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Pathogenesis, diagnosis and treatment of GERD patients with asthma as extra esophageal manifestations

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ABSTRACT

Asthma is one of the clinical manifestations of GERD. Both symptoms can occur simultaneously even though they occur in different organs. Asthma occurs in the respiratory tract while GERD occurs in the digestive tract. One of the factors of these two diseases is the lifestyle of people who tend to be more easily exposed to the diseases, such as the large number of smokers and fast food outlets that can increase the obesity. This study aims to determine the correlation between GERD and asthma. This is very important to be observed in order to provide the good quality treatment that suits the needs of patients and cure GERD with Asthma as well as esophageal reflux and protect the esophageal mucosa thus the prognosis and quality of life of patients can increase. In regard to observe and understand the pathway in the pathogenesis, diagnosis, and therapy, this study proves that treating GERD in patients with bronchial asthma will reduce asthma attack and improve the patient's quality of life hence patients can carry out normal daily activities.

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INTRODUCTION

Gastroesophageal reflux disease (GERD), based on the Montreal classification in 2006, is a condition that occurs due to reflux of gastric contents which can cause symptoms and or cause disturbing complications (Tjokroprawiro, Setiawan, Santoso, & Soegiarto, 2007). This disease is complex, chronic, and often causes recurrence which increase a risk of morbidity and has the potential to produce complications (Heidelbaugh, Gill, Van Harrison, & Nostrant, 2008).

Symptoms of GERD, based on the Montreal classification in 2006, are divided into two, namely the gastroesophagus and extra esophagus. Gastroesophageal manifestations are classic symptoms such as heartburn and regurgitation, while extra esophageal manifestations include asthma, chronic cough, sore throat, or chest pain. Establishing the diagnosis of GERD can be conducted by various methods such as endoscopy, barium esophagography, esophageal pH monitoring, esophageal manometry, acid perfusion tests, PPI tests, and new esophageal scintigraphy techniques (Naik & Vaezi, 2013).

Asthma, according to the Global Initiative for Asthma (GINA) in 2015, is a heterogeneous disease. It is usually with symptom by chronic airway inflammation. The other respiratory symptoms are wheezing, shortness of breath, chest feels heavy, and cough that varies from time to time and episodic, accompanied by limited variable expiratory air flow. Asthma attacks can be triggered by a variety of factors. One of the is gastroesophageal reflux which can be the potential triggers in patients with asthma (Health, 1995).

GERD and asthma can occur together in a patient without being interconnected and both can be mutually burdensome. Besides that, both can arise from the occurrence of one another, GERD which causes asthma or asthma that causes GERD (Jiang & Huang, 2005). The mechanism of the correlation between GERD and asthma is very important to be known by the clinician in order to provide comprehensive management to reduce the recurrence rate thus it can improve the quality of life of patients. This article will discuss the pathogenesis, diagnosis, and treatment of GERD with asthma as an extra esophageal manifestation.

Epidemiology

The prevalence of GERD and its complications in Asia, including Indonesia, are generally lower compared to western countries, however recent data shows that the prevalence is increasing due to lifestyle changes that increase the risk of person affected by GERD, such as smoking and obesity. Indonesia has yet to have completed epidemiological data regarding this condition. Reports from the Lelosutan SAR et al in FKUI / RSCM-Jakarta study show that out of 127 research subjects undergoing SCBA endoscopy, 22.8% (30 subjects) suffered from esophagitis (Indonesian Society of, 2014).

The study of 6,000 GERD patients from several countries in Europe shows that the most common extrasophageal symptoms were chest pain (14.5%), followed by chronic cough (13%), laryngeal disorders (10.4%), and asthma (4, 8%). Similar results were also found in a study in Korea of 1712 GERD patients whose most symptoms were chest pain (48.4%), chronic cough (32%), laryngitis (24.2%) and asthma (17.3%) (Min et al., 2014).

Reported from 15 million Americans who suffer from asthma, around 50-80% also have GERD. Korea's national health insurance data reports that the prevalence of GERD symptoms is around 45-71% in patients with asthma which is higher than the prevalence of GERD in patients with chronic obstructive pulmonary disease (28%) (Shirai et al., 2015). Based on a study conducted by Susanto et al., it was found that a history of oral bronchodilator use was proven endoscopically to have

erosive esophagitis in 59.3% of patients with moderate persistent asthma with symptoms of GERD (Assyifa, 2020).

