Impact of obesity on severity of esophageal reflux in gastroesophageal reflux disease measured by pH-Meter impedance

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Abstract. The prevalence of gastroesophageal reflux disease (GERD) is increasing worldwide, and it is correlated with obesity. To ascertain if there is an association between obesity and severity of esophageal reflux, GERD must be diagnosed with greater precision and accuracy. Further, no studies have specifically examined the relationship between obesity and severity of esophageal reflux in patients with GERD. This study aimed to assess the impact of obesity on severity of esophageal reflux in GERD patients. This cross-sectional study was conducted from August to October 2017, and we enrolled GERD patients from Jakarta. Using consecutive sampling, 98 GERD patients were recruited and divided into two groups: (1) patients with body mass index (BMI) $\geq 25$ kg/m$^2$ (obese, n = 49) and (2) patients with BMI 18.5–23.5 kg/m$^2$ (normal, n = 49). Upper gastrointestinal endoscopy was performed to assess hiatal hernia and erosive esophagitis. All patients underwent multichannel intraluminal impedance pH-meter (MII-pH) monitoring for quantification of the DeMeester score and acid exposure time. The results were analyzed using bivariate analysis. The DeMeester scores were significantly different between the obese and normal groups (166.65; $p < 0.05$). Bivariate analysis showed a significant difference between the two groups in terms of acid exposure time ($p < 0.05$; Relative Risk (RR) = 6.12 (3.25–11.54); CI 95%) and incidences of hiatal hernia ($p < 0.05$; RR = 7; 95% CI, 3.28–14.94) and erosive esophagitis ($p < 0.05$; RR = 4.5; 95% CI, 2.57–7.87). Obese patients had a higher DeMeester score than the normal BMI patients, along with greater risk of prolonged acid exposure time, hiatal hernia, and erosive esophagitis.

1. Introduction

Gastroesophageal reflux disease (GERD), a prevalent communal health problem, is defined as a condition wherein the contents of the stomach are refluxed into the esophagus, resulting in symptoms and/or complications [1]. Although rarely the cause of death, GERD is associated with increased
morbidity and negatively affects the quality of life [2]. Epidemiological studies show that the prevalence of GERD in Western countries is approximately 20%, with a 4% annual increase in prevalence [1,3]. Based on the studies in several Asian countries, its prevalence in Asia appears to be lower than that in the United States or Europe, but the prevalence has nonetheless increased in the past few decades [4-6]. In a hospital-based study, Syam et al. (2003) reported an increase in the prevalence of esophagitis from 5.7% in 1997 to 25.18% in 2002 [7]. Lelosutan et al. (2001) reported that GERD was diagnosed in 22.8% of 127 patients, based on upper GI endoscopy [8]. Recent data from 2016 also showed the prevalence of GERD among medical doctors to be 27.4% in Indonesian doctors [9].

The National Health and Nutrition Examination Survey (USA) reported that among 20–74-year-old adults, the prevalence of obesity increased from 15.0% in 1976–1980 to 32.9% in 2003–2004. It is estimated that by 2020, 77.6% of men will be overweight, and 40.2% will be obese; in addition, 71.1% of women will be overweight, and 43.3% will be obese [9]. Although the association between GERD and obesity remains unclear, they are believed to be positively related [10]. Syam et al. reported that obese patients have a higher risk of GERD, with the causative factors being higher dietary intake, decreased physical activity, and genetic predisposition. However, to the best of our knowledge, no studies have specifically examined the relationship between obesity and severity of esophageal reflux in GERD patients [11].

Currently, the GERD questionnaire (GerdQ) is used as a screening tool for GERD, with a specificity and specificity of 64.6% and 71.4%, respectively [12]. In Indonesia, GERD is diagnosed based on symptoms assessed using the GerdQ and upper gastrointestinal endoscopy. Unfortunately, because approximately 70% of GERD patients do not show esophageal damage during upper gastrointestinal endoscopy, the diagnosis of GERD requires methods that provide greater precision, one such method being the multichannel intraluminal impedance pH-meter (MII-pH) test, an esophageal manometric method that detects the incidence of reflux for 24 h and can be used to measure the strength of esophageal acidity; the latter represents severity of esophageal reflux. MII-pH results are expressed as the DeMeester or pH composite score [12,13].

