Original Article

Correlation between symptomatic improvement and quality of life in patients with reflux and dyspeptic symptoms

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We investigated the correlation between symptomatic improvement and quality of life in Japanese gastroesophageal reflux disease patients with PPI. Eighty one patients with reflux and dyspeptic symptom were enrolled. The evaluation of the symptom was used he Frequency Scale for the Symptom of GERD in 3 categories: total score of 12 questions, score related to reflux symptoms, and score related to dyspeptic symptoms and the evaluation of the quality of life was use the 8-item Short Form Health Survey in 2 categories, the physical component summary score and mental component summary score. All patients administered rabeprazole 10 mg/day for 8 weeks. We investigated the correlation between symptomatic improvement with proton pump inhibitor and quality of life. Significant symptomatic improvement was seen in the total score of 12 questions (26.7 ± 8.8 → 17.5 ± 5.9, $p<0.0001$), score related to reflux symptoms (14.9 ± 5.4 → 9.6 ± 3.6, $p<0.0001$), and score related to dyspeptic symptoms (11.8 ± 4.3 → 8.0 ± 2.9, $p<0.0001$). Significant improvement in quality of life was seen in the physical component summary score (47.8 ± 6.6 → 50.0 ± 5.9, $p = 0.0209$) and mental component summary score (47.4 ± 8.5 → 50.4 ± 5.3, $p = 0.0133$) with proton pump inhibitor. With proton pump inhibitor, a significant positive correlation was seen between the improvement rates in total score of 12 questions, score related to dyspeptic symptoms and in mental component summary score at 8 weeks (total score of 12 questions: $r = 0.275$, $p = 0.0265$, score related to dyspeptic symptoms: $r = 0.367$, $p = 0.0027$). In conclusion, quality of life was associated with improvement in dyspeptic symptoms with proton pump inhibitor treatment.

Key Words: reflux symptom, dyspeptic symptom, pharmacological management, proton pump inhibitor, quality of life

The ultimate aims of pharmacological management for gastroesophageal reflux disease (GERD) are rapid symptomatic control and improved quality of life (QOL).[1] The results of rapid symptomatic resolution of symptoms with pharmacological management achieve greater improvements in QOL.[2] Accordingly, rapid symptomatic control is important in the treatment of GERD. For non-erosive reflux disease (NERD), symptom resolution within 7 days after proton pump inhibitor (PPI) treatment has been reported to correlate with the rate of symptom resolution 4 weeks later.[3] For reflux esophagitis (RE), symptom resolution on the first day after PPI treatment has been reported to correlate with the rate of symptom resolution 4 weeks later.[4] On the other hand, for functional dyspepsia (FD)[5] and uninvestigated dyspepsia,[6] the symptom resolution rate or symptomatic improvement rate after 1 week of PPI treatment reportedly do not fully predict the

degree of symptomatic improvement 4 or 8 weeks later. These studies have been conducted with Western patients, however, and very few studies have examined the relationship between symptomatic improvement and QOL in Japanese GERD patients. In this study, we investigated the correlation between symptomatic improvement and QOL in Japanese GERD patients with PPI.

Methods

Patients. Eighty one Japanese outpatients with reflux and dyspeptic symptoms were enrolled between March 2008 and March 2009 (Table 1). Inclusion criteria were 20 years or older and willingness to informed consent. Patients were excluded if they had the history of gastric and duodenal ulcer, cancer and esophageal structure.

Symptom assessment. The reflux symptom defined as heartburn and acid regurgitation and the dyspeptic symptom defined as postprandial fullness and early satiation, mainly. These symptoms were evaluated using the Frequency Scale for the Symptom of GERD (FSSG), a questionnaire developed for use with Japanese patients[7] (Fig. 1). The questions of FSSG are related to the 12 symptoms that Japanese patients with GERD complain of most often, not only 'heartburn' and 'regurgitation', but also dyspeptic symptoms such as 'heavy stomach' and 'feeling full quickly'.[8] The FSSG is designed to score the frequency at which patients experience symptoms, and has been shown to be useful in the diagnosis of GERD,[9] assessment of response to GERD therapy[10] and prediction of optimum treatment.[11]

The FSSG was devised from these 12 questions, which were scored to indicate the frequency of symptoms, as follows: never/0; occasionally/1; sometimes/2; often/3; and always/4. The FSSG was evaluated using the total score (F-TS), the score for the 5 questions concerning acid reflux-related symptoms (F-RS), and for the seven questions concerning dyspeptic symptoms (F-DS) as indicated in Fig. 1.

