Esophageal transit scintigraphy and structured questionnaire in patients with systemic sclerosis with endoscopically proven reflux esophagitis

doi: 10.1007/s12149-009-0310-0

Accepted for publication in Ann Nucl Med 2009

Esophageal transit scintigraphy and structured questionnaire in patients with systemic sclerosis with endoscopically proven reflux esophagitis

Kenichi Nakajima*, Anri Inaki*, Takashi Hiramatsu*, Minoru Hasegawa**, Manabu Fujimoto**, Kazuhiko Takehara**, Seigo Kinuya*

*Department of Nuclear Medicine, Kanazawa University Hospital, Kanazawa, Japan;
**Department of Dermatology, Kanazawa University Hospital, Kanazawa, Japan

Address for correspondence
Kenichi Nakajima, M.D.
Department of Nuclear Medicine, Kanazawa University Hospital
13-1 Takara-machi, Kanazawa, 920-8641 Japan
Tel 076-265-2335, Fax 076-234-4257
E-mail: nakajima@med.kanazawa-u.ac.jp
Short title
Esophageal transit study in systemic sclerosis

published in Ann Nucl Med 2009; 23: 771-776

Abstract

Objectives: Esophageal complication is common in patients with systemic sclerosis (SSc). The relationship between gastroesophageal reflux (GER) symptoms and dysmotility was examined in endoscopically confirmed patients with suspected of having reflux esophagitis.
Methods: A total of 32 patients with limited and diffuse type SSc (lSSc, dSSc) were examined based on a structured questionnaire score (QS) of GER symptoms, retention fraction of esophageal scintigraphy at 90 seconds (R90) and gastric emptying time.
Results: The QS was significantly higher in the reflux esophagitis group than in the non-esophagitis group (5.4 ± 3.5, 1.4 ± 2.9, p=0.003). When the non-esophagitis group was further divided into lSSc and dSSc groups, R90 was higher in the reflux esophagitis group (31% ± 18%) and the non-esophagitis group with dSSc (34% ± 32%) than in the non-esophagitis group with lSSc (8% ± 3%, p=0.02). Both high R90≥15% and QS≥4 indicated reflux esophagitis. Conversely both normal R90 and QS indicated no reflux esophagitis.
Conclusion: A combination of esophageal scintigraphy and structured questionnaire demonstrated different aspects of esophageal dysfunction, namely dysmotility and GER. Patients with high QS and dysmotility may be indicated for further evaluation including endoscopic examination and medical treatment.

Key words: systemic sclerosis, esophageal transit scintigraphy, esophageal dysmotility, gastroesophageal reflux, structured questionnaire

Introduction

Systemic sclerosis (SSc) is a generalized disorder involving multiple organs and tissues of heart, lung, kidney and gastrointestinal tracts. [1] Of these generalized involvements, typical esophageal complications include dysphagia and esophageal reflux. Major esophageal and gastric complications seem to be related to neuropathy of the gastrointestinal nervous system and collagen deposition or fibrosis in the smooth muscle layer.

Since the 1980's, nuclear studies have shown the usefulness of esophageal transit scintigraphy to identify transit disorders, and high prevalence of transit delay or retention has been demonstrated in patients with SSc. [2-9] As an indicator of dysmotility in both early and advanced disease, a study has demonstrated that esophageal scintigraphy has a higher sensitivity than that of manometry and barium swallows [3], although new manometric techniques have been developed currently. However, the relationship between nuclear esophageal transit studies and reflux esophagitis has not been defined yet. When symptoms are typical for gastroesophageal reflux (GER), effective response to medication such as proton-pump inhibitors may further support the diagnosis of GER. Considering the high morbidity of GER, careful examination is required in patients with gastrointestinal abnormalities even for those patients without symptoms. [10] A nuclear esophageal transit study might reflect motility after ingestion and thus might not directly detect esophagitis.

Thus, we hypothesized that combined use of structured GER symptom scoring and an esophageal transit study can differentiate the nature of esophageal complications. The aims of this study were to evaluate the incidence of esophageal transit and gastric emptying abnormalities in comparison with GER symptoms in patients with endoscopically confirmed reflux esophagitis.

