Gastroesophageal Reflux Disease in Obese Patients

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ABSTRACT

Incidence of gastroesophageal reflux disease (GERD) has been significantly increased, and nearly 25% of the population has experienced GERD. It appears to be correlated to an increasing number of obesity in the population (BMI $\geq$ 30 kg/m^2).

Mechanism of the GERD is affected by multifactor. Increased intra-abdominal pressure is considered as one of risk factors for GERD. The development of GERD is virtually associated with a down turning of lower esophageal sphincter tonus, increased transient lower esophagus sphincter relaxation (TLESR), and decreased capacity of esophageal clearance.

Management of GERD in obesity includes weight loss treatment, pharmacotherapy by using prokinetics, H_2-receptor antagonists, proton pump inhibitor and surgical approach including fundoplication, gastric banding and vertical banded gastroplasty.

Keywords: *GERD, obesity, BMI, TLESR, weight loss, abdominal pressure*

INTRODUCTION

Gastroesophageal reflux disease (GERD) is defined as a pathological condition in esophagus caused by reflux of gastric contents into esophagus. Typical GERD symptoms include heart burn, but occasionally it may also be accompanied by other symptoms such as regurgitation (sour and bitter taste on tongue), epigastric pain, dysphagia, or odinophagia.

A gold standard for GERD diagnosis is endoscopic examination of upper gastrointestinal tract and 24 hours pH-metry.[1,2] Based on endoscopic examination, we will find esophagitis features. When the esophagitis features are interfered by mucosal break, then it is called Gastroesophageal Reflux Disease (GERD), but it is called Non Erosive Reflux Disease (NERD) when it has no mucosal break.

Incidence of GERD is fairly high. In Western countries, the prevalence is about 10-20%. However, it is only about 3% in Asia, except in Japan 13-15% and Taiwan 15%.[2] Syafruddin reported that all patients with dyspepsia who had endoscopic examination demonstrated 22.8% esophagitis cases.[3] Syam AF et al, reported that among 1,718 patients who had endoscopic examination of upper gastrointestinal tract by indication of dyspepsia that had last for 5 years (1997-2002), appeared to have an increase of esophagitis prevalence from 5.7% in 1997 to 25.18% in 2002 (approximately 13.13%).[4]

In USA, incidence of GERD has been significantly increased, and nearly 25% of the population has experienced GERD. It appears to be correlated to an increasing number of obesity in the population with body mass index (BMI) $\geq$ 30 kg/m^2, i.e. around 30% of adult population (more than 6 million people).[5] In a cross sectional study in the USA, people with obesity has 2.8 times risk of reflux symptoms than people with normal body weight.[6]

Mechanism of the GERD is affected by multifactor. Increased intra-abdominal pressure is considered as one of risk factors for GERD. Kang MS et al, reported a strong association between BMI and abdominal obesity with the prevalence of reflux (8.2%), and with the prevalence of erosive esophagitis (6.6%). The prevalence of erosive esophagus is 5.6% on BMI $\leq$ 25; 8.1% on

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BMI 25 -30; 15.5% on BMI ≥ 30 with p = 0.002. It appears to be a correlation between abdominal obesity and erosive esophagitis (OR 2.3; CI 95%, 1.6-3.1).[7] Frezza et al, demonstrated that among patients with obesity who had undergone Laparoscopic Roux-en-Y-Gastric Bypass (LRYGB) operation, they found 55% patients with GERD. However, the pathophysiology of GERD in patients with obesity is remained unclear. But so far, some experts believe that a correlation between GERD and obesity exist, although its conjectural relationship remains unproven.