To the best of our knowledge, no studies in Indonesia have correlated BMI and severity of esophageal reflux events measured by MII-pH in GERD patients. Therefore, using MII-pH, we aimed to assess the association between increased BMI and severity of esophageal reflux in GERD patients.

2. Methods

2.1. Study design

A cross-sectional study involving 98 GERD patients was conducted between January and October 2017 at the Department of Internal Medicine, Cipto Mangunkusumo Hospital (Jakarta, Indonesia). The study participants were recruited by consecutive sampling from inpatient and outpatient departments.

The inclusion criteria included the following:
1. Adults, aged 18–60 years;
2. normal BMI (18.5–23.5 kg/m²) or obese BMI (≥25 kg/m²); the BMI cut-off was based on the criteria for the Asia-Pacific population;
3. fulfill GERD criteria assessed using GerdQ;
4. have undergone upper gastrointestinal tract endoscopy; and
5. willing to participate by providing written informed consent.

The exclusion criteria included the following:
1. Severe blood clotting disorders, severe heart disease, persistent asthma, decompensated liver cirrhosis, and chronic kidney disease;
2. prescribed benzodiazepine drugs, tricyclic antidepressants, dihydropyridine calcium channel blockers, adrenergic alpha inhibitors, beta blockers, or nonsteroidal anti-inflammatory drugs; and
3. diagnosed with psychological disorders.
Patients diagnosed with Barrett’s esophagus, peptic ulcers, or severe NSAID gastropathy; those suffering from hematemesis, melena, gastric cancer, esophageal cancer, pharyngeal obstruction, or upper esophagus on endoscopic examination; those in whom MII-pH meter could not be attached; uncooperative patients; and those unable to understand or follow instructions were also excluded from this study. From 110 subjects who met the inclusion criteria, we excluded 12 subjects due to the above reasons.

All 98 eligible subjects (59 female and 39 male) were recruited, provided anamnesis, and underwent a physical examination that included measurement of their weight and height. The GerdQ was administered to all subjects, and those with a score of \( \geq 8 \) points were diagnosed as having GERD. All patients with diagnosed GERD underwent upper gastrointestinal endoscopy, during which hiatal hernia and erosive esophagitis were also evaluated. The patients with diagnosed GERD also underwent MII-pH examination for 24 h for the quantification of the DeMeester score.

2.2. MII-pH
MII-pH test was performed after an 8-h fast and after being PPI-free for seven days. The MII-pH system comprises a portable data storage unit and a catheter with one pH electrode and eight impedance electrodes at positions 3, 5, 7, 9, 15, and 17 cm from the tip. The electrode was placed 5 cm above the LES boundary, as determined by manometry. The patients were asked to press an event marker button on the data storage unit when they experienced symptoms and subsequently record information on the timing of symptoms, start and finish time, and changes in body position (lying or upright) in a diary. They were also required to at least eat three meals a day and were asked to maintain normal activity. Data were recorded on a 256 MB compact flash card, downloaded onto a computer for analysis using semi-automated software, and manually verified.

2.3. Data analysis
The data were analyzed using the STATA program (StataCorp). Categorical variables are presented as frequency and percentage, whereas numerical variables are presented as mean (with standard deviation) for normally distributed data. The median (with minimum and maximum range) is used for non-normally distributed data. Dichotomous categorical variables were analyzed using the chi-square test. Normality was evaluated using …, and non-normal data was subjected to bivariate analysis using the Mann–Whitney U-test to compare the DeMeester score between the two groups. Statistical significance was set at \( p < 0.05 \), with 95% confidential interval (CI). The study protocol was approved by Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia-Cipto Mangunkusumo Hospital (No. 719/UN2.F1/ETIK/2017).

3. Results
3.1. Study participant characteristics
98 subjects were enrolled for this study. The mean age was 41.38 ± 11.34 years and median BMI was 24.1 kg/m\(^2\) (range, 18.67–37.89). Based on BMI, 49 subjects (50%) were categorized as normal BMI and the other 49 subjects (50%) were categorized as obese. Upper GI endoscopy revealed that 48.9% (\( n = 48 \)) subjects had hiatal hernia and 53.1% (\( n = 52 \)) had erosive esophagitis (Table 1). Female patients showed a similar prevalence of ERD and NERD (47.5% and 52.5% respectively); on the other hand, ERD (61.6%) was more prevalent in males than NERD (38.4%). The prevalence of ERD (89.7%) was higher than that of NERD (10.3%) in obese patients.