Methods

Patients

A total of 32 patients (24 females and 8 males, average age 58 ±12 (SD) years) were examined based on esophageal transit and gastric emptying studies. The patients were diagnosed with systemic sclerosis (SSc) in the Department of Dermatology at Kanazawa University based on American Rheumatism Association diagnostic criteria. The final diagnosis of SSc was made based on skin lesions, serological examinations and multiple organ surveys. The classification into diffuse and limited cutaneous SSc types (dSSc, lSSc) was based on skin lesions, other clinical findings and laboratory data according to LeRoy et al. [11, 12] All the patients underwent esophageal and gastric endoscopy for the diagnosis of reflux esophagitis and were classified by the standard Los Angeles classification system. [13] Chest X-ray and respiratory function were evaluated for the diagnosis of interstitial lung disease.

The study protocol was approved by Institutional Review Board of Kanazawa University. Written informed consent was obtained from all patients.

Esophageal transit study

Technetium-99m (99mTc) diethylenetriaminepentaacetic acid (DTPA) was mixed in a semi-liquid enteral feeding formula (Racol(R), Otsuka Pharmaceutical Company Ltd, Japan), which included 200kcal with 8.76 g of protein, 4.46 g of lipids, and 31.24 g of carbohydrates in addition to vitamins and minerals per 200 mL. Patients were instructed to retain 7-10 mL of the liquid, in which ~10 MBq of Tc-99m was mixed, and to swallow one gulp. After 30 seconds, the patients repeated dry swallows during each 15-second interval. After practice attempts of several swallows, the studies were repeated twice in the sitting and supine positions, but only the results from the supine position were analyzed in this study. [9] The fragmentation of the bolus in the swallow could be avoided by the practice of using unlabeled liquid. Serial anterior images were acquired in 64 x 64 matrices for 96 seconds at 0.5 seconds per frame. A large rectangular field of view camera (53 x 39 cm) equipped with a low-energy high-resolution collimator (ecam, Toshiba/Siemens, Tokyo, Japan) was used. After the esophageal transit study, the remaining semi-liquid meal (~180 mL) was ingested in one minute, resulting in 200 mL in the stomach. The images of the stomach were obtained in the left anterior oblique projection at 3, 10, 20, 30, 45, 60 and 90 minutes after ingestion.

Structured questionnaire

To evaluate the GER symptom, a structured questionnaire was used. [14, 15] The questionnaire was comprised of scoring of (1) the nature of main discomfort, (2) the timing of the symptoms, (3) relation to the food type, (4) effects of ingestion medicine, (5) effects of bending or stooping, (6) effects of straining and lifting and (7) changes of symptoms after return of food or acid (Table 1). The threshold score of 4 or more was used for suggesting reflux esophagitis. [16] The summed score ranged from -7 to 18 points, in which the higher points indicated severer reflux symptoms.

Data analysis

After observing tracer transit on a cinematic display, esophageal transit was analyzed by time-activity curves as previously described. [9] A

region of interest (ROI) was drawn over the whole esophagus ranging from the upper esophagus to the gastroesophageal junction. The retention fraction at 90 seconds (R90) was defined as the retained activity at 90 seconds divided by the maximum activity of the time-activity curve. To calculate gastric emptying time, manual ROIs were set on the stomach and the time-activity curve was plotted. The retention fraction at 60 minutes (%) and half emptying time (min) were calculated by exponential fitting.

Statistics

Values were expressed as a mean ± standard deviation (SD). The differences of the variance and mean values were examined by a multiple-comparison test following a significant finding in the one-way analysis of variance (ANOVA). The difference of the contingency table was examined by chi-square and likelihood ratio and Pearson p-values. A p value < 5% was considered significant.

Results

The questionnaire score (QS) and esophageal R90 in SSc types are summarized in Table 2. Both high and low QS were observed in the dSSc and lSSc groups (p=n. s.), while high R90 >15% was observed in 12 of 18 (67%) patients in the dSSc type and 3 of 14 (21%) in the lSSc type. The frequency of reflux esophagitis did not differ significantly between dSSc and lSSc groups

When QS and R90 were compared with esophageal hernia (n=3) excluded, the numbers of patients in groups with high QS≥4 and high R90≥15%, high QS≥4 and low R90<15%, low QS<15% and high R90≥15% and low QS and low R90<15% were 5, 4, 9 and 11 (p=n. s. by $\chi 2$ analysis). Distribution of R90 and QS with regard to reflux esophagitis is shown in Figure 1. When both QS and R90 were high, all patients had reflux esophagitis except for a case with esophageal hernia. When both QS and R90 were low, no patient with reflux esophagitis was included. However, retention-dominant (high R90) and symptom-dominant (high QS) patients were also noted. Reflux esophagitis was observed in 70% (3/10) of the dysmotility-dominant group and in 50% (2/4) in the reflux symptom-dominant group.