GASTROESOPHAGEAL REFLUX DISEASE

The gastroesophageal reflux disease is defined as a pathological condition in esophagus caused by reflux of gastric contents through incompetent gastro-esophageal junction to cause trauma and inflammation of esophageal mucosa.[8] It is characterized by esophagitis positive findings of esophagitis features with or without mucosa lesion (mucosal break). The diagnosis of such disease is confirmed by histophatological examination of esophageal tissues. However, endoscopic examination of upper gastro-intestinal tract is now considered as a gold standard and well-support for GERD diagnosis.[1,2] When the endoscopic examination of upper gastrointestinal tract reveals esophagitis features interfered by mucosa lesion (mucosal break), then it is called Gastro-esophageal Reflux Disease (GERD), but it is called Non Erosive Reflux Disease (NERD) when it has no mucosal break.[2]

Esophagitis on GERD will occur when there is a long-contact between refluxate and esophageal mucosa, and also when there is a decrease of mucosal resistance or protection effect for esophageal tissues to cause trauma and inflammation of esophageal mucosa that will lead to development of GERD signs and symptoms. Therefore, it may be said that the pathogenesis of GERD correlated to imbalance between defensive factors of esophageal mucosa and aggressive factors of gastric refluxate, which the defensive factors has more shortcoming than the aggressive factors.[9]

Classic symptoms of GERD are heart burn and regurgitation. Clinical symptoms of GERD may be atypical such as non-cardiac chest pain, and may also be accompanied by dysphagia and odynophagia. Furthermore, it may be associated with pulmonary diseases such asthma, chronic cough, wheezing, and also associated with mouth problem such tooth decay and gingivitis.[10] Chronic GERD may cause complications such as ulcers, hemorrhage, stricture, metaplasia (Barrett's esophagus), or even esophageal adenocarcinoma.[2,11]

PATHOPHYSIOLOGY

Basically, GERD is a dismotility problem, which involves reflux of gastric contents into the esophagus. The pathogenesis of GERD is affected by multifactor, which may occur separately or concomitantly. In general, the factors that have important roles include:

Anti Reflux Barrier

During the swallowing process, an Upper Esophageal Sphincter (UES) is relaxed to allow food on its way down to esophagus and prevent it to enter respiratory tract. Food will be moved by peristaltic movement and pass thorough lower esophageal sphincter (LES) which is also relaxed, allowing food come into stomach. Having through the esophagus, the LES contracts to prevent regurgitation of gastric content back into the esophagus. Upright position, mucosal fold on lowest part of the esophagus, an angle between lower esophagus and upper part of stomach (the angle of his), and contraction of diaphragm crura, they all rule to prevent reflux of gastric acid into esophagus. A down turning of basal tonus from lower esophagus sphincter and transient lower esophageal sphincter relaxation may cause gastroesophageal reflux.[8,12,13]

Esophageal Clearance

When there is a reflux of gastric content into esophagus, the severity of damaged esophageal mucosa is depend on duration of contact between refluxate and gastric mucosa and also efficient esophageal clearance.[14,15] Esophageal clearance is depend on gravitation forces, peristaltic movement, and saliva (pH > 6) to neutralize the remained gastric acid. Ineffective peristaltic movement is characterized by low amplitude of contraction and esophageal dismotility.[16] Esophageal clearance is divided into two steps, i.e. volume clearance and chemical clearance.[8] Volume clearance occurs through gravitation forces and esophageal peristaltic movement. During swallowing process, primary esophageal peristaltic movement will push food and liquid/water to go down into stomach; while secondary esophageal movement will occur when it is interfered by stimulation of esophageal irritation due to gastric reflux and it will start at a starting point where the irritation begin and distributed further into the stomach. There is an abnormality of esophageal clearance in GERD patients, i.e. an increase of induction threshold of secondary esophageal peristaltic movement, which will cause decreased amplitude of secondary peristaltic movement and eventually will decrease esophageal clearance.[8,15] Decreased saliva amount may also cause long exposure of gastric acid on esophagus. A damaging of esophagus is depend on acidity and activity of refluxate

pepsin.[17] Nevertheless, hypersecretion of gastric acid is not the main factor to cause GERD.[18]

Delayed Gastric Emptying

A delayed gastric emptying also has an important role to GERD development since in this condition; a relative excessive volume of gastric content will have a reflux into esophagus. Such delay of gastric emptying will also cause gastric distention that will affect the frequency of transient lower esophageal sphincter relaxation.[8,19] Cunningham KM et al, has reported that more than 50% of GERD patients have delayed gastric emptying.[20] McCallum et al, has reported that 41% of GERD patients have delayed gastric emptying.[21] Richer J, reported that there is 10-15% of the Delayed Gastric Emptying (DGE) in GERD patients.[22] Potential factors of the DGE include: gastroparesis in diabetes mellitus and partial obstruction of stomach.[23] Mercer et al, has also reported a delayed esophageal transit in patients with obesity compared to the control.[24]

