

# The Role of Gastric Acidity and Lower Esophageal Sphincter Tone on Esophagitis among Dyspeptic Patients

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## ABSTRACT

**Background:** Esophagitis implies an organic damage of the esophagus due to several pathophysiologic factors, predominantly: (1) degree of gastric acid secretion (gastric pH), whereabouts are rapidly or slowly to be mucosal breaks onto esophagus were under the influenced by: (a) gastric pH  $\leq 4$  and (b) the contact of gastric acid into esophageal mucosal. (2) Lower esophageal sphincter (LES) as a important factor for antireflux mechanisms, which antireflux mechanism cannot serve as a barrier system whenever tone of LES comes down until  $\leq 10$  mmHg that causes feeble resting LES pressure. Esophageal injuries are recognized endoscopically by the presence of the Savary-Miller's classification (1985), but there are not definitely which ones principally to pathophysiologic factor.

**Methods:** This was a consecutive non-random sampling cross sectional study. Thirty subject from 127 patients with dyspepsia undergoing elective upper-endoscopic examination with collecting of the gastric juice and biopsies of lower esophageal mucosal, also esophageal manometric examination. Before that, clinical inclusive and exclusive criterias until laboratory examination were performed. Significant interval was 95%. Analyzing data with Fisher's Exact Test One-Tail to correlate between gastric pH and hypotonic LES into esophagitis.

**Results:** Esophagitis prevalence was 22.8%. Fisher's Exact Test One-Tail to correlate esophagitis with gastric pH  $\leq 4$  was significant ( $p=0.013798$ ), but with hypotonic LES (tones of LES  $\leq 10$  mmHg) was not ( $p=0.60269$ ). The combined roles of gastric pH and tones of LES into esophagitis are included: (1) Frequency of roles of pH  $\leq 4$  and hypotonic LES are 48.2%. (2) Frequency of role of pH  $\leq 4$  without hypotonic of LES are 33.3%. (3) Frequency of role of hypotonic LES without pH  $\leq 4$  are 11.1% and (4) Frequency of esophagitis without roles of pH  $\leq 4$  and hypotonic of LES are 7.4%.

**Conclusions:** The sum of gastric pH  $\leq 4$  and hypotonic of LES together are more than each separate factor. Onto statistically was significant between esophagitis and gastric pH, but there is no correlation with tones of LES. So, gastric pH plays a more important role than LES.

**Key words:** gastric pH, tones of LES, roles of pH and tones of LES, esophagitis

## INTRODUCTION

Dyspepsia is a syndrome that consists of clinical symptoms of the gastrointestinal tract and hepatopancreaticobiliary system, or a part of a systemic disease.<sup>1</sup> The problem of dyspepsia is encountered in 30 to 50% of all patients who visit everyday practice for the first time or as well as control patients. Lately, the significance of dyspepsia has risen due to the following reasons: (1) esophagitis is gaining attention from experts as an etiologic factor of dyspepsia, (2) it is costly for the patient, and (3) there is increased knowledge on the pathophysiology of esophagitis in dyspepsia patients.<sup>2</sup> The

most important pathophysiologic factors of esophagitis are (1) anti-reflux barrier performance by the lower esophageal sphincter tone (LESt) and (2) aggressive factors of gastric content, especially influenced by the gastric acidity level (pH).<sup>3</sup> The role of LESt is directly related to the physiology of the lower esophagus, which under normal conditions is a 1.5-4 cm length site of constriction in the diaphragmatic hiatus,<sup>4</sup> and functions as an anti-reflux barrier with a resting tone of 10-49 mmHg, at least 3-5 mmHg higher than the gastric tone.<sup>5</sup> If there is a dysfunction in the lower esophageal tone (LESt  $\leq 10$  mmHg) or in cases where the gradient pressure of the

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LES-gaster is lost, gastroesophageal reflux (GER) may occur, allowing contact of gastric contents with the esophagus, thus destroying the esophageal mucosa.<sup>6</sup> However, Cucchiara noted that lower pH levels of gastric fluid play a greater role in the development of esophagitis compared to the duration and frequency of contact between the esophagus and gastric contents due to GER.<sup>7</sup> The prevalence of esophagitis in Asia is still lower (0.8-22.2%) compared to that of Europe (59-79%).<sup>8-13</sup> Clinical symptoms of dyspepsia due to esophagitis are especially as follows: (1) pyrosis/heartburn, (2) ptyalism/hypersalivation, (3) ructus/burp, (4) regurgitation/emergence of gastric content in the mouth without force, and (5) dysphagia/difficulty swallowing.<sup>2,3,7,14</sup> Several other reports also demonstrate the presence of conditions such as recurrent pneumonia,<sup>7</sup> esophageal tuberculosis,<sup>15</sup> linked angina or non-cardiac discomfort,<sup>16-17</sup> as well as malignancy.