Esophageal and gastric transit studies are summarized in patients with endoscopically confirmed reflux esophagitis (Table 3). The QS was significantly higher in patients with reflux esophagitis (5.4±3.5) than those without (1.4±2.9) (p=0.003), while R90 did not reach statistical significance. Gastric retention at 60 minutes and half-emptying time did not differ between both groups.

Patients without reflux esophagitis were divided into lSSc (n=10) and dSSc (n=10) subgroups and compared with esophageal reflux groups (n=9) (Table 4). Both R90 and QS differed significantly among the three groups. The R90 was higher in dSSc without esophagitis and reflux esophagitis, and the QS was higher in patients with reflux esophagitis. Gastric retention did not differ significantly among three groups. Total skin thickness score was slightly higher in the reflux esophagitis group and the non-esophagitis group with dSSc compared with the non-esophagitis group with lSSc (p=0.05).

Interstitial lung disease was observed in 13 of 18 (72%) with dSSc and 3 of 14 (21%) lSSc types (p=0.004 by Pearson statistics). When patients without esophagitis were similarly divided into lSSc and dSSc groups, interstitial lung disease was observed in 2 (20%) with lSSc and in 7 (70%) with dSSc in comparison with 5 (56%) with reflux esophagitis (n. s., p=0.07 by Pearson statistics).

Discussion

An esophageal transit study combined with a structured questionnaire for GER could characterize the esophageal complication in SSc. Patients with both positive QS and dysmotility highly indicated reflux esophagitis. Conversely, patients with good motility and normal QS indicated no reflux esophagitis. Two aspects of dysfunction in SSc, namely, dysmotility-dominant and GER symptom-dominant groups, were separately evaluated in this study.

In multiple organ involvements associated with SSc, digestive systems were most frequently involved including esophagus, duodenum and small and large intestines.[1] The common underlying pathology was atrophy of smooth muscles and fibrous changes, which resulted in peristaltic disturbances. The incidence of complication in the digestive system was approximately 50 to 80%, and the abnormal esophageal scintigraphic findings were found in 70-90% of patients. [2-5, 8] This study showed abnormal esophageal retention in ~70% of dSSc type and ~20% of lSSc type, demonstrating a difference in SSc types. However, all patients with esophageal scintigraphic abnormality did not necessarily have subjective symptoms. In general, the most frequent site of involvement was in the esophagus, followed by small and large intestines, and the site of the stomach was less frequent. [7, 17, 18]

Common esophageal manifestations in SSc include motility abnormalities, GER, Barrett's esophagus, adenocarcinoma, infectious esophagitis, and drug-induced esophagitis.[10] The GER symptom which was not associated with pathologically-confirmed reflux esophagitis might be actually more common. The symptom of heartburn was aggravated by bending forward, straining, or lying recumbent. In this study, the

diagnosis of reflux esophagitis was endoscopically made based on visible pathological changes. Although scintigraphic abnormality with GER symptoms was considered false positive if the pathological change was not evident by endoscopic study, actual functional abnormality could not be denied. However, since esophagitis was determined by strict definition using an endoscope, this study may be used to find the appropriate candidates for further endoscopic examinations.

The usefulness of the structured questionnaire was examined, since the symptoms were somewhat vague based on the complaints of the patients. A study showed that the questionnaire had a sensitivity of 92% but a low specificity of 19%. [15] The diagnostic test characteristics of the questionnaire were comparable with those of the physician's provisional classification. [14] However, the questionnaire score was successfully used to evaluate treatment of GER with proton-pump inhibitors. [19] A Japanese study using this questionnaire (Osaka GERD study) showed that diagnostic performance of the score using a threshold of ≥4 showed sensitivity of 72%, specificity of 54% and accuracy of 56% to predict reflux esophagitis in 675 patients (347 males and 328 females) who underwent endoscopic examination. [16] Thus, the diagnostic ability of this symptomatic questionnaire alone was still limited, but the scoring system could be used to semi-quantify subjective GER symptoms as an adjunct to a non-invasive nuclear esophageal transit study.