Hiatal Hernia

Hiatal hernia is a circular protrusion of esophageal mucosa at 2 cm superior to hiatal esophagus of the diaphragm. Correlation between hiatal hernia and GERD has been proven in several studies, but yet it has not been fully understood. Many theories have tried to explain the correlation between hiatal hernia and development of reflux. Some have stated that hiatal hernia is the main etiology of GERD. Increased intra-abdominal pressure that occurs in pregnancy, tumor, and obesity may cause hiatal hernia.[8] Current theory explaining on it is called sum theory, i.e. during acid clearance, a small amount of gastric acid will be trapped in part of gastric herniation superior to the diaphragm. Relaxation of lower esophageal sphincter during swallowing may cause reflux.[25] The pathophysiology of reflux in hiatal hernia is illustrated on figure 1.

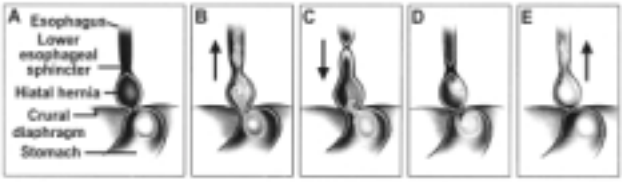

Figure 1. The pathophysiology of reflux in hiatal hernia.[23]
A. Hiatal hernia is defined as herniation of gastric part across the diaphragm
B. A reflux episode of gastric content into esophagus
C. An esophageal contraction to move gastric acid out of the esophagus
D. Gastric acid in hiatal hernia
E. A relaxation of lower esophageal sphincter during swallowing process allowing a reflux of acid from hiatal hernia

The Role of *Helicobacter pylori*

Thus far, the association of *Helicobacter pylori* with GERD remains controversial. *Helicobacter pylori (H. pylori)* infection will cause atrophy of gastric mucosa that reduces the amount of gastric acid, which will further decline the incidence of traumatic acid on esophagus. Labenz et al, has reported a double incidence of increasing GERD in patients with duodenal ulcers who had successful *H. pylori* eradication therapy compared with the infected patients.[26] Hiatal hernia and gastritis in the stomach body have important role in affecting esophageal reflux, despite after *H. pylori* eradication therapy.[27] Another study by Goh KL et al, has reported that there is no increasing incidence of esophageal reflux in patients with duodenal ulcers who have been treated by *H. pylori* eradication therapy.[28]

Other Factors

Regurgitation of bile acid may also contribute to trauma and inflammation of esophageal mucosa. Bile acid reflux will lead to more extensive damage of esophageal mucosa. It is possibly caused by a synergism between gastric acid and taurine conjugated (taurodeoxycholate and taurocholate) in the bile acid.[29] Regurgitation of gastric acid is more frequently found in patients with Barrett's esophagus or esophagitis. However, the pathophysiology has not been fully understood.[8,16,30] Other factors may act as a inducer or stimulator of GERD development including certain food (e.g. onion, chocolate, coffee, peppermint, alcoholic food, tomato), dietary habit of a large portion meal, obesity, alcohol, smoking, certain physical activity, pregnancy, consuming hormonal agents and drugs (anticholinergic, sedative or tranquilizer particularly benzodiazepine, tricyclic antidepressant, theophylline, prostaglandin, dihydropyridin, calcium channel blocker, alpha-adrenergic blocker, beta-blocker, progesterone hormone, potassium tablet, nonsteroidal anti-inflammatory drugs (NSAIDs), and alendronate.[22]

GERD IN OBESITY

Obesity is a heterogeneous chronic metabolic disorder characterized by excessive fat accumulation in the body.[31] Obesity is also defined as a condition of body mass index $\geq$ 30 kg/m^2. Body mass index (BMI) is a calculated ratio between body weight (kg) and body height in square (m^2).[32,33] BMI is divided into groups:

