

# Delayed Gastric Emptying in an Indonesian Population with Reflux Esophagitis

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## ABSTRACT

**Aim:** to observe the delayed gastric emptying in patients with reflux esophagitis as well as to recognize the proportion of GERD patients who have delayed gastric emptying in Indonesian population by using standard scintigraphic method.

**Methods:** patients with heartburn and/or regurgitation in the last six-month period were included in the study. After endoscopic examination of upper gastrointestinal tract, scintigraphic examination was performed in appropriate to Consensus Recommendation for Gastric Emptying Scintigraphy with standard <sup>99</sup>Tc-labeled egg-white meal of 255 kcal. Delayed gastric emptying was defined when there was gastric retention >90% at 1 hour, >60% at 2 hours and >10% at 4 hours.

**Results:** twenty-three patients with reflux esophagitis were compared to 23 subjects with Non-erosive reflux disease (NERD). Subjects with reflux esophagitis demonstrated slower gastric emptying compared to subjects with NERD at 1 hour ( $p<0.05$ ), 2 hours ( $p<0.05$ ) and 4 hours ( $p<0.05$ ). Gastric retention >10% at 4 hours was found in 6% patients with GERD (2 patients with reflux esophagitis and 1 patient with NERD).

**Conclusion:** gastric emptying in patients with reflux esophagitis is significantly slower than in patients with NERD.

**Key words:** GERD, reflux esophagitis, gastric emptying, standard scintigraphy, Indonesia.

## INTRODUCTION

Gastroesophageal Reflux Disease (GERD) is a condition which occurs when the reflux of gastric content produces troublesome symptoms and or complication.<sup>1</sup> The fundamental pathogenesis of GERD includes the exposure of gastric secretion on esophageal or supra-esophageal epithelial which causes histopathological damages or produces symptoms. It may occur due to various causes such as Transient Lower Esophageal Sphincter Relaxation (TLESR), low pressure of the Lower Esophageal Sphincter (LES), excessive acid exposure on esophagus, delayed gastric emptying and disruption of tissue defence.<sup>2</sup> The esophageal complications of GERD are reflux esophagitis, hemorrhage, stricture, Barrett's esophagus and adenocarcinoma. Reflux esophagitis is the most common manifestation of esophageal injury.<sup>1</sup> Delayed gastric emptying in patients with GERD ranges between 6-41%.<sup>3,4</sup> Delayed gastric emptying causes greater volume of reflux material and it may also cause gastric distention.<sup>5</sup> The mechanisms of reflux development in gastric emptying disorder are: (1) Delayed clearance of gastric content which contains acid and it may increase the possibility of regurgitation into the esophagus since the gastric is full for longer period of time; (2) Increased pressure which is necessary for emptying the stomach may cause high intra-gastric pressure over the rest pressure of LES; (3) delayed gastric emptying that may cause gastric dilatation and produces reflux.<sup>6</sup>

The role of gastric emptying on reflux esophagitis is still controversial. Several studies have demonstrated delayed gastric emptying has no role on reflux esophagitis and Barrett's esophagus,<sup>3,7,8</sup> while other studies have indicated that development of esophagitis is related to delayed gastric emptying.<sup>6,9</sup> Such differences

in those studies may be resulting from different standard of examination in each study. To overcome such diversity, The American Neurogastroenterology and Motility Society and Society of Nuclear Medicine has recommended a standard method to measure the gastric emptying by using scintigraphy and having a low-fat diet, i.e. food containing egg-white.<sup>10</sup> Therefore, the aim of our study was to obtain data on gastric emptying in patients with reflux esophagitis, which was compared to patients without reflux esophagitis in GERD patients population. It also was aimed to recognize the proportion of patient with GERD who had gastric emptying disorder in Indonesian population.

## METHODS

Our study was a cross-sectional study, which was conducted at the Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine University of Indonesia/Cipto Mangunkusumo Hospital, Jakarta, Indonesia. The study was conducted from October 2008 to June 2009 by using consecutive sampling. The inclusion criteria were: GERD patient with heartburn and/or regurgitation symptoms, age  $\geq 18$  years, was not using any acid suppression treatment, including H<sub>2</sub> blocker and proton pump inhibitor in the last 7 days prior to scintigraphy, was not consuming calcium antagonist, was not using any drugs that may affect the motility of upper gastrointestinal tract (metoclopramid, erythromycin, domperidone) in the last 2 days prior to scintigraphy, was not consuming opiate analgesics (codeine, morphine) in the last 2 days prior to scintigraphy and willing to participate in our study. The exclusion criteria were: history of gastrectomy, diabetes mellitus, cirrhosis hepatic, chronic renal disease, scleroderma, peptic ulcer, malignancy of upper gastrointestinal tract, pregnancy, and egg allergy. The subjects were then categorized based on their endoscopic results into the group of reflux esophagitis and non-erosive reflux disease. Both groups had undergone gastric emptying examination by using scintigraphy. The patients had at least 6-hour-fasting before the examination. They had to stop smoking on the morning of examination day and during the examination. The standard meal was 120 g of <sup>99</sup>Tc-labeled egg-white meal and 0.5 – 1 mCi of <sup>99m</sup>Tc sulphur colloid, 2 pieces of white bread, 30 g strawberry jam, and 120 ml water. There were 255 kcal in total (i.e. 72% of carbohydrate, 24% of protein, 2% of fat and 2% of fiber). Our subjects took 10 minutes to finish their meal. When they could not complete the meal, at least 50% of each component of the meal

