Maximum Tolerated Volume and Plasma Acylated Ghrelin Levels after Drink Tests in Patients with Functional Dyspepsia

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ABSTRACT

Background: *Impaired gastric accommodation and visceral hypersensitivity are major pathophysiological mechanism in functional dyspepsia (FD). Ghrelin, as gut hormone, may play a pathophysiological role in functional dyspepsia. Nutrient drink test was developed to assess impaired gastric accommodation in FD patients. The aims of this study are to compare maximum tolerated volume, postprandial symptoms and acylated ghrelin levels between dyspepsia functional patients and healthy subjects as controls.*

Method: *A cross sectional study was conducted from July 2014 to November 2014, at Sardjito General Hospital, Yogyakarta. Twenties functional dyspepsia patients and 20 healthy subjects ingested nutrient drink tests (Ultra Milk ® contain 0.6 kcal/mL). The maximum tolerated volume was recorded. After ingested maximal tolerated volume, nausea, bloating and pain were rated using visual analogue scales (VAS) with 100 mm lines. The levels of acylated ghrelin was recorded before and 30 minutes after maximal drinking.*

Results: *The demographic characteristics (age, sex, and body mass index) between dyspepsia patients and healthy subjects were compared. Patients with functional dyspepsia ingested 600 (350–1000) mL and healthy subjects ingested 1375 (1000–1900) mL ($p < 0.001$). The total symptom scores were higher in dyspepsia patients compared healthy subjects; 215 (110–350) vs. 75 (50–120) ($p < 0,001$). The fasting plasma levels of acylated ghrelin (20.65 : 2 – 31.37 pg/mL) in FD patients were significantly lower than healthy subjects (30.61 : 2 – 251.19 pg/mL) ($p = 0.012$).*

Conclusion: *Patients with functional dyspepsia ingested significantly lower volume and significantly have higher score symptoms than healthy subjects. The fasting plasma levels of acylated ghrelin in functional dyspepsia patients were significantly lower than healthy subjects.*

Keywords: *nutrient drink test, impaired gastric accommodation, functional dyspepsia, acylated ghrelin level*

ABSTRAK

Latar belakang: *Gangguan akomadasi dan hipersensitivitas viseral merupakan patofisiologi utama terjadinya dispepsia fungsional. Ghrelin, sebagai hormon usus, kemungkinan terlibat dalam patofisiologi dispepsia. Uji minum mengandung nutrien dikembangkan untuk menilai gangguan akomodasi gaster pada pasien dispepsia fungsional. Tujuan penelitian ini adalah untuk membandingkan kemampuan minum maksimal, skor simptom dispepsi dan kadar acylated ghrelin antara pasien dispepsia fungsional dan partisipan sehat sebagai kontrol.*

Metode: *Studi potong lintang dilakukan mulai bulan Juli 2014 hingga November 2014 di Rumah Sakit Umum Pusat) RSUP Dr Sardjito, Yogyakarta, Indonesia. Dua puluh (20) pasien dispepsia fungsional dan 20 kontrol sehat diminta untuk minum minuman mengandung nutrien (Ultra Milk ®, 0,6 kcal /mL). Kemampuan minum maksimal pasien dan kontrol dicatat dan dibandingkan. Setelah minum maksimal, keluhan mual, kembung, nyeri ulu hati dan rasa kenyang dinilai menggunakan visual analogue scale (VAS) dengan skala 100 mm. Kadar acylated ghrelin diukur sebelum dan 30 menit setelah minum maksimal pada kedua kelompok.*

Hasil: *Tidak ada perbedaan bermakna antara kedua kelompok dalam hal karakteristik demografi (usia, jenis kelamin, indeks masa tubuh). Pasien dispepsia fungsional mempunyai kemampuan minum lebih sedikit secara bermakna dibandingkan kontrol sehat: 600 (350 – 1000) mL vs. 1375 (1000 – 1900) mL (p < 0,001). Skor simptom total lebih tinggi secara bermakna pada pasien dispepsia dibandingkan kontrol, masing masing yaitu : 215 (110 – 350) vs. 75 (50 – 120) (p < 0,001). Kadar ghrelin plasma puasa (20.65:2 – 31.37 pg/mL) pada pasien lebih rendah secara bermakna dibandingkan kontrol (30.61:2 – 251.19 pg/mL) (p = 0,012).*