Up to now, there is still a lack of discussion on the data on esophagitis with destruction of esophageal mucosa and its corresponding pathophysiology in Indonesia. According to literature, histopathologic findings of esophagitis include thickening of the cells of the basal zone, elongation of the subepithelial papillae, and hyperplasia of the esophageal squamous epithelial cells.<sup>3,19</sup> However, many experts still argue over their various findings.<sup>20</sup> Tobey, et al found histopathologic findings of the early stages in the form of widening of the intercellular space between esophageal epithel, considered significant if the width is  $\geq 2.4$  mm under the electron microscope.<sup>13</sup> Ishii, et al found histopathologic finding in the form of increased layers of sebaceous glands under the squamous epithel.<sup>21</sup> During the last decade, there were still few reported cases of esophagitis,<sup>22</sup> but current development shows that esophagitis is now a widely discussed topic, especially due to the tendency for reflux-type dyspepsia to be considered as a separate diagnostic entity called gastroesophageal reflux disease (GERD), with chief complaints mainly from the upper abdomen or epigastric region.<sup>23</sup> Several issues still in question are as follows: what is the current prevalence rate for esophagitis in adults? What are the roles of pH and LEST as well as histopathologic findings of esophagitis in dyspepsia? These questions inspired the authors to conduct this study.

## STUDY DESIGN

Designed as a cross-sectional study with non-random consecutive samples, this study selected 30 patients who fulfilled the inclusion and exclusion criteria as study

subjects. The sample population consisted of dyspepsia patients who visited/came for control visits at the Gastroenterology Division of the Department of Internal Medicine of the Faculty of Medicine of the University of Indonesia/Cipto Mangunkusumo National Public Central of Referral Hospital from September 22<sup>nd</sup> to November 27<sup>th</sup>, 1997.

All study subjects underwent the following examinations:

- (1) Endoscopy of the upper gastrointestinal tract (UGIT) (FUJINON P-10 and PENTAX EG-3400 Japan) to evaluate esophageal, gastric, and duodenal mucosa.
- (2) Gastric fluid extraction to evaluate gastric acidity (pH) using a basal pH measurement instrument (Gastro Jet P-DVP-0003, MIC Swiss).
- (3) Biopsy of the 1/3 lower esophageal mucosa to evaluate the histopathology of mucosal tissue.
- (4) Examination of the lower esophageal sphincter tone using an esophageal manometer (Polygraph System RM-6000 NIHON KOHDEN Co, Ltd. Japan) at the Physiology Department of the Faculty of Medicine of the University of Indonesia.

Esophageal conditions were classified according to the Savary-Miller<sup>22</sup> or Los Angeles<sup>24</sup> Classification for Esophagitis (1985) (see table 1). Gastric acidity (pH) is an acidic condition due to the presence of free  $[H^+]$  in gastric fluid during fasting, indicated from pH measurement.<sup>25</sup> The initial limit of disturbance in the esophageal mucosa (lesion changes) were evaluated at a pH level of  $\leq 4$ .<sup>3,25</sup> LEST hypotension is a condition where the LES tone is  $\leq 10$  mmHg when examined using an esophageal manometer.<sup>26,27</sup> This manometer uses water-centimeter units of measurement (cm H<sub>2</sub>O). To adjust to mmHg units, each measurement value is divided by the constant value of 1.36.<sup>28</sup>

The collected data was processed and analyzed us-

Table 1 Savary-Miller Classification for Esophagitis (1985)

Gradation of lesion	Note
Grade 1	More than one erosive lesion, in the form of a red spot with or without a white membrane at the proximal of the Z line.
Grade 2	The presence of erosive lesions with clear white membranes. The lesion widens but does not encircle the lumen.
Grade 3	Erosive lesions encircle the lumen with an ulcer and necrotic tissue in its center
Grade 4	More than one deep ulcerative lesion, difficult to differentiate from malignant lesions. There is fibrosis resulting in deformity and findings corresponding to Barrett esophagitis.

ing 2 by 2 tables with a reliability interval of 95% using the Fisher's Exact One-Tail Test using SPSS (Statistical Package for Social Science).