QOL assessment. We evaluated QOL in 2 categories, the physical component summary score (PCS) and mental component summary score (MCS), using the 8-item Short Form Health Survey (SF–8™).[12] The mean scores for the Japanese general population are 50 points in PCS and MCS scores. A score of <50 thus indicated impaired QOL and the score of ≥50 is considered to indicate the improved QOL.

Endoscopic findings. Endoscopy was underwent at pretreatment and evaluated according to 2nd modified Los Angeles (LA) classification[13,14] (Grade N, no endoscopic mucosal changes;

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Table 1. Baseline characteristics

Age	55.7 ± 14.0		
Gender (male/female)	43/38		
Height (cm)	163.6 ± 7.8		
Weight (kg)	61.3 ± 8.9		
BMI (kg/m²)	22.8 ± 2.5		
History of GERD	No history	62	
	Recurrent	10	
	Known	9	
History of anti-acid secretion treatments (number/%)	23/27.4%		
Received the life-style modification (number/%)	50/61.7%		
Complicated diseases (number/%)	30/37.0%		
Endoscopic findings	RE	Grade A	25
		Grade B	4
	NERD	Grade N	17
		Grade M	19
	Uninvestigated		16
Symptom score (FSSG)	Total symptom score	26.7 ± 8.8*	
	Reflux symptom score	14.9 ± 5.4*	
	Dyspepsia symptom score	11.8 ± 4.3*	
QOL score (SF-8)	PCS	47.8 ± 6.6*	
	MCS	47.4 ± 8.5*	

*mean ± SD.
RE: Reflux esophagitis. NERD: Non-erosive reflux disease. PCS: physical component summary score. MCS: mental component summary score.

Grade M, minimal change; Grade A, one or more mucosal breaks ≤5 mm long that do not extend between the tops of two mucosal folds; Grade B, one or more mucosal breaks >5 mm long that do not extend between the tops of two mucosal folds; Grade C, one or more mucosal breaks that are continuous between the tops of two or more mucosal folds, but do not involve the entire esophageal circumference; and Grade D, a mucosal break that involves the entire esophageal circumference) among the patients who were able to obtain agreement.

Treatment. All Patients were administered rabeprazole 10 mg/day for 8 weeks, and completed these 2 questionnaires about their symptoms and QOL at pre-treatment and after 4 and 8 weeks. All the patients had signed an informed consent. Our study was approved by our hospital Ethics Committee.

Statistical analysis. We investigated the correlation between reflux and dyspeptic symptoms and QOL at pre-PPI treatment. And we examine the relation between the improvement rates in these symptoms and in QOL with PPI. Results are expressed as mean ± SD. Continuous variables were compared using one-way factorial analysis of variance (ANOVA), and discontinuous variables using Fisher's exact test. Correlations between variables were examined using Spearman's correlation coefficient between ranks. The improvement of F-TS, F-RS and F-DS associated with improvement of QOL (PCS or MCS scores ≥50) were identified by univariate logistic regression analysis. Results are presented as odds ratios with 95% confidence interval (CI). For all analyses, $p < 0.05$ was considered to signify a significant difference. Statistical analysis was performed using SPSS ver.19 (Chicago, IL).

Results

Changes in FSSG scores and QOL (PCS and MCS) during PPI treatment. Significant symptomatic improvement was seen in the F-TS, F-RS and F-DS at each evaluation point (F-TS: pre 26.7 ± 8.8, 4 weeks 20.1 ± 6.5, $p < 0.0001$, 8 weeks 17.5 ± 5.9, $p < 0.0001$; F-RS: pre 14.9 ± 5.4, 4 weeks 11.1 ± 4.0, $p < 0.0001$, 8 weeks 9.6 ± 3.6, $p < 0.0001$; F-DS: pre 11.8 ± 4.3, 4 weeks 9.1 ± 3.2, $p < 0.0001$, 8 weeks 8.0 ± 2.9, $p < 0.0001$) (Fig. 2). Significant improvement in QOL was seen in both the PCS (pre 47.8 ± 6.6, 4 weeks 50.2 ± 5.2, $p = 0.0015$, 8 weeks 50.0 ± 5.9, $p = 0.0209$) and MCS (pre 47.4 ± 8.5, 4 weeks 50.6 ± 5.9, $p = 0.0103$, 8 weeks 50.4 ± 5.3, $p = 0.0133$) with treatment (Fig. 3).