The DeMeester score was significantly higher in the obese group (175.0 ± 128.05) compared with that in the normal group (8.35 ± 13.01); the mean difference in terms of the DeMeester score between the two groups was 166.65 (\( p < 0.05; 95\% \text{ CI}, 129.7–203.6; \text{Table 2} \)).
Table 1. Demographic characteristics of the study participants

| Characteristic          | n (%)      |
|-------------------------|------------|
| Sex                     |            |
| Male                    | 39 (39.8%) |
| Female                  | 59 (60.2%) |
| Body mass index         |            |
| Obese                   | 49 (50%)   |
| Normal                  | 49 (50%)   |
| Hiatal hernia           |            |
| Yes                     | 48 (48.9%) |
| No                      | 50 (51.1%) |
| Erosive esophagitis     |            |
| Yes (ERD)               | 52 (53.1%) |
| No (NERD)               | 46 (46.9%) |
| Refluxate discharged    |            |
| Liquid                  | 39 (39.8%) |
| Gas                     | 4 (4.1%)   |
| Mixture                 | 55 (56.1%) |
| Refluxate type          |            |
| Acid                    | 84 (85.7%) |
| Non-acid                | 14 (14.3%) |
| Acid exposure time      |            |
| High                    | 36 (48%)   |
| Normal                  | 39 (52%)   |

Table 2. Mean difference in composite pH score between the obese and normal BMI groups

|          | Mean (SD)     | Mean Difference (95% CI) |
|----------|---------------|--------------------------|
| Obese    | 175.0 ± 128.05| 166.65 (129.7–203.6)     |
| Normal BMI| 8.35 ± 13.01  |                           |

Further, our study revealed a significant difference in terms of acid exposure time between the two groups, and obese GERD patients had a 6.12-fold higher risk of having prolonged acid exposure ($p < 0.05$; CI 95%, 3.25–11.54); Table 3.

Table 3. Difference in acid exposure time between the obese and normal BMI groups

| Acid Exposure Time | Prolonged n (%) | Normal n (%) | RR (95% CI)       |
|--------------------|-----------------|--------------|-------------------|
| Obese              | 49 (100%)       | 0 (0%)       | 6.12 (3.25–11.54) |
| Normal             | 8 (16.3%)      | 41 (83.7%)   |                   |

Moreover, we also found that 85.7% of the obese patients had hiatal hernia, but the normal patients
had a hiatal hernia incidence rate of only 12.3% (Table 4), indicating a 7-fold greater risk of hiatal hernia in obese patients ($p < 0.05$; RR 7.0; 95% CI, 3.28–14.94).

**Table 4. Association between bmi and hiatal hernia**

| Hiatal Hernia |    |    | RR (95% CI) |
|---------------|----|----|-------------|
| Yes n(%)      | 42 (85.7%) | 7 (14.3%) | 7.0 (3.28–14.94) |
| No n(%)       | 6 (12.2%)  | 43 (87.8%) |              |

Lastly, 45 obese patients (91.8%) showed erosive esophagitis on upper gastrointestinal endoscopy, whereas only 10 subjects (20.4%) in the normal group were found to have erosive esophagitis (Table 5). Based on this result, the obese patients would have a 4.5-time higher risk of having erosive esophagitis ($p < 0.05$; RR 4.5; 95% CI, 2.57–7.87).

**Table 5. Association between bmi and erosive esophagitis**

| Erosive Esophagitis |    |    | RR (95% CI) |
|---------------------|----|----|-------------|
| Yes n (%)           | 45 (91.8%) | 4 (8.2%) | 4.5 (2.57–7.87) |
| No n (%)            | 10 (20.4%) | 39 (75.6%) |              |

4. **Discussion**

4.1. **Characteristics of study subjects**

In our study, the age of GERD patients was predominantly within the productive age range (mean, 41 years); this is similar to epidemiological studies in Korea reporting an average age of 43.9 ± 13.4 years. GERD during the productive age could result in decreased productivity and affect quality of life [14]. In our study, the female: male ratio was approximately 2:1; however, the association between sex and GERD symptoms remains uncertain and inconsistent. An epidemiologic study in Brazil found that women more often complained of heartburn symptoms; in contrast, a study in Korea found that GERD symptoms did not significantly differ between men and women (2.5% vs 2.6%) [15].

