± 0.4	12.1 ± 0.5	13.0 ± 0.5	11.5 ± 0.6	0.012	0.370	0.064
Environment domain	13.3 ± 0.5	13.3 ± 0.7	13.3 ± 0.6	11.6 ± 0.4	12.1 ± 0.5	11.7 ± 0.7	0.010	0.990	0.617

¹*t*-test was used; ²Between males and females; ³Higher score denotes more severe symptom; ⁴Higher score denotes better quality of life. FD: Functional dyspepsia; HADS: Hospital anxiety and depression scale; WHOQOL-BREF: World health organization quality of life abbreviated version.

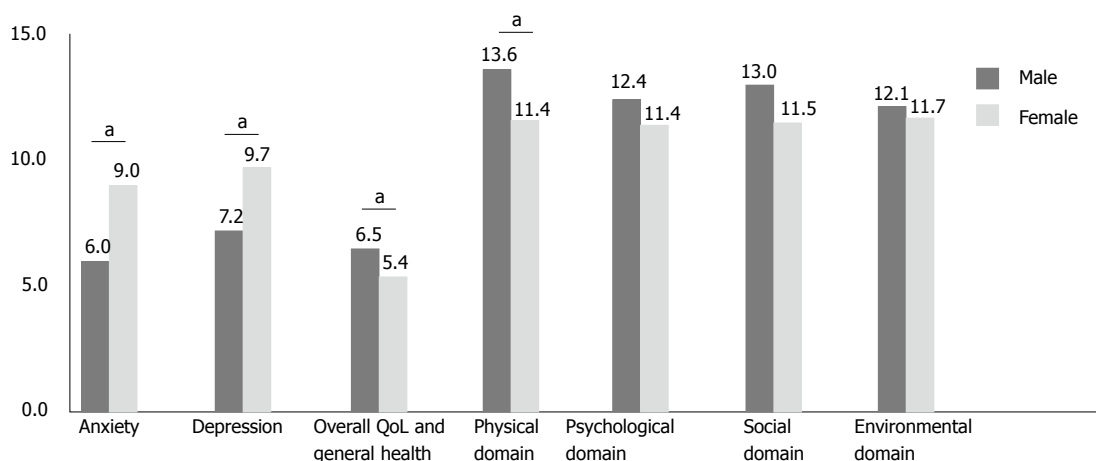


Figure 1 HADS and WHOQOL-BREF scores of patients with functional dyspepsia according to gender. HADS: Hospital anxiety and depression scale; WHOQOL-BREF: World health organization quality of life abbreviated version; QOL, quality of life. "a" denotes statistical significance.

patients. Epigastric burning or pain was correlated with anxiety score only in women. Women who underwent any gynecologic surgery showed more severe overall abdominal symptoms than women who did not. To our knowledge, this is the first study to evaluate the differences between males and females in terms of clinical characteristics of FD and the expression of ghrelin and nociception-related genes.

Women are more likely than men to meet the criteria for most FGIDs^[5,9,27,28], although some studies reported no difference in the prevalence of FD between men and women^[14,29,30]. One of the most essential factors characterizing an individual biologically male and female is the sex hormone. The representative female hormones estrogen and progesterone can interfere with gastric motility. Gastric emptying in premenopausal females is delayed compared to that in males^[31-34] and gastric emptying during luteal phase when the levels of the sex hormones are high is prolonged in comparison with the follicular phase^[33]. Generally accepted slower

gastric emptying in females than in males^[35] may be at least partially attributable to the female sex hormone, which hampers gastric motility by reducing gastric smooth muscle contractility^[36].