Esophageal retention after repeated swallowing was higher in dSSc patients than in lSSc patients, which was comparable with findings of precedent studies, although lSSc patients may have had reflux esophagitis. [9, 20] In patients with endoscopic evidence of esophagitis, the QS was significantly high and was considered to correspond to patient GER symptoms. On the other hand, R90 was relatively high in patients with endoscopically confirmed esophagitis, but it was not significant. Therefore, esophageal reflux and peristaltic abnormality seemed to show different aspects of the esophageal complications in patients with SSc. In addition, gastric emptying time did not correlate with reflux esophagitis. A study using solid meal revealed 57% abnormality in gastric emptying, while delayed esophageal transit was abnormal in 73%. [18] The study also found weak correlation between esophageal transit time and gastric emptying time using a solid meal. The lower frequency of gastric abnormality in our study may be related to the food type as we used semi-liquid meal, and it may also have been related to the characteristics of the patient population.

Patients who underwent endoscopy were examined, but control patients were not included. The lSSc patients who had no evidence of esophagitis were the least severe groups, and parameters of esophageal transit and gastric emptying were comparable with those of the control patients in our preceding study. [9, 21] The mean QS was also within normal range in this lSSc group.

Higher prevalence of interstitial lung disease in patients with severe esophageal motor impairment was demonstrated, and it suggested that GER might be one of the contributing factors of interstitial lung disease. [20, 22, 23] Comprehensive follow-up will be required since SSc involves multiple organs, particularly in digestive systems, lung, heart and kidney in addition to scleroderma changes. Appropriate non-invasive evaluations for complications would lead to early diagnosis and management of the SSc patients.

The number of patients was limited, because all non-symptomatic patients with SSc could not be diagnosed by endoscopic examinations. The relationship between the severity by Los Angeles classification and QS or R90 could not be analyzed because of the limited number in each subgroup. Esophageal sliding and/or hiatus herniation showed abnormal transit patterns, but this could not be differentiated by scintigraphy and a questionnaire. However, typical herniation may be diagnosed by an X-ray esophageal barium study or X-ray CT.

In conclusion, patients with high R90 (dysmotility) and high QS (reflux symptom) strongly suggested reflux esophagitis, and further endoscopic examination or treatment strategy would be required. In contrast, patients with both normal R90 and QS may not be indicated for endoscopic examination. The GER-dominant group and dysmotility-dominant group suggested different aspects of esophageal dysfunction.

Acknowledgement

This work was supported by funds for research on intractable diseases from the Ministry of Health, Labour and Welfare of Japan (2006-2008).

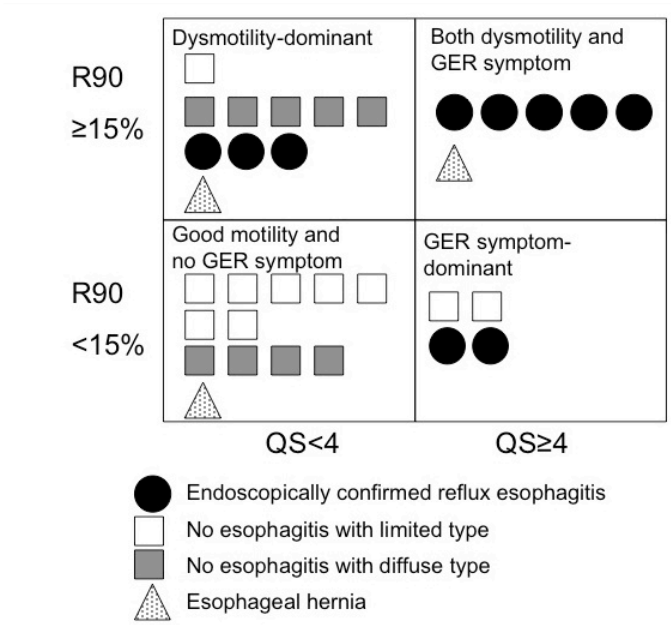

Figure 1
Esophageal retention fraction at 90 seconds (R90) and questionnaire score for GER symptoms (QS). Endoscopic findings were classified into 4 groups using threshold values of R90=15% and QS=4 points.

Table 1. Questionnaire for scoring gastroesophageal reflux symptoms

Please answer the following questions by ticking one box only, except for Q3, where you must tick one box for each statement.