Correlation between GERD symptoms and QOL at pre-treatment. At pre-treatment, QOL correlated negatively with F-TS (PCS: $r = -0.0359$, $p = 0.0010$; MCS: $r = -0.356$, $p = 0.0011$), F-RS (PCS: $r = -0.0273$, $p = 0.0136$, MCS: $r = -0.249$, $p = 0.0253$) and F-DS (PCS: $r = -0.398$, $p = 0.0002$; MCS: $r = -0.422$, $p < 0.0001$) (Fig. 4).

Correlation between improvements in FSSG scores and QOL after 8 weeks with PPI treatment. Examination of the correlation between the improvement rate in FSSG scores and QOL after 8 weeks of treatment showed a significant positive correlation was seen between in MCS at 8 weeks and the improvement rates in F-TS ($r = 0.275$, $p = 0.0265$) and in F-DS ($r = 0.367$, $p = 0.0027$). However, No significant correlations were seen between the improvement rate in F-RS and either in PCS or in MCS (Fig. 5).

Associated with improvement of QOL. By univariate logistic regression analysis, only improvement of F-SD was

DATE:

NAME (ID;) AGE
GENDER M · F

*Do you have any of following symptoms?
If so, please circle the appropriate response below.

	Question	Fill-in space				
		NEVER	OCCA-SIONALLY	SOME-TIMES	OFTEN	ALWAYS
1	Do you get heartburn?	0	1	2	3	4
2	Does your stomach get bloated?	0	1	2	3	4
3	Does your stomach ever feel heavy after meals?	0	1	2	3	4
4	Do you sometimes subconsciously rub your chest with your hand?	0	1	2	3	4
5	Do you ever feel sick after meals?	0	1	2	3	4
6	Do you get heartburn after meals?	0	1	2	3	4
7	Do you have an unusual (e.g. burning)sensation in your throat?	0	1	2	3	4
8	Do you feel full while eating meals?	0	1	2	3	4
9	Do some things get stuck when you swallow?	0	1	2	3	4
10	Do you get bitter liquid (acid) coming up into your throat?	0	1	2	3	4
11	Do you burp a lot?	0	1	2	3	4
12	Do you get heartburn if you bend over?	0	1	2	3	4
	Please describe any other symptoms you experience.					

SUM POINTS ☐ + ☐ + ☐ + ☐ = ☐ TOTAL POINT

Acid reflux related symptom = ☐ POINTS
Dyspeptic (Dysmotility) symptom = ☐ POINTS

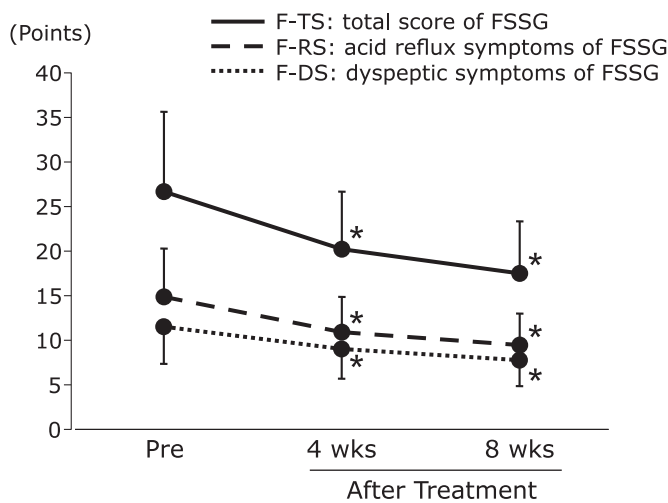**Fig. 1.** Frequency Scale for the Symptoms of GERD (FSSG).