## RESULTS

The prevalence of esophagitis in the population of dyspeptic patients (n=127) who underwent endoscopy during the study time frame was 22.8%. Out of the study subjects (n=30), 27 patients (90.0%) suffered from esophagitis of the 1/3 lower esophagus, while 3 patients (10.0%) were found with normal esophageal mucosa (see table 2 for further details).

**Table 2 Endoscopic Findings of The Lower Gastrointestinal Tract in Study Subjects**

No	Esophageal condition	Count (%)
1.	Grade I Esophagitis: Only esophagitis Other lower gastrointestinal tract abnormalities	7 (23.3) 19 (63.4)
2.	Grade II Esophagitis: Only esophagitis Other lower gastrointestinal tract abnormalities	1 (3.3) -
3.	No esophagitis: Only esophagitis Other lower gastrointestinal tract abnormalities	- 3 (10.0)
4.	Other lower gastrointestinal tract abnormalities (in the gaster): Mild gastritis Mild erosive gastritis Moderate erosive gastritis Moderate erosive gastritis with bile reflux	7 (23.) 11 (36.6) 2 (6.7) 2 (6.7)

Positive acidity ( $\text{pH} \leq 4$ ) was found in 22 subjects (73.3%), while negative acidity ( $\text{pH} > 4$ ) was found in 8 subjects (26.7%). The hypotonic group ( $\text{LESt} \leq 10$  mmHg) consisted of 17 subjects (56.7%), while normal tone ( $\text{LESt} > 10$  mmHg) was found in 13 subjects (43.3%). Histopathologic (PA) findings of esophagitis were found in 26 subjects (86.7%) while 4 subjects (13.3%) did not have histopathologic findings of esophagitis (see table 3 for the report on histopathologic findings).

The statistical tests demonstrate:

1. A significant correlation between esophagitis according to histopathologic findings and endoscopic findings of esophagitis ( $p=0.03941$ ).
2. A significant correlation between positive acid condition and incidence of esophagitis ( $p=0.01379$ ).
3. No significant correlation between  $\text{LESt}$  hypotony and the incidence of esophagitis ( $p=0.60296$ ).

**Table 3. Esophageal histopathologic (PA) findings on study subjects**

No.	Type of mucosal change / PA results	Frequency (%)
1.	Consistent with esophagitis:	
	♦ Pure PMN/MN (without further changes)	3 (10.0)
	♦ Thickening of the cells of the basal zone, others normal	3 (10.0)
	♦ Combination of elevated subepithelial papillae, thickening of the cells of the basal zone, hyperplasia of squamous epithelial cells, without signs of acute/chronic inflammation	2 (6.7)
2.	♦ PMN/MN with a combination of other changes	18 (60.0)
	Normal mucosa/no change	4 (13.3)

The relationship between the role of gastric acidity (pH) and lower esophageal sphincter tone (LESt) concurrently with findings of esophagitis was as follows:

- a. The frequency of the role of  $\text{pH} \leq 4$  and  $\text{LESt}$  hypotony concurrently was 48.2%.
- b. The frequency of the role of  $\text{pH} \leq 4$  without  $\text{LESt}$  hypotony was 33.3%
- c. The frequency of the role of hypotony  $\text{LESt}$  without  $\text{pH} \leq 4$  was 11.1%
- d. The frequency of esophagitis without the influence of either  $\text{pH} < 4$  or hypotony was 7.4%.

## DISCUSSION

### 1. Gastric acidity (pH) evaluation

Based on endoscopy, only Grade I and II esophagitis, also known as mild esophagitis, was found. Moderate (Grade III) and severe (Grade IV) esophagitis were not found.

The average gastric acidity level for all study subjects (n=30) was  $\text{pH}=3.1$ , which already has an effect on the esophageal mucosa. Subjects with esophagitis (27 subjects) had an average pH level of =2.04. One subject with Grade II esophagitis had a pH level of 1.8. When we correlated the incidence of a pH level of  $\leq 4$  with esophagitis, the results for the study subjects were as follows:

- (a) In the group with  $\text{pH} > 2.41 - \leq 4$ , there were 8 subjects (26.7%) positive for esophagitis and 1 subject (3.3%) without esophagitis.
- (b) In the group with a pH level of  $\leq 2.41$ , 14 subjects

(46.7%) were found positive for esophagitis. No subject was found without esophagitis. This proved that the higher the level of gastric acidity (lower pH level), the greater the risk for esophagitis. These findings demonstrated a strong statistical correlation ( $p=0.01379$ ).