has to be ingested. Imaging was performed soon after they had finished their meal at 1, 2, and 4 hours after the ingestion. The patients stood upright in front of gamma camera (Siemens; Symbia T2; Truepoint Spect CT, Germany). Each acquisition consists of a 1 minute anterior and posterior images. Delayed gastric emptying was defined when there was gastric retention  $> 90\%$  at 1 hour,  $> 60\%$  at 2 hours and  $> 10\%$  at 4 hours. Informed consent was obtained in written from our patients. Our study has been approved by the Ethics Committee at the Faculty of Medicine, University of Indonesia. Data analysis for our hypothesis was using unpaired t-test to observe the difference of gastric emptying at 1, 2 and 4 hours between the patients with reflux esophagitis and patients without esophagitis in GERD-patient population. The p value of  $< 0.05$  was regarded as statistically significant. The statistical analysis was processed by using SPSS 11.0.

## RESULTS

There were 46 subjects who participated in our study, there was one drop out patient who did not complete the scintigraphy.

**Table 1. Demographic characteristics and clinical measures**

|                          | Patients (n=23)   | Control (n=23)   |
|--------------------------|-------------------|------------------|
| Age (years) mean         | 47.09 $\pm$ 12.71 | 44.0 $\pm$ 11.42 |
| Sex (M:F)                | 7 : 16            | 7 : 16           |
| BMI (kg/m <sup>2</sup> ) | 22.99 $\pm$ 3.69  | 25.69 $\pm$ 4.62 |
| Symptoms                 |                   |                  |
| - Nausea                 | 12                | 14               |
| - Vomiting               | 4                 | 5                |
| - Early satiety          | 13                | 15               |
| - Belching               | 17                | 18               |
| Smoking                  |                   |                  |
| - Yes                    | 1                 | -                |
| - No                     | 22                | 23               |

No subjects with delayed gastric emptying were found at 1 and 2 hours. However, 3 subjects (6%) were found to have delayed gastric emptying at 4 hours with food retention more than 10%. Two subjects were patients with reflux esophagitis, while 1 patient without reflux esophagitis.

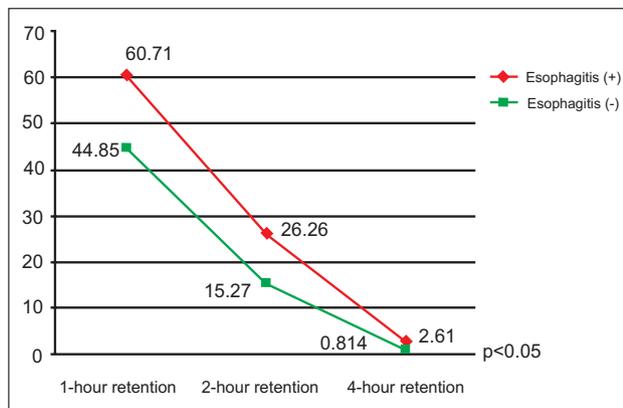
**Table 2** shows the mean value on retention of gastric emptying at 1, 2 and 4 hours following the specific diet meal. Normality test demonstrates normal data distribution on mean percentage of 1-hour and 2-hour retention; while the mean percentage of the

4-hour retention demonstrates normal data distribution following the log transformation. Data were analyzed by using unpaired t-test and we found  $p < 0.05$  for those retentions. (**Figure 1**)

**Table 2. Result of percentage mean difference test on gastric emptying retention at 1, 2, and 4 hours of all patients with esophagitis (+) and esophagitis (-)**

|                      | Patients (n=23) | Control (n=23) | p value |
|----------------------|-----------------|----------------|---------|
| 1-hour retention (%) | 60.71 ± 12.85   | 44.85 ± 14.15  | 0.000†  |
| 2-hour retention (%) | 26.26 ± 12.69   | 15.27 ± 10.82  | 0.003†  |
| 3-hour retention (%) | 2.61 ± 3.65     | 0.8143 ± 0.4   | 0.021†  |

†Unpaired t-test (normal data distribution)