Fig. 2. Changes in FSSG score at each time of assessment. Mean ± SD. FSSG: the Frequency Scale for the Symptom of GERD. *p<0.05 comparison with Pre treatment.
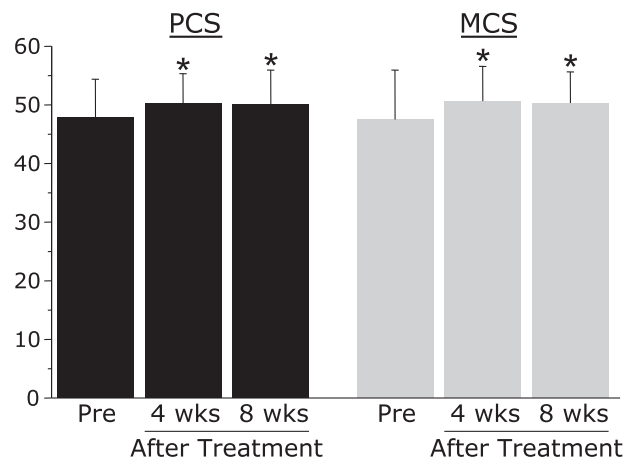

Fig. 3. Change rates in QOL at each time of assessment. QOL: Quality of Life. PCS: physical component summary score. MCS: mental component summary score. *p<0.05 comparison with Pre treatment. Spearman's correlation coefficient.
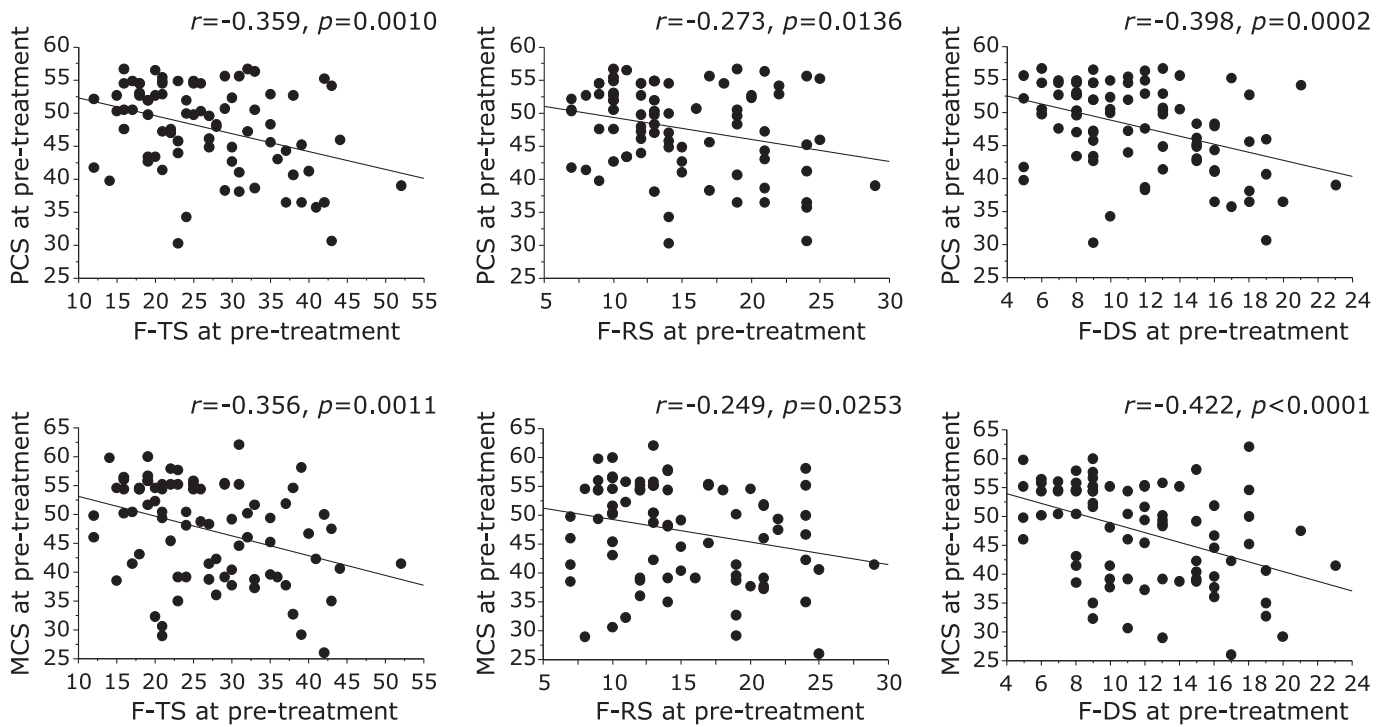
Fig. 4. Correlation of FSSG and QOL at pre-treatment. F-TS: total score of FSSG. F-RS: acid reflux symptoms of FSSG. F-DS: dyspeptic symptoms of FSSG. QOL: Quality of Life. PCS: physical component summary score. MCS: mental component summary score. Spearman's correlation coefficient.

