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IMPACT OF OBESITY ON SEVERITY OF ESOPHAGEAL REFLUX IN GASTROESOPHAGEAL REFLUX DISEASE MEASURED BY PH- METER IMPEDANCE

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I. BACKGROUND

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 sensitivity 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].

II. OBJECTIVE AND HYPOTHESIS

A. General Objective

To ascertain if there is an association between obesity and severity of esophageal reflux, GERD must be diagnosed with greater precision and accuracy.

B. Specific Objective

1. To measure the acid exposure time obese patients and normal BMI patients.
2. To record the number of observed hiatal hernia in obese patients and normal BMI patients.
3. To record the number of erosive esophagitis in obese patients and normal BMI patients.

C. Hypothesis

1. Obese patients had higher DeMeester score and acid exposure time compared to normal BMI patient.
2. Obese patient had a higher number of observed hiatal hernia.
3. Obese patient had a higher number of observed erosive esophagitis.

III. METHODS

A. Study Design

This study is a cross sectional study.

B. Time and Place

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).

C. Study Population

1. **Targeted population:** Adult patients with GERD

2. **Sample:** Adult patients with GERD in in Cipto Mangunkusumo Hospital, Jakarta.

3. Inclusion Criteria

- Adults, aged 18–60 years;
- Normal BMI (18.5–23.5 kg/m²) or obese BMI (\geq 25 kg/m²); the BMI cut-off was based on the criteria for the Asia-Pacific population
- Fulfill GERD criteria assessed using GerdQ
- Gave undergone upper gastrointestinal tract endoscopy
- Willing to participate by providing written informed consent.

4. Exclusion Criteria

- Severe blood clotting disorders, severe heart disease, persistent asthma, decompensated liver cirrhosis, and chronic kidney disease.
- Prescribed benzodiazepine drugs, tricyclic antidepressants, dihydropyridine calcium channel blockers, adrenergic alpha inhibitors, beta blockers, or nonsteroidal anti-inflammatory drugs.
- Diagnosed with psychological disorders.

5. **Drop Out Criteria:** Patients who have signed the informed consent but wish to stop participating before completed the study.

D. Study Procedure

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 ≥ 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.

MMI-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.

E. Ethics

The study protocol was approved by Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia-Cipto Mangunkusumo Hospital (No. 719/UN2.F1/ETIK/2017).

IV. STUDY ANALYTICAL PLAN

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)..

REFERENCES

1. Fock K M, Talley N J, Fass R, Goh K L, Katelaris P, and Hunt R. 2008 Asia-Pacific consensus on the management of gastroesophageal reflux disease: update. *J Gastroenterol Hepatol.* 23 8-22
2. Shaw M J, Talley N J, Beebe T J, Rockwood T, Carlsson R, and Adlis S 2001 Initial validation of diagnostic questionnaire for gastroesophageal reflux disease. *Am J Gastroenterol.* 96 52-57
3. El-Serag H B 2007 Time trends of gastroesophageal reflux disease: a systematic review. *Clin Gastroenterol Hepatol.* 5 17-26
4. Goh K L, Wong H T, Lim C H, Rosaida M S 2009 Time trends in peptic ulcer, erosive reflux oesophagitis, gastric and oesophageal cancers in a multiracial Asian population. *Aliment Pharmacol Ther.* 29 774-780
5. Ho K Y, Chan Y H, Kang J Y 2005 Increasing trend of reflux esophagitis and decreasing trend of *Helicobacter pylori* infection in patients from a multi-ethnic Asian country. *Am J Gastroenterol.* 100 1923-1928
6. Sollano J D, Wong S N, Andal-Gamutan T 2005 Erosive esophagitis in the Philippines: a comparison between two time periods. *J Gastroenterol Hepatol.* 22 1650-1655
7. Syam A F, Abdullah M, Rani A A 2003 Prevalence of reflux esophagitis, Barrett's esophagus and esophageal cancer in Indonesian people evaluation by endoscopy. *Canc Res Treat.* 5 83
8. Lelosutan S A, Manan C, Nur B M 2001 The role of gastric acidity and lower esophageal sphincter tone on esophagitis in patients with dyspepsia. *J Gastroenterol Hepatol Endoscopy.* 2 6- 11
9. Syam A F, Hapsari C P, and Makmun D 2016 The prevalence and risk factors of GERD among Indonesian medical doctors. *Makara J Health Res.* 20 35-40
10. Ruhm C J 2007 Current and future prevalence of obesity and severe obesity in the United States. National Bureau of Economic Research (NBER) Working Paper No. W13181
11. Kang J H E, Kang J Y 2015 Lifestyle measures in the management of gastro oesophageal reflux disease: clinical and pathophysiological considerations. *Ther Adv Chronic Dis.* 6 51-64
12. The Indonesian Society of Gastroenterology 2014 National consensus on the management of gastroesophageal reflux disease in Indonesia. *Acta Med Indones.* 46 263-271
13. Kim G H 2010 How to interpret ambulatory 24 hr esophageal pH monitoring. *J Neurogastroenterol Motil* 16 207-210
14. Kim N, Lee S W, Cho S I, Park C G, and Yang C H 2008 The prevalence of and risk factors for erosive oesophagitis and non-erosive reflux disease: a nationwide multicentre