Q1. Which one of following statements best describes the main discomfort in your stomach or chest?
(5) □ A burning feeling rising from your stomach or lower chest up to your neck
(0) □ Feelings of sickness or nausea
(2) □ Pain in the middle of your chest when you swallow
(0) □ None of the above, please describe below:

Q2. Please choose which one of the next statements best describes the timing of your main discomfort?
(-2) □ Any time, not made better or worse by taking food
(3) □ Most often within 2 hours of taking food
(0) □ Always at a particular time of day or night without any relationship to food

Q3. How do the following affect your main discomfort?

	Worsens	Improves	No effect/Unsure
○ Larger than usual meals	(1) □	(-1) □	(0) □
○ Food rich in fat	(1) □	(-1) □	(0) □
○ Strongly flavored or spicy food	(1) □	(-1) □	(0) □

Q4. Which one of the following best describes the effect of indigestion medicines on your main discomfort?
(0) □ No benefit (3) □ Relief within 15 minutes (0) □ Relief after 15 minutes
(0) □ Not applicable (I don't take indigestion medicines)

Q5. Which of the following best describes the effect of lying flat, stooping, or bending on your main discomfort?
(0) □ No effect (1) □ Makes it worse (-1) □ Gives relief
(0) □ Don't know

Q6. Which of the following best describes the effect of lifting, straining or any other activity that makes you breath heavily on your main discomfort?
(0) □ No effect (1) □ Makes it worse (-1) □ Gives relief
(0) □ Don't know or this does not apply to me

Q7. If food or acid-tasting liquid returns to your throat or mouth what effect does it have on your main discomfort?
(0) □ No effect (2) □ Makes it worse (0) □ Gives relief
(0) □ Don't know or this does not apply to me

The weighted scores within parentheses were added to obtain the diagnostic score. These scores were not disclosed on the questionnaire form.

Table 2
Diffuse versus limited cutaneous types of systemic sclerosis

	Diffuse	Limited	p values
Number	18	14	
Age	56 ± 14	61 ± 10	n. s.
Esophageal R90 (%)	31 ± 27	16 ± 14	n. s. (0.06)
High R90≥15%	12 (67%)	3 (21%)	0.009*, 0.02**
QS (points)	2.5 ± 3.9	2.7 ± 3.1	n. s.
High QS≥4	5 (28%)	5 (36%)	n. s.
Gastric retention at 60 min (%)	34 ± 13	41 ± 13	n. s.
Gastric half-emptying time (min)	41 ± 16	49 ± 20	n. s.
Reflux esophagitis	6 (33%)	3 (21%)	n. s.

QS, Questionnaire score; R90, retention (%) at 90 seconds
P values of likelihood ratio* and Peason statistics**

Table 3
Esophageal and gastric transit in patients with endoscopically confirmed reflux esophagitis

	No esophagitis	Reflux esophagitis	p values
Number	20	9	
Esophageal transit study			
R90 (%)	21 ± 26	31 ± 18	n. s.
Questionnaire			
QS (points)	1.4 ± 2.9	5.4 ± 3.5	0.003
Gastric emptying study			
Retention at 60 min (%)	39 ± 13	31 ± 8	n. s.
Half-emptying time (min)	47 ± 16	35 ± 8	n. s.

Table 4
Esophageal and gastric transit study in the groups of SSc type and esophagitis

	No esophagitis		Reflux esophagitis	p values
	Limited SSc	Diffuse SSc		
Number	10	10	9	
Esophageal transit study				
R90 (%)	8 ± 3	34 ± 32	31 ± 18	0.02
Questionnaire				
QS (points)	1.6 ± 2.8	1.2 ± 3.2	5.4 ± 3.5	0.01
Gastric emptying study				
Retention at 60 min (%)	41 ± 10	37 ± 16	31 ± 8	n. s.
Half-emptying time (min)	47 ±15	46 ± 18	35 ± 8	n. s.
Scleroderma				
Total skin thickness score	5 ± 2	22 ± 13	29 ± 12	0.05