Simpulan: *Pasien dispepsia fungsional minum lebih sedikit secara bermakna dan mempunyai simptom skor dispepsia lebih tinggi secara bermakna dibandingkan kontrol. Kadar ghrelin plasma puasa pada pasien lebih rendah secara bermakna dibandingkan kontrol.*

Kata kunci: *uji minuman bernutrisi, gangguan akomodasi gaster, dispepsia fungsional, kadar acylated ghrelin*

INTRODUCTION

Dyspepsia is a common term used for a heterogeneous group of abdominal symptoms, includes early satiety, fullness, epigastric pain or burning, belching, nausea and vomiting. The 2006 Rome III criteria defined functional dyspepsia (FD) as epigastric pain syndrome and postprandial distress syndrome.[1] Epidemiologic surveys suggest that 15–20% of the general population in Western Countries experience dyspepsia over the course of 1 year.[2] Together with visceral hypersensitivity and delayed gastric emptying, impaired gastric accommodation is the most frequently observed pathophysiological mechanism in patients with FD.[3] Using gastric barostat invasive study, impaired gastric accommodation was present in 40% of the FD patients.[1] Drink tests are advocated as an inexpensive, non-invasive technique to assess gastric accommodation. Many study showed that patients with FD will often achieve satiation at lower drink test volumes and report greater dyspepsia symptoms than healthy controls during the test.[4]

Ghrelin (deacylated and acylated form) is the endogenous ligand for the growth hormone secretagogue receptor, and it has potent growth hormone-releasing activity. The physiologic function of ghrelin are pleiotropic to stimulate food intake, regulaes gastric acid secretion, promotes gastric emptying and generation of nitric oxide and prostaglandins.[5,6] Ghrelin may be associated with FD through its effect on the regulation of gut motility. However, the association between ghrelin and FD has remained controversial in earlier study.[7]

The aim of this study was to compare maximum tolerated volume, dyspepsia symptoms and ghrelin levels between dyspepsia functional patients and healthy subjects.

METHOD

A cross sectional study was conducted from July 2014 to November 2014, at Sardjito General Hospital, Yogyakarta, Indonesia. Twenty (20) FD patients and 20 healthy controls were matched by gender, age, and body mass index. Adults of both sexes > 18 years of age diagnosed with FD according to the Rome III Criteria that signed statements of informed consent were included in the study. The exclusion criteria were evidence of organic systemic diseases and structural diseases (such as esophagitis, erosive gastroduodenal lesions or ulcers), the use of prokinetis agents, calcium blockers, anti-depressives, opioids analgetics, non-steroidal anti-inflammatory drugs or iron supplements and milk intolerance. Healthy participants that did not fit any of the Rome III Criteria for FD and no personal history of digestive diseases, and that were not taking any medication for digestive disorders, and not milk intolerance were recruited as controls.

Plasma levels of acylated ghrelin was taken after a fasting periode of 8 hours, and then the subjects were asked to ingest a nutrient drink (Ultra milk ®, 0.6 kcal/mL) at a constant rate of 100 mL/minute. At 5 minutes intervals, participants scored theirs fullness using a scale graded 0 – 5 (0 = no symptoms; 1 = first sensation of fullness; 2 = mild; 3 = moderate; 4

= severe; 5 = maximum). The subjects were told to stop intake when a score of 5 was obtained. The total calori intake at maximum fullness was estimated from the volume of nutrient drink ingested. Thirty minutes after completing the test, participants scored their symptoms of bloating, fullness, nausea and pain using visual analogue scale (VAS) with 100 mm lines. The aggregate symptoms score was defined as the sum of the four 100-mm VAS scales for each symptoms.[8,9] Maximum tolerated volume (MTV) was defined as total ingested volume that the test had to be stopped because the FD patients or healthy controls could not tolerate more volume.

Postprandial acylated ghrelin samples were obtained after finishing the symptoms score. The results of the different groups were compared using the corresponding Chi-square test for the qualitative data and Student's t-test or Mann-Whitney test for the quantitative variables, according to normal or non-parametric distribution, respectively. Statistical significance was considered when there was a $p < 0.05$.