- prospective study in Korea. *Aliment Pharmacol. Ther.* 27 171-173
15. Chung S J, Kim D, Park M J, Kim Y S, Kim J S 2008 Metabolic syndrome and visceral obesity as risk factors for reflux oesophagitis: a cross-sectional case-control study of 7078 Koreans undergoing health check-ups. *Gut.* 57 1360-1365
 16. Zheng Z, Nordenstedt H, Pedersen N L, Lagergren J, Ye W 2007 Lifestyle factors and risk for symptomatic gastroesophageal reflux in monozygotic twins. *Gastroenterol.* 132 87-95
 17. Gutschow C A, Bludau M, Vallbo D 2008 NERD, GERD, and Barrett's Esophagus: Role of Acid and Non-acid Reflux Revisited with Combined pH-Impedance Monitoring. *Dig Dis Sci.* 53 3076- 3081
 18. Fujiwara Y, Arakawa T 2009 Epidemiology and clinical characteristics of GERD in the Japanese population. *J Gastroenterol Hepatol.* 44 518-534
 19. Crowell M D, Bradley A, and Hansel S 2009 Obesity is associated with increased 48-h esophageal acid exposure in patients with symptomatic gastroesophageal reflux. *Am J Gastroenterol* 104 553-559
 20. Ayazi S, Hagen J A, and Chan L S 2009 Obesity and gastroesophageal reflux: quantifying the association between body mass index, esophageal acid exposure, and lower esophageal sphincter status in a large series of patients with reflux symptoms. *J Gastrointest Surg.* 13 1440-1447
 21. Vela M F 2009 Non-acid reflux: detection by multichannel intraluminal impedance and pH, clinical significance and management. *Am J Gastroenterol.* 104 277-280
 22. El-Serag H B, Graham D Y, Satia J A. 2005 Esophagitis is a independent risk factor for GERD symptoms and erosive esophagitis. *Am J Gastroenterol.* 100 1243-1250
 23. Bortoli N, Salvetti G, Bertani L 2014 Obesity is risk factor for erosive gastroesophageal reflux disease: prospective case-control study. *J Gastroint Dig Syst.* 4 3
 24. Locke G R 3rd, Talley N J, and Fett S L 1999 Risk factors associated with symptoms of gastroesophageal reflux. *Am J Med.* 106 642-649
 25. Hampel H, Abraham N S, El-Serag H B. 2005 Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. *Ann Intern Med.* 143 199-211
 26. Nocon M, Labenz J, Jaspersen D, Meyer-Sabellek W, and Stolte M 2007 Association of body mass index with heartburn, regurgitation and esophagitis: results of the progression of gastroesophageal reflux disease study. *J Gastroenterol Hepatol.* 22 1728-1731
 27. Lee S W, Lien H C, Chang C S, Peng Y C, and Ko C W 2012 Impact of body mass index and gender on quality of life in patients with gastroesophageal reflux disease. *World J Gastroenterol.* 18 5090-5095