**Figure 1.** Mean percentage on retention of gastric emptying

## DISCUSSION

Lind T indicated that in GERD patients without esophagitis, acid reflux has the same central role as in reflux esophagitis; however, there is a difference, i.e. in some GERD patients without esophagitis, the acid exposure to the esophagus is lesser than in patients with reflux esophagitis.<sup>11</sup> Martinez SD indicated that NERD patients significantly have lesser abnormal pH test compared to erosive esophagitis patients and Barrett's esophagus.<sup>12</sup> Patients with Barrett's esophagus also have the highest approximate incidence rate than those with erosive esophagitis and the incidence of erosive esophagitis acid reflux is higher than that of NERD.<sup>12</sup> Xu X et al found that individual with reflux esophagitis significantly has more frequent and longer duration of duodenogastroesophageal reflux episodes than NERD patients.<sup>13</sup>

Several studies showed inconsistent results regarding the role of gastric emptying on reflux esophagitis. Such different results may be caused by different standard of examination in each research center. There are also different gold standard methods

for examining gastric motility by using scintigraphy in each research center including diet, the technique and duration of imaging. Our study had utilized low-fat diet and four examinations at 0, 1, 2, and 4 hour(s), which are the most novel standard of scintigraphy in order to reach similar results. It is demonstrated that compared to scintigraphy with 15-minutes interval, the simplified scintigraphy method has 62% specificity and 93% of sensitivity.<sup>14</sup> Guo et al indicated that the most accurate measurement of gastric emptying is the 4-hour retention, which >10% retention is regarded as abnormal. The percentage of less than 4 hour retention is unlikely used for predicting the delayed gastric emptying since it may cause false-negative in patients who apparently have delayed gastric emptying.<sup>15</sup>

Our study showed 6% subjects with delayed gastric emptying, which was detected at 4 hours examination and >10% retention (2 subjects in esophagitis group and 1 subject in NERD group). By using the most novel standard method, Buckles et al found that 33% GERD patients had experienced delayed gastric emptying at 2-hour examination and 26% subjects had experienced delayed gastric emptying at 4 hours.<sup>16</sup> Such differences may occur since Buckles had used a reference of >40% at 2 hours and >6% at 4 hours. Buckles has also included 16% diabetes mellitus patients in their study. As we have known, diabetes mellitus has been proven as the risk factor of delayed gastric emptying. In contrast, our study has excluded risk factors that may disrupt gastric emptying, including diabetes mellitus. The limitation of our study includes no normal value for gastric emptying in Indonesian population which may be different from the overseas standard. In our study, we used the international standard and we found that there is only small percentage of GERD patients with delayed gastric emptying. Our other limitation is that we did not perform the pH-metry examination in NERD patients despite the fact that 37-60% patients with NERD has normal pH result, which may be categorized as the functional heartburn group.<sup>12</sup> Our study found gastric retention in patients with and without esophagitis by using low-fat diet. In both groups, we found significant differences at 1, 2 and 4 hours of examination. The scintigraphic method by using standard consensus - the gold standard of gastric emptying - used in our study has become the strength of our study. Little AG et al found that gastric emptying (using the oatmeal scintigraphy) was significantly delayed in patients with esophagitis compared to patients without esophagitis, who have similar result to normal individual.<sup>6</sup> Kujime S et al demonstrated that the gastric emptying was significantly lesser in patients with severe esophagitis

(grade C and D) by using USG compared to patients with mild esophagitis (grade A and B).<sup>17</sup> Johnson indicated that delayed gastric emptying (by using scintigraphy with egg-diet for 2 hour-examination) seemed not to be the main factor in the development of Barrett's esophagus.<sup>7</sup> Shay S, did not find any difference of gastric emptying between asymptomatic patients and patients with and without reflux esophagitis (by using scintigraphy with chicken-liver diet and 2.5 hours of imaging duration).<sup>3</sup> Cadiot et al found that gastric emptying in NERD patients was not significantly different compared to patients with reflux esophagitis (by using 450 kcal scintigraphy for 200 minutes).<sup>18</sup> Other studies using semisolid<sup>19</sup> and liquid<sup>20</sup> diet found that the proximal gastric emptying actually has great contribution on the number of reflux episode and not the total gastric emptying.

In our study, gastric emptying in GERD patients with reflux esophagitis is significantly more delayed compared to the group without reflux esophagitis; however, the correlation between gastric emptying disorder and reflux esophagitis has not been clearly explained. Further studies are necessary to find the direct correlation, which would consider other factors that have important role in pathophysiology of reflux esophagitis, including other risk factors for GERD such as *Helicobacter pylori*, physical activity and psychosomatic disorder.

## CONCLUSION

Our study demonstrates significantly delayed gastric emptying in patients with reflux esophagitis compared to patients without reflux esophagitis of GERD population by using standard method. About 6% of GERD patients have delayed gastric emptying. We suggest further studies on correlation between gastric emptying disorder and reflux esophagitis by controlling other risk factors that have role in pathophysiology of esophagitis and to determine the normal limit of gastric emptying in Indonesian population which may be different from the overseas standard.

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