Fig. 5. Correlation of the improvements rate of FSSG and QOL after 8 weeks. F-TS: total score of FSSG. F-RS: acid reflux symptoms of FSSG. F-DS: dyspeptic symptoms of FSSG. QOL: Quality of Life. PCS: physical component summary score. MCS: mental component summary score. Spearman's correlation coefficient.
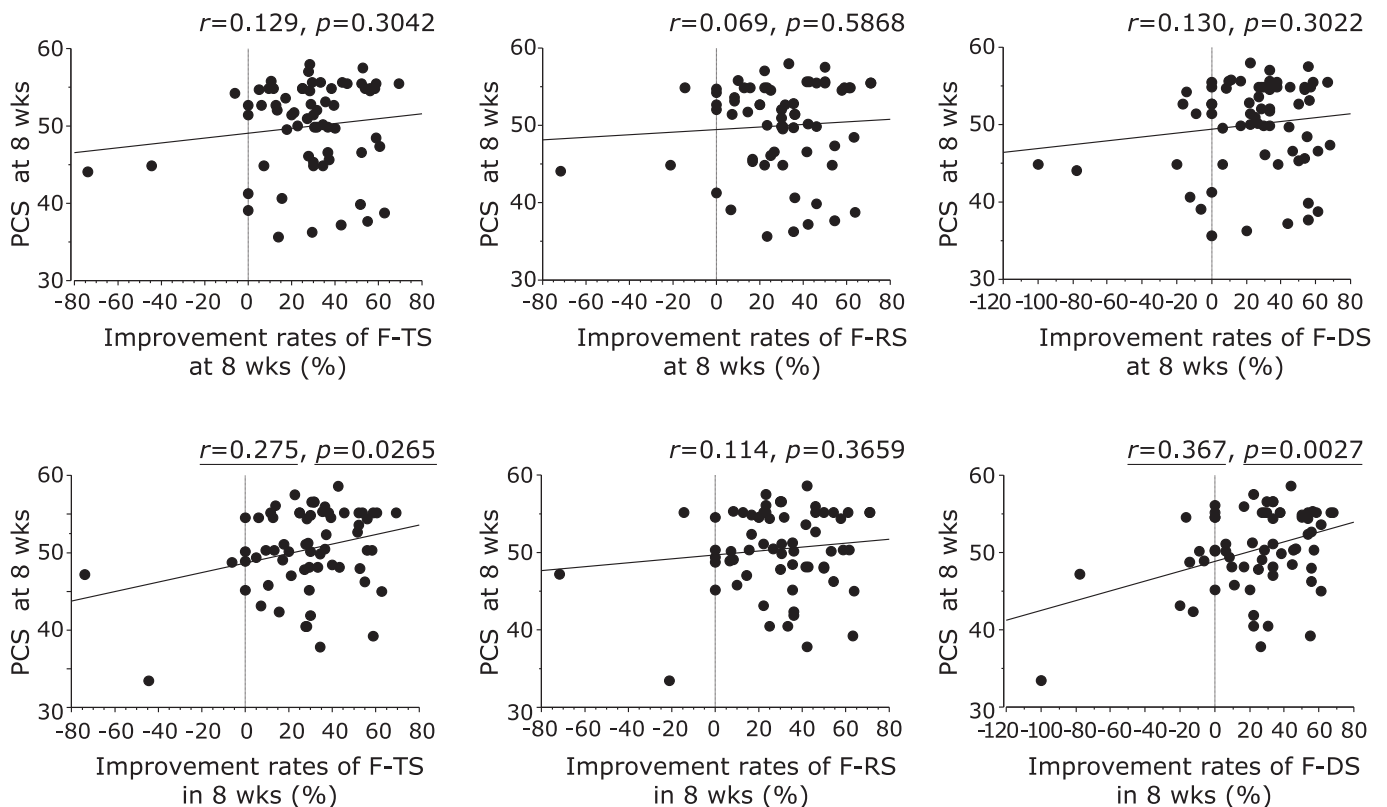
associated with improved MCS. (odds; 1.021, 95% CI; 1.001–1.041, *p* = 0.0391) F-TS and F-RS were not significant.