Such evidence is in accordance with references, which state that gastric acidity level (pH) is determined by high levels of hydrochloride acid (HCl) due to hypersecretion by parietal cells (oxyntic cells) measured by a more acidic pH level in the gastric fluid.<sup>29</sup> It is also in accordance with the report by Cucchiara, which mentions that gastric acidity plays a greater role in adult dyspepsia patients than esophagitis.<sup>7</sup>

The method for pH level evaluation in this study is a modified part of the method for gastric fluid analysis by Daldiyono,<sup>12</sup> the extraluminal pH level evaluation procedure. For this particular study, the gastric fluid was not collected using a Levine or nasogastric tube, but instead using suction during endoscopy, while pH level measurement was conducted using a Gastro Jet pH indicator.

The reasoning for such an examination was as follows:

- Clinical examination of gastric juices – both during fasting or after stimulation – is not a routine examination, but instead a way of investigating an associated disease of the upper gastrointestinal tract.<sup>30</sup>
- In subjects who fasted during the night and is in resting/inactive condition, the gastric acid secreted is called basal acid production. A basal pH level of  $\leq 4$  is a sign of hypersecretion of basal acid, resulting in free HCl.<sup>3,30</sup>
- Hypersecretion of HCl in the gastric fluid would create lesion changes in the esophageal mucosa, especially on the lower 1/3<sup>rd</sup>, since this is a physiologic site of continuous contact with gastric fluid. Maximal proteolytic effect occurs if the gastric acidity level reaches  $\leq 2$ , due to activation of the pepsin enzyme as an aggressive factor, in addition to HCl.<sup>29,31</sup>
- Daldiyono defined a cut-off point of  $pH \leq 2.41$  to determine hyperacidity.<sup>12</sup>

Such method of basal pH evaluation has never been conducted by other researchers – since this method does not allow the determination of the correlation between the patient's complaint and the incidence of gastric fluid reflux into the esophagus – as supposed to the use of 24-hour pH monitoring in the esophagus (ambulatory esophageal pH monitoring).<sup>20</sup> The latter monitors the

esophageal pH level LES and is connected to an ambulatory pH recorder, which continuously records the pH level and is carried around by the patient for 24 hours.<sup>32,33</sup> The recorder could measure the amount of gastroesophageal acid reflux, which can then correlated with the timing of the patient's complaints.<sup>32,33</sup> The problem and objection with the use of this device is its high cost and unavailability, aside from difficulty in convincing and assuring subject cooperation. Due to such an impossible situation, the extraluminal pH examination – as used in this study – becomes a worthy choice.

## 2. Evaluation of lower esophageal sphincter tone (LESt)

As stated in literature, hypotension of the lower esophageal sphincter tone (LESt) could stimulate the incidence of gastroesophageal reflux (GER), if the LESt is  $\leq 10$  mmHg.<sup>2,3,5,6,27</sup> This reference cut-off point was used for this study. However, some experts mention that GER occurs only at a lower tone: a resting LESt of  $\leq 6$  mmHg.<sup>31</sup> These experts agree that the decrease in LESt is especially caused by: (1) weakness of the lower esophageal sphincter muscles, (2) inadequate LESt response towards gastric pressure under various conditions – such as after meals, obesity, acid secretion hyperacidity, gastric stasis, decubitus position, pregnancy, ascites, cough reflux, sneezing, stress – as well as (3) under conditions where the gradient between the lower esophageal sphincter and the gaster is lost.<sup>2,3,5,6,27,31</sup>

Examination of LESt resulted in hypotony in 17 subjects (56.7%) and normal tone in 13 subjects (43.3%) with a tone threshold level (TTL) – lowest LESt value – of 9.7 mmHg. In the hypotony group the lowest LESt level is 7.6 mmHg. This value is obviously lower than the normal cut-off point (LESt  $> 10$  mmHg). However, such findings do not show a statistical correlation with the incidence of esophagitis ( $p=0.60296$ ). Based on such results, we could conclude that in adult dyspepsia patients, the incidence of mild esophagitis (Grades I-II) is not influenced by the presence or absence of LESt disturbance ( $p > 0.05$ ). This conclusion has not been determined for moderate/severe esophagitis (Grades III-IV).