RESULTS

Table 1 showed about age, body weights, body height, body mass index (BMI) and gender characteristics of FD patients and controls. There was no statistical difference between these variables of the two groups. Dyspepsia symptoms (nausea, bloating and epigastric pain) were more frequent in FD patients compared controls ($p < 0.001$) (Table 2). Table 3 showed symptom scores between dyspepsia patients and healthy controls. Nausea, bloating, epigastric pain and aggregate symptom scores were significantly more higher in FD patients compared controls.

Tabel 1. The demographic characteristics of functional dyspepsia patients and healthy controls

Variabel	Patients (n = 20)	Controls (n = 20)	p
Age (years)	32.35 ± 9.48	31.60 ± 6.60	0.773*
Body weights (kg)	55.45 ± 9.98	60.55 ± 10.63	0.126*
Body height (cm)	161.90 ± 7.59	165.55 ± 9.41	0.185*
Body mass index	21.09 ± 0.9	22.00 ± 2.68	0.312*
Sex			
Male	12	12	1.000
Female	8	8	

*T-test

Table 2. The difference of dyspepsia symptoms between FD patients and healthy controls measured 30 minutes after maximal tolerated drinking

Dyspepsia symptoms	Patients (n = 20)	Controls (n = 20)	p
Nausea	19 / 20 (95%)	5 / 20 (25%)	< 0.001*
Bloating	15 / 20 (75%)	3 / 20 (15%)	< 0.001*
Epigastric pain	12 / 20 (60%)	0 / 20 (0,0%)	< 0.001*
Fullness	20 / 20 (100%)	19 / 20 (95%)	0.695*

*Chi-square

Table 3. Symptom scores between dyspepsia patients and healthy controls

Symptoms	Patients (n = 20)	Controls (n = 20)	p
Nausea	65 (0 – 100)	0 (0 – 60)	< 0.001*
Bloating	50 (0 – 100)	0 (0 – 50)	< 0.001*
Epigastric pain	25 (0 – 100)	0 (0 – 0)	< 0.001*
Postprandial fullness	80 (40 – 100)	70 0 – 100)	0.095*
Total scores	215 (110 – 350)	75 (50 – 120)	< 0.001*

*Man-Whitney test

Table 4. Maximum tolerated volume and calorie intake between patients and controls

Variable	Patients (n = 20)	Controls (n = 20)	p
Total volume (mL)	600 (350 – 1000)	1375 (1000– 1900)	< 0.001*
Calorie (kcal)	384 (224 – 640)	880 (640 – 1216)	< 0.001*

*Man-Whitney test

The patients had significantly lower calorie intake and drinking capacity (600: 350–1000 mL) than the healthy controls (1375: 1000–1900 mL) ($p < 0.001$) (Table 4). Table 5 showed the maximum tolerated volume according sex between patients and controls. In the patients from FD group, there were no different of maximum tolerated volume between male and female. But, in the healthy controls group, male ingested significantly more higher than women ($p = 0.026$). Fasting acylated ghrelin levels were significantly lower in FD patients compared healthy control ($p = 0.012$), but not difference at postprandial (Table 6).

Table 5. Maximum tolerated volume according gender between patients and controls

Variable	Male (n = 12)	Female (n = 8)	p
Patients (volume)	650.00 ± 112.82	656.25 ± 209,48	0.932*
Controls (volume)	1700 (1000– 1900)	1150 (1000– 1500)	0.026**

* T-test; **Mann-Whitney test

Table 6. Fasting and postprandial acylated ghrelin level between patients and controls

Variable	Acylated grelin levels (pg/mL)		p
	Patients (n=20)	Controls (n=20)	
Fasting	20.65 (2 – 31.37)	30.61 (2 – 251.19)	0.012*
Postprandial	19.1 (3.14 – 47.79)	21.35 (2 – 235.32)	0.645*
p	0.485*	0.297*	

*Mann-Whitney test

DISCUSSION

Accomodation of the stomach to a meal consists of a relaxation of the proximal stomach, providing the meal with a reservoir and enabling an increase in volume without an increase pressure. Impaired gastric accommodation was present in 40% of the patients.[2] Patients with dyspepsia will generally drink less and report more symptoms than do healthy subjects.[4]

Dyspepsia symptoms in functional dyspepsia are commonly exacerbated by meals rich in fat.[2] Nutrient drink tests were developed as a symptom provocative technique for patients with dyspeptic complaints.[4] Male ingest greater volumes than female patients but there appear to be less of an influence with respect to age and BMI.[4] Our study also showed similar results. But in FD patients, male and female ingested similar volume, it was because of impaired gastric accommodation.