Discussion

From the report by Fujiwara *et al.*,[15] we know that the incidence of GERD has risen markedly in Japan from 1990 until now. The reasons for this trend increased gastric acid secretion in the Japanese population,[16] the reduced prevalence of *Helicobacter pylori* infection,[17] and obesity associated with Westernized eating habits,[18] Untreated GERD impairs QOL more than untreated angina pectoris or hypertension,[19] and the ultimate aim of GERD treatment is improved QOL.[1] To reverse this decline in QOL in patients with GERD, it is important to ameliorate GERD-related symptoms through treatments that prevent acid reflux.[20] A number of studies have identified a correlation between QOL and GERD-related symptoms. Several have indicated that GERD-related symptoms are the key to QOL, with greater Japan F-scale and SF-8 Trial (J-FAST) impairment of QOL as the severity of GERD-related symptoms increases,[21–23] greater impairment of QOL as the frequency of nocturnal GERD symptoms increases,[24] a correlation between the frequency of heartburn and regurgitation and impairment of QOL,[25] and a marked decrease in QOL with 2 or more episodes of heartburn per week.[26]

Our results also showed a negative correlation between the severity of both reflux and dyspeptic symptoms and QOL at pre-treatment PPI. The FSSG used in this study scores the frequency of typical GERD-related symptoms. The FSSG total score of 12 symptoms in Japanese GERD patients can also be subdivided into a score related to reflux symptoms such as heartburn and regurgitation (F-RS) and a score related to dyspeptic symptoms such as bloating and fullness (F-DS).[7,8] Greater impairment in QOL prior to PPI treatment was seen as symptom severity increased, as evidenced by the F-TS, F-RS and F-DS. Not only was a correlation seen between QOL and acid reflux symptoms, but the severity of dyspeptic symptoms also impaired QOL. This finding agrees with previous studies that suggest dyspeptic symptoms impact adversely on QOL.[27]

We administered rabeprazole 10 mg/day for 8 weeks, resulting in significant improvements in the F-TS, F-RS and F-DS, as well as improvement in QOL. Kusano *et al.*[8] also used the FSSG to evaluate the efficacy of 8 weeks of treatment with rabeprazole 10 mg/day. As with this study, they found that not only acid reflux symptoms, but also dyspeptic symptoms were improved, so they defined dyspeptic symptoms that respond to a PPI as 'acid related dyspepsia'.

We also examined the correlation between the improvement rate in GERD symptoms and in QOL. Earlier studies found a correlation between the rate of symptom resolution with pharmacological management and the improvement rate in QOL,[28] and showed that complete resolution of symptoms is required to achieve high improvements in QOL.[21] In our study, a significant positive correlation was seen between the improved MCS and the improvement rates in F-TS and F-DS. However, no correlations