## 3. The prevalence of esophagitis

In this study, the prevalence rate for esophagitis was 22.8%, a rate higher than previous data from Asia. Rani (Jakarta, 1990) reported a prevalence rate of 22.2%, and Djajaprana (Surabaya, 1992) reported a prevalence rate of 11.5%.<sup>8,9</sup> Goh (1996) reported a prevalence rate of 0.8% in Malaysia and 4.5% in Singapore.<sup>10</sup> Daldiyono (Jakarta, 1995) reported a prevalence rate of

8.0%, while Nizam (Jakarta, 1997) reported a prevalence rate of 9.0%.<sup>12,14</sup> Such findings are still lower than in Europe, which has a 59.0% prevalence of esophagitis, as reported by Tobey et al.<sup>13</sup> According to Goh, the low prevalence rate for esophagitis in Asia may be due to: (1) underdiagnosis, (2) few cases of esophagitis being reported, (3) lack of attention towards diagnostic devices for esophagitis, as well as (4) gastric disorders that cause atrophic gastritis and a reduction of acid production.<sup>10</sup>

#### 4. Histopathologic (PA) findings of the esophageal mucosa

The histopathologic findings turned out to reflect esophagitis dominated by acute (PMN) and chronic (MN) inflammatory cells both with/without other abnormalities (10.0%) or in combination with/together with other forms of lesion changes (60.0%).

#### 5. The influence of gastric acidity level (pH) and lower esophageal sphincter tone (LESt) towards esophagitis

The degree of gastric acidity (pH) as the most important gastric content factor and the lower esophageal sphincter tone (LESt) as the most important esophageal anti-reflux performance factor are the two chief etiologic factors in the pathophysiology of esophagitis.<sup>34</sup> However, unlike in the gaster and duodenum where the role of pH has been greatly understood as the chief aggressive factor that destroys the mucosa – known as peptic ulcer – there is yet a clear theory on the role of pH in the destruction of the esophageal mucosa.<sup>3,12,30,35,36</sup> Many experts consider transient lower esophageal sphincter relaxation (tLESR) as the basis of the role of gastric acid in the development of esophagitis.<sup>35,37</sup> They write that in normal subjects, 74-80% of gastric acid reflux to the esophagus occurs simultaneously with transient relaxation of the LESt (tLESR), which is considered a physiological condition. Only ± 20% of cases occur due to pathologic disturbance of the LESt. Recurrent and prolonged contact between gastric acid and the esophageal mucosa due to tLESR would not have any effect if the pH level is over 4 or the esophageal clearance performance is good. Several researchers have suspected this. Hunt even quoted a study by Hirschowitz (1991) to conclude that the role of pH is not influenced by basal acid, fasting, or maximal secretion of gastric acid and pepsin, but is instead affected by a pH level of ≤ 4. This was proven by Hunt by quoting the study by Bell et al (1992) where if the pH of gastric fluids can be continuously maintained at a level above 4, there would be significant improvements in esophagitis.<sup>37</sup>

A decrease in LESt to the point of hypotony, which stimulates gastric acid reflux to the esophagus, cannot be the sole cause of esophagitis. Such condition must also be influenced by the presence or absence of disturbance in the acid clearance performance in the esophagus, and whether or not there is a delay in gastric emptying.<sup>27</sup>

However, in this study, if the influence of pH and LESt are simultaneously observed, LESt also contributes in the incidence of esophagitis, even though pH plays a more dominant role.

#### CONCLUSION

We conducted a 9-week study from September 22<sup>nd</sup> to November 27<sup>th</sup>, 1997 to evaluate the role of the degree of gastric acidity (pH) and lower esophageal sphincter tone (LESt) towards esophagitis in dyspepsia patients at the Department of Internal Medicine of dr. Cipto Mangunkusumo Public National Referral Center Hospital/Faculty of Medicine of the University of Indonesia.

The results can be summarized as follows:

1. The influence of the level of gastric acidity (pH ≤ 4) together with LESt hypotony (LESt ≤ 10 mmHg) on esophagitis in dyspepsia patients is greater than the influence of the two factors separately.
2. The role of pH towards the incidence of esophagitis in dyspepsia patients was statistically significant (p=0.01379), while the role of LESt was not statistically significant (p=0.60296).
3. The role of gastric acidity (pH) in the development of esophagitis in dyspepsia is more dominant than that of the lower esophageal sphincter tone (LESt).

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