However, sex hormones may not be the single factor contributing to the delayed gastric emptying in females, because this has also been observed during the follicular phase of the menstrual cycle^[32]. In terms with gastric motility, a reduced acyl ghrelin level has been reported to be correlated with an impairment of gastric emptying^[13]. We previously published the data of decreased plasma acyl ghrelin levels in the PDS type of FD compared to the control group^[16]. PDS symptom was thought to be associated with the delayed gastric emptying. Based on the literature, a decreased tendency of plasma acyl ghrelin in the female control group in the present study may reflect the delayed gastric emptying in women. Interestingly, the difference in plasma acyl ghrelin between FD patients and control was statistically significant in male but not

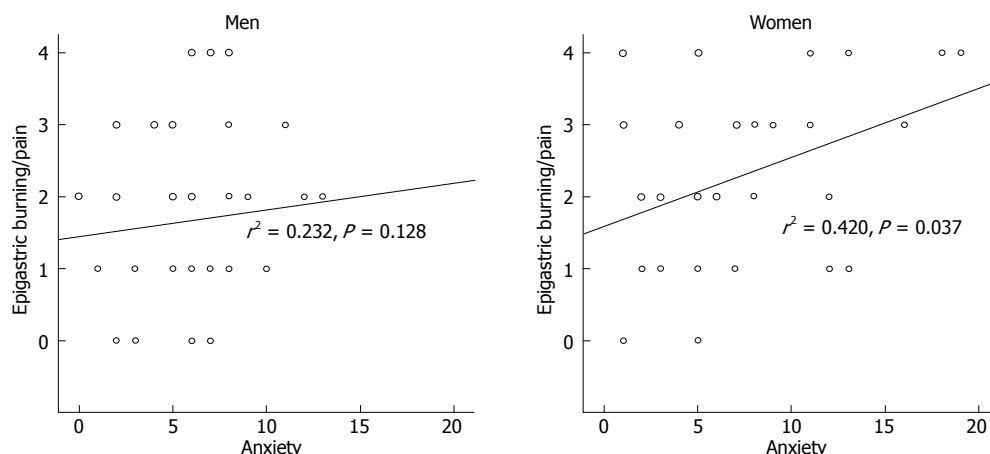


Figure 2 Correlation between epigastric burning/pain score and HADS anxiety score according to gender. Spearman correlation was used.

in female. Similarly, elevated level of NGF, GDNF and TRPV1 mRNA expression in the FD group was more prominent in men than in women. We also previously reported that FD patients showed an elevated level of NGF, GDNF and TRPV1 mRNA expression^[15]. Indeed, visceral hypersensitivity is another important mechanism for the FD and the upregulation of TRPV1 has been proposed to be associated with visceral hypersensitivity of FD. The present results suggest that ghrelin and visceral hypersensitivity are important underlying mechanisms of male FD but female FD needs more other decisive mechanism.

There is evidence of a lack of the association between physiological mechanisms with dyspeptic symptoms^[37]. Instead, recent epidemiological studies have provided increasing evidence for the positive association between anxiety or depression and functional gastrointestinal symptoms^[4,38]. In the present study, female FD patients showed more anxious and depressive mood than male patients. Although it is unclear whether psychosocial factors mainly determine healthcare seeking or have a direct influence on symptom perception in FGID, anxiety has been recently reported to be negatively correlated with pain threshold^[39]. It is interesting to note that the severity of epigastric pain correlated with HADS anxiety score only in female FD patients in the present study. This indicates that dyspepsia symptoms, particularly epigastric burning or pain in females, may be related more with psychological factors. Therefore, more attention is required in terms of psychological evaluation and management when treating female FD patients.

It is also conceivable that the gynecological condition of female may affect the varied clinical presentations in comparison with male, but most studies evaluated the association between GI symptoms and surgeries in IBS patients^[17]. In the present study, female FD patients who received gynecologic surgery reported more severe general abdominal pain. However, because this abdominal pain was not restricted to the epigastric area, overlap with gynecologic conditions may contribute to dyspepsia in females. This needs further study.