were seen between the improvement rate in F-RS and either the improvement rates in PCS or in MCS. This lack of correlation between the improvement rate in acid reflux symptoms and in PCS or MCS is extremely interesting. The reason that the severity of acid reflux symptoms, typical symptoms of GERD, correlated with QOL, but in our study, the improvement of reflux symptoms was not correlated with the improvement of QOL, is unclear. There is possibility of two reasons. First, the ratio of RE was low in our study (35.8%). Pooled response rates of PPI were significantly higher for patients with RE compared with NERD.[29] There is a possibility that acid reflux symptoms correlates to QOL, if there are a lot of ratios of RE. Second, it is a difference of the symptom improvement speed and the QOL improvement speed. The symptom improvement speed was prompt, and the QOL improvement speed was slow. Especially, the improvement speed of acid reflux symptoms was quickly, and the improvement speed of dyspeptic symptoms was more gradual. The improvement speed of acid reflux symptoms did not catch up at the QOL improvement speed for promptness, and the improvement speed of dyspeptic symptoms caught up oppositely at the QOL improvement speed. In a current report, the symptom resolution within 7 days after PPI treatment has been correlated with the rate of symptom resolution 4 weeks later, but not with QOL improvement.[3–6] In our study, it is thought that the improvement of dyspeptic symptoms associated in QOL improvement, importantly. The resolution rate for heartburn symptoms with PPI treatment is lower in the presence of multiple dyspeptic symptoms.[30] Consideration of these factors suggests that improvement in dyspeptic symptoms is a factor that strongly influences improved QOL with PPI therapy.

Study Limitation

Our study is a single arm open label study without placebo control.

Conflict of Interest

No conflict of interest has been declared by the authors.

Abbreviations

FD   functional dyspepsia
F-DS   dyspeptic symptoms of FSSG
F-RS   acid reflux symptoms of FSSG
F-TS   total score of FSSG
GERD   gastroesophageal reflux disease
MCS   mental component summary score
NERD   non-erosive reflux disease
PCS   physical component summary score
PPI   proton pump inhibitor
QOL   quality of life
RE   reflux esophagitis

References

1 Kahrilas PJ, Shaheen NJ, Vaezi MF, *et al.*; American Gastroenterological Association. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. *Gastroenterology* 2008; **135**: 1383–1391.

2 Bytzer P. Goals of therapy and guidelines for treatment success in symptomatic gastroesophageal reflux disease patients. *Am J Gastroenterol* 2003; **98**: S31–S39.

3 Talley NJ, Armstrong D, Junghard O, Wiklund I. Predictors of treatment response in patients with non-erosive reflux disease. *Aliment Pharmacol Ther* 2006; **24**: 371–376.

4 McQuaid KR, Laine L. Early heartburn relief with proton pump inhibitors: a

systematic review and meta-analysis of clinical trials. *Clin Gastroenterol Hepatol* 2005; **3**: 553–563.

5 Talley NJ, Vakil N, Lauritsen K, *et al.*; STARS I Study Group. Randomized-controlled trial of esomeprazole in functional dyspepsia patients with epigastric pain or burning: does a 1-week trial of acid suppression predict symptom response? *Aliment Pharmacol Ther* 2007; **26**: 673–682.

6 van Zanten, Flook N, Talley NJ, *et al.*; STARS II Study Group. One-week acid suppression trial in uninvestigated dyspepsia patients with epigastric pain or burning to predict response to 8 weeks' treatment with esomeprazole: a randomized, placebo-controlled study. *Aliment Pharmacol Ther* 2007; **26**: 665–672.

7 Kusano M, Shimoyama Y, Sugimoto S, *et al*. Development and evaluation of FSSG: frequency scale for the symptoms of GERD. *J Gastroenterol* 2004; **39**: 888–891.

8 Kusano M, Shimoyama Y, Kawamura O, *et al*. Proton pump inhibitors improve acid-related dyspepsia in gastroesophageal reflux disease patients. *Dig Dis Sci* 2007; **52**: 1673–1677.

9 Danjo A, Yamaguchi K, Fujimoto K, *et al*. Comparison of endoscopic findings with symptom assessment systems (FSSG and QUEST) for gastro-esophageal reflux disease in Japanese centres. *J Gastroenterol Hepatol* 2009; **24**: 633–638.

10 Kusano M, Shirai N, Yamaguchi K, Hongo M, Chiba T, Kinoshita Y.; Acid-Related Symptom (ARS) Research Group. It is possible to classify non-erosive reflux disease (NERD) patients into endoscopically normal groups and minimal change groups by patientive symptoms and responsiveness to rabeprazole—a report from a study with Japanese patients. *Dig Dis Sci* 2008; **53**: 3082–3094.