References

1. D'angelo W, Fries J, Masi A, Shulman L. Pathologic observation in systemic sclerosis (scleroderma). A study of fifty-eight autopsy cases and fifty-eight matched controls. Am J Med. 1969;46:428-40.
2. Pitrez EH, Bredemeier M, Xavier RM, Capobianco KG, Restelli VG, Vieira MV, et al. Oesophageal dysmotility in systemic sclerosis: comparison of HRCT and scintigraphy. Br J Radiol. 2006;79:719-24.
3. Mariani G, Boni G, Barreca M, Bellini M, Fattori B, AlSharif A, et al. Radionuclide gastroesophageal motor studies. J Nucl Med. 2004;45:1004-28.
4. Klein HA, Wald A, Graham TO, Campbell WL, Steen VD. Comparative studies of esophageal function in systemic sclerosis. Gastroenterology. 1992;102:1551-6.
5. Davidson A, Russell C, Littlejohn GO. Assessment of esophageal abnormalities in progressive systemic sclerosis using radionuclide transit. J Rheumatol. 1985;12:472-7.
6. Russell CO, Hill LD, Holmes ER 3rd, Hull DA, Gannon R, Pope CE 2nd. Radionuclide transit: a sensitive screening test for esophageal dysfunction. Gastroenterology. 1981;80:887-92.
7. Maddern GJ, Horowitz M, Jamieson GG, Chatterton BE, Collins PJ, Roberts-Thomson P. Abnormalities of esophageal and gastric emptying in progressive systemic sclerosis. Gastroenterology. 1984;87:922-6.
8. Carette S, Lacourciere Y, Lavoie S, Halle P. Radionuclide esophageal transit in progressive systemic sclerosis. J Rheumatol. 1985;12:478-81.
9. Nakajima K, Kawano M, Kinuya K, Sato S, Takehara K, Tonami N. The diagnostic value of oesophageal transit scintigraphy for evaluating the severity of oesophageal complications in systemic sclerosis. Nucl Med Commun. 2004;25:375-81.
10. Ntoumazios SK, Voulgari PV, Potsis K, Koutis E, Tsifetaki N, Assimakopoulos DA. Esophageal involvement in scleroderma: gastroesophageal reflux, the common problem. Semin Arthritis Rheum. 2006;36:173-81.
11. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, Jr., et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol. 1988;15:202-5.
12. LeRoy EC, Medsger TA, Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol. 2001;28:1573-6.
13. Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut. 1999;45:172-80.
14. Numans ME, de Wit NJ. Reflux symptoms in general practice: diagnostic evaluation of the Carlsson-Dent gastro-oesophageal reflux disease questionnaire. Aliment Pharmacol Ther. 2003;17:1049-55.
15. Carlsson R, Dent J, Bolling-Sternevald E, Johnsson F, Junghard O, Lauritsen K, et al. The usefulness of a structured questionnaire in the assessment of symptomatic gastroesophageal reflux disease. Scand J Gastroenterol. 1998;33:1023-9.
16. Nagano K, Kubo M, Goto M, Tatsuta M, Iishi H, Kanda T, et al. The diagnosis of GERD: a study by questionnaire (QUEST) in patients complaining upper digestive symptoms [in Japanese]. J New Remedies and Clinics. 1998;47:841-51.
17. Weston S, Thumshirn M, Wiste J, Camilleri M. Clinical and upper gastrointestinal motility features in systemic sclerosis and related disorders. Am J Gastroenterol. 1998;93:1085-9.
18. Wegener M, Adamek RJ, Wedmann B, Jergas M, Altmeyer P. Gastrointestinal transit through esophagus, stomach, small and large intestine in patients with progressive systemic sclerosis. Dig Dis Sci. 1994;39:2209-15.
19. Tsugeno H, Mizuno M, Fujiki S, Okada H, Okamoto M, Hosaki Y, et al. A proton-pump inhibitor, rabeprazole, improves ventilatory function in patients with asthma associated with gastroesophageal reflux. Scand J Gastroenterol. 2003;38:456-61.
20. Kinuya K, Nakajima K, Kinuya S, Michigishi T, Tonami N, Takehara K. Esophageal hypomotility in systemic sclerosis: close relationship with pulmonary involvement. Ann Nucl Med. 2001;15:97-101.
21. Nakajima K, Kawano M, Kinami S, Fujimura T, Miwa K, Tonami N. Dual-radionuclide simultaneous gastric emptying and bile transit study after gastric surgery with double-tract reconstruction. Ann Nucl Med. 2005;19:185-91.
22. Marie I, Ducrotte P, Denis P, Hellot MF, Levesque H. Oesophageal mucosal involvement in patients with systemic sclerosis receiving proton pump inhibitor therapy. Aliment Pharmacol Ther. 2006;24:1593-601.
23. Lock G, Pfeifer M, Straub RH, Zeuner M, Lang B, Scholmerich J, et al. Association of esophageal dysfunction and pulmonary function impairment in systemic sclerosis. Am J Gastroenterol. 1998;93:341-5.