Although women have been reported to be more likely than men to exhibit dysmotility-like symptoms and men are more likely to experience food regurgitation and heartburn^[28,40], there were no significant differences in FD symptoms or FD symptoms subtypes between male and female FD in the present study. Only female FD patients suffered more epigastric pain than male FD patients. Although some studies in Europe and Japan reported that female predominance in the prevalence of FD^[41-45], little gender analysis was conducted except for prevalence. The comparison of various aspects including prevalence, symptom subtype, dominant symptoms, natural course and QoL between males and females by different geographical areas or ethnicity could help to better understand the related pathophysiology of FD.

Concerning QoL, FD patients manifested more impaired QoL status than the control group, especially in the social and environmental domains, which indicates the need of more active intervention to ameliorate the FD symptoms. When comparing males and females, even though aspects of QoL did not reach statistical significance, every aspect of QoL was poorer in females than in males. Particularly, overall QoL and general health and physical domain scored significantly lower in females. Thus, modulating physical aspects would be effective for the alleviation of FD symptoms.

There are several limitations in the present study. This study is a single center study with a possible sample bias. Symptom scores were evaluated by questionnaire; this is not free from the risk of a recall bias. The sample size was relatively small. The effect of female sex hormones on the pathogenesis on FD was not evaluated. In spite of these limitations, our study clearly demonstrated gender differences of FD in terms of clinical characteristics of FD and the expression of ghrelin and nociception-related genes.

In conclusion, our study presents that the lower level of plasma acyl ghrelin and higher expressions of nociception-related genes are associated with pathogenesis of FD in males. On the other hand, female FD patients had more serious anxious and depressive mood, and anxiety score

was correlated with epigastric pain in female FD patients. This psychological predisposition might underlie the perception of symptom, especially in female FD patients. There was not a large difference in pattern or severity of FD symptoms, except for female predominance in epigastric pain. However, considering that the impairment of overall QoL and general health was more prominent in female FD patients than in male patients, more careful assessment of psychological or emotional status is needed for the better treatment of female FD patients.

ARTICLE HIGHLIGHTS

Research background

Although gender is assumed to be an important factor in the pathogenesis, progression and prognosis of certain diseases, there have been only a few reported gender differences in functional gastrointestinal disorders, and attention has focused mostly on irritable bowel syndrome.

Research motivation

Most functional gastrointestinal disorders, including functional dyspepsia, show female predominance.

Research objectives

We compared the possible etiological factors including ghrelin, nociception-related genes, psychological aspects and history of abdominal operation as well as basal characteristics, dyspepsia symptoms and quality of life between male and female functional dyspepsia patients.

Research methods

Total of 191 persons [87 subjects (male 38, female 49) and 104 patients (male 39, female 65)] were prospectively enrolled between March 2013 and May 2016 in Seoul National Bundang Hospital. They were classified into control and FD group (PDS, EPS and mixed subgroups) on the basis of ROME III criteria. Questionnaire included assessment for dyspepsia symptoms, quality of life by WHOQOL-BREF scores and anxiety or depression by HADS scores were analyzed. Preproghrelin and nociception genes were analyzed by RT-PCR from the gastric mucosa. Plasma acyl/des-acyl ghrelin were measured by ELISA method.

Research results

Differences in plasma acyl ghrelin and the gastric expressions of most nociception-related gene between dyspepsia and control groups were significant only in men. In contrast, female functional dyspepsia patients had a more anxious and depressive mood, and showed a more apparent impaired quality of life compared to male dyspeptic patients. Epigastric burning or pain was correlated with anxiety score only in women. Women who underwent any gynecologic surgery showed more severe overall abdominal symptoms than women who did not.

Research conclusions

Different mechanisms might underlie the perception of dyspeptic symptom by gender and the negative impact of the functional dyspepsia on the quality of life can be more prominent in women than men.

Research perspectives

More careful assessment of psychological or emotional status is required particularly for the female FD patients.

University Bundang Hospital for statistical analyses.

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