- Underweight : BMI < 18.5 kg/m^2
- Normal weight : 18.5 $\leq$ BMI < 25 kg/m^2
- Overweight : 25 $\leq$ BMI < 30 kg/m^2
- Obesity class I : 30 $\leq$ BMI < 35 kg/m^2
- Obesity class II : 35 $\leq$ BMI < 40 kg/m^2
- Obesity class III : BMI $\geq$ 40 kg/m^2

Obesity is one of potential predisposition factors in pathophysiology of GERD. An analysis of 1,524 sample demonstrated that obesity (BMI > 30 kg/m^2) roles as a strong risk factor in GERD incidence.[34] Fox et al, has reported that 52% of 52 patients with obesity have fulfilled the GERD diagnostic criteria.[35]

An individual with obesity will experience heart-burn symptom 3 times more frequent than an individual with normal body weight.[36] In general population, increased BMI is associated with abnormal findings of endoscopic examination for upper gastrointestinal tract such as erosive gastritis, gastric ulcer, duodenal ulcer, and esophagitis.[37,38] A meta-analysis study evaluated correlation between obesity and GERD found an association between overweight (BMI 25-29 kg/m^2) and obesity (BMI > 30 kg/m^2) with GERD symptoms (OR 1.43, 1.94; $p < 0.001$).[39] Nilsson M et al, has also reported a correlation between increased body weight and development of reflux symptoms ($p < 0.001$).[40] However, another study in Sweden by Lagergern et al, has reported that there is no correlation between body weight and GERD incidence.[41]

PATHOPHYSIOLOGY OF GERD IN OBESITY

Pathophysiology of GERD in obesity is considered as multifactor condition. The development of GERD is virtually associated with a down turning of lower esophageal sphincter tonus, increased Transient Lower Esophagus Sphincter Relaxation (TLESR), and decreased capacity of esophageal clearance.[31] The etiology of increased GERD development in obesity has not been fully understood. It has been reported that the lower esophageal sphincter tonus has similar or a slight down-turning in patients with obesity compared to normal subject.[42,43]

Increased intra-abdominal pressure in obesity may cause development of GERD signs and symptoms. Such increase of intra-abdominal pressure may be resulted from accumulation of body fat, especially in abdominal region. Distribution of body fat (male-pattern obesity) is considered more important than BMI which has a role as predisposition factor of GERD.[44] Accumulated body fat is also affected by hormonal factor, which is associated with adipose tissue to play role in pathogenesis of GERD. However, the exact mechanism remains unclear.[45] According to Kang MS et al, there is an increase GERD incidence in patients with obesity, where abdominal obesity is an important independent risk factor. Based on that study, we found that abdominal circumference is more important compared to either normal body weight or obesity.[7]

In obesity, there is an increasing intragastric basal pressure compared to the normal control.[46] Increased intragastric basal pressure will as well increasing GERD incidence. It is possibly due to an increasing incidence of increased TLESR which will affect and will decrease the lower esophagus sphincter tonus as a mechanism of reflux. Aside from abnormality in TLESR and lower esophagus sphincter tonus, there is also an increased risk of hiatal hernia in obesity,[47,48,49] and as well as delayed clearance of esophagus[23] and GDE as an effect of gastric distention and increased intragastric basal pressure.[21,48] Wilson et al, found that individual with obesity has 4 times risk of increased hiatal hernia compared to individual without obesity.[48] In hiatal hernia, a contact between gastric refluxate which contained of gastric acid will be long-lasting and an increased intra-abdominal pressure will affect the lower esophagus sphincter tonus to cause reflux. Mercer et al, reported that individual with obesity will have significant increase gradient of gastroesophageal pressure, and increased ratio between gradient of gastroesophageal pressure and the lower esophageal pressure. In this study, it is also found that patients with obesity is more sensitive to acid in the esophagus than normal subject.[47] Wisen et al, reported that at rest, there is an increase secretion of bile acid and pancreatic enzyme, as well as increased pancreatic polypeptide serum level in subjects with obesity compared to subjects with normal body weight. An alteration of pancreatic and bile function in obesity is correlated to composition of the produced refluxate, which will be more toxic for esophagus.[50]