Loza et al reported their study about maximum tolerated volume and symptom scores between FD patients and controls. FD patients ingested maximum tolerated volume lower than controls (652 ± 168 mL vs. 1278 ± 275 mL; $p < 0.001$) and symptom scores significantly higher than controls (186.7 ± 26.1 vs. 64.1 ± 8.9; $p < 0.001$).[10] Hjelland et al also reported the same results. FD patients ingested maximum tolerated volume lower than controls (830 ± 254 mL vs. 1120 ± 349 mL ; $p < 0.005$) and symptom scores significantly higher than controls (174 ± 44 vs. 123 ± 25; $p < 0.007$).[11] From pathopysiological point of view, there is abundant evidence to accept that impaired accommodation may contribute to the generation of dyspeptic symptoms. Impaired relaxation will result in increased fundic pressure, shown to be related to symptoms especially in the precense of visceral hypersensitivity. In addition, the meal will be pushed towards the less compliant antrum leading to overfilling and consequently dyspeptic symptoms. Calderella et al showed that FD patients are more sensitive to antral filling compared controls. In this study, FD patients reached their threshold for discomfort at approximately 138 mL filling of a balloon in the distal stomach, whereas controls did not report discomfort up to the highest volume tested (400 mL).[12] Van Den Elzen et al also showed the same results. They demonstrated that the distal stomach volume at the end of the drink test was significantly lower in FD (321 ± 35 mL) compared to controls (605 ± 49 mL).[3]

Ghrelin has a well-establised role in increasing appetite and food intake regulation and in stimulating gastric emptying and acid secresion; these functions are mediated, at least in-part, via vagal nerve pathway.[13] The level of ghrelin is higher during periods of fasting, starvation and the preprandial period and it is lower after eating or post prandial period.[14] Plasma ghrelin levels in patients with functional dyspepsia is still a controversial topic. While total serum ghrelin is reported to be higher in patients with FD in some studies. [14,15] Other studies show lower levels of serum ghrelin.[16,17,18] Nishizawa et al reported that plasma acyl ghrelin levels were significantly higher in FD patients, especially in those with dysmotility-like FD, as compared with levels in controls. He proposed that compensatory secresion of ghrelin may be enhanced in FD patients to normalize the impaired gastrointestinal motility, and as results, plasma ghrelin levels were increased.[15] Shindo et al reported that acyl ghrelin levels were significantly lower in PDS patients than in healthy volunteers. He also demonstrated that T-max value (T-max is a marker of gastric emptying that is measured using the 13-C acetate breat test) in PDS patients was significantly higher than in healthy volunteers, and that only PDS patients showed a significantly inverse relationship between plasma acyl ghrelin and T-max values.[16] These results suggested that acyl ghrelin might play a role in the pathophysiology of postprandial distress syndrome (PDS) through its effect on gastric emptying.

In normal condition, plasma acylated ghrelin levels is increase during fasting and decrease after eating. In our study, the levels of plasma acylated ghrelin during fasting was lower significantly compared healthy controls and it was increase 30 minutes after drinking. This abnormal patterns suggested that acylated ghrelin might play role in the pathophysiology of FD. The limitations of our study should be noted. First, the sample size as relatively small, which permitted only the use of non-parametric test in the statistical analysis. Second, we did not examine for serial of acylated ghrelin as conducted by other investigators. Third, we did not explore menstrual cycles of the participants. A study found that fasting ghrelin plasma consentrations were at least 85% greater in the subjects with exercise-associated amenorrhea.[6]

CONCLUSION

Patients with functional dyspepsia ingested significantly lower volume and significantly higher score symptoms than healthy subjects. These condition reflected of impaired gastric accommodation. The fasting plasma levels of acylated ghrelin in functional dyspepsia patients was significantly lower than healthy subjects. This abnormal acylated ghrelin levels may play in FD pathophysiology.

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