Upper gastrointestinal endoscopy is useful for the diagnosis of GERD in the presence of erosive esophagitis, and we found evidence of erosive esophagitis (ERD) in 56.1% of the subjects, suggesting that routine endoscopies may be necessary even when no alarm symptoms exist. Currently, NERD is suspected to be present in most GERD patients as epidemiological studies have reported that NERD prevalence in GERD populations is approximately 70% [16]. Meanwhile, a study in Germany found that ERD was more prevalent (56.5%) than NERD in 92 patients [17]. Similarly, we also reveal that 56.1% of the subjects had NERD.

4.2. **Differences in the DeMeester score between the obese and normal-weight patients**

Monitoring of 24-h pH and pH-impedance in the obese patients showed that there was an increase in reflux episodes, particularly in the postprandial period, with increasing BMI [18]. In the MII-pH test, reflux events were reported as the type of reflux, distribution, and discharge. MII checks can determine the following parameters: reflux type (fluid, air, or mixture) and refluxate clearance time. pH monitoring provides information about the nature of reflux (acid vs. non-acid) and acid clearance time [17]. The MII-pH test is an important advancement in GERD diagnosis and recording of reflux episodes as the reflux episodes are categorized as acid reflux if accompanied by a decrease in pH below 4.0 and non-acid reflux if the pH is above 4.0. Low esophageal acidity indicates severity of reflux and is expressed as the DeMeester or pH composite score. A score of >14.72 indicates significant esophageal reflux. This score is based on six parameters that assess global measures after exposure to esophageal acid, i.e., percent of acid exposure time (AET) at pH < 4, time percentage at
pH < 4 exposure in upright position, time percentage at pH < 4 while lying, the number of reflux episodes, the number of reflux episodes of ≥5 min, and the duration of the longest reflux episode [13].

Our results revealed significantly higher DeMeester score in obese GERD patients compared with that in normal BMI patients. Azayi et al (2009) reported similar results, wherein the effect of BMI on exposure to esophageal acid seems to be linear, with no specific BMI cut-off being associated with a difference in total time percentage at pH < 4 exposure [19].

4.3. Differences of the DeMeester scores in the obese and normal BMI patients
LES function is directly dependent on intrinsic pressure of LES, total length of LES, and the frequency and duration of temporary relaxation of the LES. Indirectly, LES function is influenced by the pressure gradient between intragastric and intra-esophageal pressures. In obese individuals, there is an increase in intra-abdominal pressure due to the accumulation of adipose tissue around the stomach. This stretches the LES, results in esophageal reflux, and longer exposure of the esophageal mucosa to stomach contents [11].

The results presented here prove that obesity plays an important role in GERD. AET in the obese GERD patients was six times longer than that in the normal BMI patients. Ayazi et al. (2009) stated that for each BMI unit increase, the increasing percentage in postprandial time was 0.48 compared with 0.35 for the total time percentage [20]. Mechanical risk factors, humoral factors, and motility disorders are believed to cause prolonged AET. Further, obesity itself causes an increase in intra-abdominal pressure and hiatal hernia incidence, along with greater sensitivity in transient lower esophageal sphincter relaxations (TLESR) induced by obesity-associated distension. Additionally, decreased pressure of the LES also leads to delayed gastric emptying and esophageal clearance. Jung et al (2009) retrospectively reviewed data from 24-h pH monitoring and reported a significant positive association between BMI and acid exposure of the esophagus [19]. In a cross-sectional study of 206 patients, El-Serag, et al. (2007) demonstrated that obesity is associated with a significant increase in the number and duration (>5 min) of acid reflux episodes, pH time <4, and the DeMeester scores [3]. Similar findings have also been reported by Crowell et al. (2009) after 48-h wireless pH monitoring [19]. Importantly, the results described herein are consistent with those from previous studies. Overall, these data support an important role of obesity in determining the severity of esophageal reflux.