The effect of food on GERD remains unclear, but it is believed that in patients with obesity there is a big volume of meal and high-fat diet as well as increased possibility of chocolate consuming, which is correlated to the development of GERD symptoms.[7,16,51]

MANAGEMENT

Weight-loss

Little has been studied about the effect of weight loss on the signs and symptoms of GERD. Murray et al, has reported a prospective study about the effect of weight loss on improved GERD signs and symptoms. Endoscopic examination is used for diagnosis and to evaluate weight loss effect on GERD signs and symptoms after 8-12 weeks. We found an improvement of symptoms and endoscopic finding after weight loss treatment with a strict diet.[52] On the contrary, Kjellin et al, reported no significant difference in GERD symptoms after weight loss.[53] This may be explained that hiatal hernia in obesity is still exist after weight loss.[16] Despite no evident of weight loss effect on decreasing GERD symptoms, weight loss treatment is still recommended for GERD patients with obesity.

Pharmacotherapy

Recommended medications for GERD include prokinetics, H_2-receptor antagonists, and proton pump inhibitor. As an agent of prokinetics, cisapride should be contraindicated in patients with history of prolonged QT interval. Cisapride for obesity should be cautiously used. Frank S et al, found 28.3% of prolonged QT interval in 1,029 patients with obesity.[54] However, no study has evaluated effectiveness of cisapride for GERD patients with obesity.[16] It is also true for metochloperamide, no study has evaluated its efficacy and safety use in patients with obesity. Utilization of metochloperamide in GERD is expected to bring an effect of decreasing gastric volume, which eventually will decrease the risk of reflux. Cimetidine, ranitidine and famotidine as agents of H_2-receptor antagonists, have an effect on decreasing gastric volume and also increasing gastric acidity (pH). A pharmacokinetic study in patients with obesity demonstrated that the dose of cimetidine and ranitidine should be adjusted based on estimation of ideal body weight rather than the actual body weight. Until now, no study has been conducted to evaluate the efficacy and safety of proton pump inhibitor administration in obesity.

Surgery

Surgery, one of modality for GERD treatment, is conducted for the obesity class III (BMI $\geq$40 kg/m^2) or obesity class II (35 $\leq$ BMI < 40 kg/m^2) with severe comorbidity.[5,16] Fundoplication is a laparoscopic surgery treatment and has been proven to decrease reflux symptoms, but it has no effect on weight loss. Therefore, it is not performed for obesity class III and obesity class II with comorbidity.[55] Gastric banding is considered as one of frequent alternative surgery due to its simplicity and also its effect on weight loss. Roux-en-Y Gastric Bypass (RYGB) is a procedure of gastric bypass surgery directly to jejunum. In this procedure, principles of calorie restriction and malabsorption are applied. Smith et al,[56] and Jones,[57] reported improvement of GERD signs and symptoms in 98% patients and found a significant weight loss after the RYGB. Vertical banded gastroplasty is a reposition surgical procedure including improvement of gastro-esophageal junction. However, the procedure is still controversial in decreasing and diminishing GERD symptoms.

CONCLUSION

In obesity, gastroesophageal reflux disease may occur due to increased intragastric and intra-abdominal pressure, which will affect on the incidence of hiatal hernia, decreased lower esophagus sphincter tonus, delayed gastric emptying, and increased TLESR considered as a risk factor of reflux. Accumulated abdominal fat has more important role as pre-disposition factor of GERD than BMI. The management of GERD in obesity may be performed by weight loss treatment, pharmacotherapy, and by taking surgical procedures as necessary.

SUGGESTION

Currently, there are several studies that have been conducted regarding to GERD prevalence in obesity, either in western countries or in Asia such as Korea. Therefore, we need to conduct a study in Indonesia to evaluate the prevalence of obesity in patients with GERD population. We also need to perform a study that may explain the appropriate pathophysiology and pathogenesis as well mechanism that explain correlation between obesity and GERD.

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