11 Miyamoto M, Haruma K, Takeuchi K, Kuwabara M. Frequency scale for symptoms of gastroesophageal reflux disease predicts the need for addition of prokinetics to proton pump inhibitor therapy. *J Gastroenterol Hepatol* 2008; **23**: 746–751.

12 Fukuhara S, Suzukamo Y. Manual of the SF-8 Japanese version: Institute for Health Outcomes & Process Evaluation Research, Kyoto, 2004.

13 Hoshihara Y. Endoscopic findings of GERD. *Nippon Rinsho* 2004; **62**: 1459–1464 (in Japanese with English abstract).

14 Hongo M. Minimal changes in reflux esophagitis: red ones and white ones. *J Gastroenterol* 2006; **41**: 95–99.

15 Fujiwara Y, Arakawa T. Epidemiology and clinical characteristics of GERD in the Japanese population. *J Gastroenterol* 2009; **44**: 518–534.

16 Kinoshita Y, Kawanami C, Kishi K, Nakata H, Seino Y, Chiba T. *Helicobacter pylori* independent chronological change in gastric acid secretion in the Japanese. *Gut* 1997; **41**: 452–458.

17 Sugiyama T, Nishikawa K, Komatsu Y, *et al*. Attributable risk of *H. pylori* in peptic ulcer disease: does declining prevalence of infection in general population explain increasing frequency of non-*H. pylori* ulcers? *Dig Dis Sci* 2001; **46**: 307–310.

18 Kubota E, Tanida S, Sasaki M, *et al*. Contribution of *Helicobacter pylori* infection and obesity on heartburn in a Japanese population. *J Clin Biochem Nutr* 2006; **39**: 168–173.

19 Dimenäs E. Methodological aspects of evaluation of Quality of Life in upper gastrointestinal diseases. *Scand J Gastroenterol Suppl* 1993; **199**: 18–21.

20 Ofman JJ. The economic and quality-of-life impact of symptomatic gastro-esophageal reflux disease. *Am J Gastroenterol* 2003; **98**: S8–S14.

21 Revicki DA, Zodet MW, Joshua-Gotlib S, Levine D, Crawley JA. Health-related quality of life improves with treatment-related GERD symptom resolution after adjusting for baseline severity. *Health Qual Life Outcomes* 2003; **1**: 73.

22 Eslick GD, Talley NJ. Gastroesophageal reflux disease (GERD): risk factors, and impact on quality of life-a population-based study. *J Clin Gastroenterol* 2009; **43**: 111–117.

23 Hongo M, Miwa H, Kusano M.; J-FAST group. Effect of rabeprazole treatment on health-related quality of life and symptoms in patients with reflux esophagitis: a prospective multicenter observational study in Japan. *J Gastroenterol* 2011; **46**: 297–304.

24 Farup C, Kleinman L, Sloan S, *et al*. The impact of nocturnal symptoms associated with gastroesophageal reflux disease on health-related quality of life. *Arch Intern Med* 2001; **161**: 45–52.

25 Eloubeidi MA, Provenzale D. Health-related quality of life and severity of symptoms in patients with Barrett's esophagus and gastroesophageal reflux disease patients without Barrett's esophagus. *Am J Gastroenterol* 2000; **95**: 1881–1887.

26 Dent J, Armstrong D, Delaney B, Moayyedi P, Talley NJ, Vakil N. Symptom evaluation in reflux disease: workshop background, processes, terminology, recommendations, and discussion outputs. *Gut* 2004; **53**(Suppl 4): iv1–24.

27 Piessevaux H, De Winter, Louis E, *et al*. Dyspeptic symptoms in the general population: a factor and cluster analysis of symptom groupings. *Neurogastro-enterol Motil* 2009; **21**: 378–388.

28 Choung RS, Locke GR, Schleck CD, Zinsmeister AR, Talley NJ. Do distinct dyspepsia subgroups exist in the community? A population-based study. *Am J Gastroenterol* 2007; **102**: 1983–1989.

29 Dean BB, Gano AD Jr., Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. *Clin Gastroenterol Hepatol* 2004; **2**: 656–664.

30 Fass R, Shapiro M, Dekel R, Sewell J. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease—where next? *Aliment Pharmacol Ther* 2005; **22**: 79–94.