4.4. Hiatal hernia and erosive esophagitis in the obese GERD patients
Hiatal hernia, a medical condition, is characterized by the protrusion of the upper part of the stomach into the chest via the diaphragm due to tearing or weakening of the diaphragm. Hiatal hernia prevents the esophageal sphincter from completely closing, causing stomach acid to enter the esophagus and leading to heartburn [21]. There are at least three distinctive features of hiatal hernia: axial length during distension, length of action at rest, and competence of the hiatal diaphragm. It is suspected that the phrenoesophageal membrane stretches during each peristaltic contraction and each episode of increased intra-abdominal pressure, thereby reducing its elasticity over a period of years.

Our data not only found an association between obesity and the incidence of hiatal hernia in GERD patients but also a 7-fold higher risk of hiatal hernia in the obese patients with GERD compared with the normal-weight patients with GERD. Vela and Crowell et al. (2009) also reported that obesity increases the risk of hiatal hernia in 157 patients with symptomatic gastroesophageal reflux [19,21]. Further, hiatal hernia can lead to GERD by lowering LES pressure, disrupting acid clearance in the esophagus, and increasing the sensitivity of distal induced TLESR.

The gastroesophageal junction protects against reflux under static and dynamic conditions. Under static conditions, the smooth muscle of LES has adequate tonus to protect against reflux and in this situation, reflux can only occur by TLESR. In contrast, under dynamic pressure conditions, including swallowing or increased intra-abdominal pressure, the ability of the gastroesophageal junction to prevent reflux depends on the LES and diaphragmatic sphincter. Upon a sudden increase in intra-abdominal pressure, the crus diaphragm usually serves as a second sphincter, but this mechanism is substantially impaired in individuals with a hiatus gap. During swallowing, the crus diaphragm
serves as a one-way valve, allowing flow only during expiration when pressure gradients flow into the abdomen. The presence of hiatal hernia interferes with the esophageal emptying, thus extending the acid cleansing time, particularly in the supine position [22].

Our results also show an association between obesity and erosive esophagitis. The GERD patients with obesity were at 4.5-time greater risk of erosive esophagitis compared with the normal BMI patients. Similar results have been demonstrated in a study by Bortoli et al. (2014) who showed that obese GERD patients had a two-fold higher risk of erosive esophagitis compared with GERD patients with normal BMI, along with larger waist circumference and more severe GERD symptoms. In addition, the prevalence of erosive esophagitis was higher in obese patients compared with that in other patients undergoing upper endoscopy for GERD symptoms ($p < 0.001$) [23].

Apart from increased intra-abdominal pressure, obesity also plays a role in GERD through a humoral factor. Visceral/abdominal fat is more metabolically active, has more inflammatory cells, and is more resistant to insulin, thus making visceral fat more harmful [13]. Moreover, visceral fat increases plasma levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which are inflammatory mediators that can induce an inflammatory reaction, resulting in esophagitis [24].

A meta-analysis by Hampel et al. (2005) documents an association between BMI $\geq 25$ kg/m$^2$ and erosive esophagitis [25], and a similar result has been reported by Kim et al. (2008) in 27,319 subjects [14]. Nocon et al. (2007) indicated that the higher BMI in GERD patients contribute to severity and frequency of symptoms of reflux (OR, 2.11) and esophagitis (OR, 2.51) [26]. Additionally, our results are similar to those from the study by Lee et al. (2012), which revealed that male obese GERD patients presented with greater severity of endoscopic and clinical findings than non-obese patients [27].

4.5. Strengths and limitations

To the best of our knowledge, no previous studies in the Indonesian population have evaluated the severity of esophageal reflux in obese GERD patients using the MII-pH test. This may be due to the invasive nature of the MII-pH assessment and the strict adherence to instructions required from the study subjects.

A limitation of this study is the absence of analysis of other factors that may affect GERD such as psychological factors and diet; however, some studies have reported no significant relationship between diet and GERD symptoms. Comorbid conditions of the subjects could not be analyzed because we collected data only via interviews and not v reviewing medical record review.

5. Conclusion

In conclusion, obesity is associated with a higher DeMeester score, longer AET, higher risk of hiatal hernia, and erosive esophagitis compared with those in normal BMI patients, suggesting that losing weight and maintaining normal BMI are important for mitigating GERD in obese patients. This may be accomplished by modifying diet and lifestyle and improving physical activity levels. It is also suggested that upper gastrointestinal endoscopy can be considered as an early diagnostic tool in obese patients, given the observed high prevalence of erosive esophagitis in this population.

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