Pathogenesis

Pathogenesis of GERD

GERD develops when aggressive factors have the potential to endanger the esophagus and defeat mechanisms protection such as: oesophago-gastric junction barrier, acid clearance in the esophagus, and mucosal defense, which contributes to maintain a balanced physiological state. Therefore, an important role in the pathogenesis of GERD is the contact between the esophageal mucosa and reflux material which consist of stomach acid, pepsin, bile, and duodenal contents. However, there are some synergies between acid and non-acid factors that cause symptoms and lesions (De Giorgi, Palmiero, Esposito, Mosca, & Cuomo, 2006). Mechanisms involved in GERD pathogenesis include mucosal defense disorders, lower esophageal sphincter (LES) disorders by the increased transient LES relaxation and decreased basal tone, decreased esophageal acid clearance, anatomical abnormalities such as hiatus hernias, increased gastric acid production, increased pressure in the stomach due to obesity and position, decreased gastric emptying and reminder of bile acid reflux (Yamada et al., 2003).

Pathogenesis of Asthma

Asthma is a chronic inflammatory airway disease involving various cells and mediators such as T lymphocytes, eosinophils, macrophages, mast cells, epithelial cells, fibroblasts, and bronchial smooth muscle. Environmental factors and various other factors act as causes or triggers of acute inflammatory responses that cause bronchoconstriction, mucous secretion, and vasodilation. The chronic inflammatory process will cause tissue damage physiologically followed by a healing process (healing process) that results in repairs (repair) and replacement of dead cells with new cells. The healing process involves regenerating and repairing damaged tissue with the same type of parenchymal cells and changing damaged tissue with connective tissue that produces scar tissue. Both of these processes will produce structural changes that have a complex mechanism called airway remodeling which causes increased symptoms and signs of asthma such as airway hyperactivity, airway distensibility and airway obstruction (Indonesia, 2006) (Health, 1995).

Pathogenesis of GERD with Asthma

Various pathological processes can be the main for the process of pathogenesis in GERD and asthma. There is only about 30% of patients diagnosed with both conditions have GERD caused by asthma (Littner, Leung, Ballard II, Huang, & Samra, 2005). Until now, there is no theory that really proves whether GERD causes asthma or vice versa. Some mechanisms proposed include.

The mechanism of esophageal reflux which can induce an exacerbation of asthma

Vagal reflex

The reflex theory states that bronchoconstriction resulting from exposure to gastric acid in the distal esophagus occurs through the vagal reflex. Acids in the esophagus stimulate acid-sensitive receptors, initiate the vagal reflex mediated by autonomic esophageal and bronchial innervation (Gaude & Karanji, 2012). This theory was developed from Anamnesis which uses to diagnose GERD can be focused on detecting 3 clinical manifestations, namely (1) classic embryological studies that show the tracheal-bronchial and esophageal branching of both embryonic foregut and various autonomic innervations through the vagus nerve (Amarasiri, Pathmeswaran, de Silva, & Ranasinha, 2013).

Increase the bronchial hyperactivity

Stimulation of esophageal receptors that is sensitive to acid also increases bronchial hyperactivity. Herve et al. analyzed the effect of esophageal acid infusion on the expiratory flow using the isocapnic hyperventilation of dry water and methacholine voluntary test in asthmatics with and without GERD. Total dose of methacholine needed to reduce FEV1 by 20% is significantly lower in esophageal acid infusion compared to normal saline solution. Furthermore, the bronchial response of esophageal acid is eliminated by atropine before therapy. This suggests that stimulation of sensitive esophageal acid receptors interacts with bronchial cholinergic through mediation of vagal reflexes, which suggests that GERD worsens asthma by increasing bronchotor response to other stimuli (Harding & Richter, 1997).

Micro-inspiration

The reflux theory states that microscopic acid aspiration into the bronchi causes local irritation in the airway epithelium and stimulation of inflammatory mediators (Flora & Knigge, 1997). Tuchman et al. reported that acid inhaled into the airways even at low concentrations causes bronchoconstriction that is more severe than direct administration of acid to the esophagus. This suggests that micro-inspiration may be an important mechanism in asthmatics with GERD. Proximal esophageal acid exposure is a requirement for micro-aspiration (Halstead, 2005).

The bronchoconstriction mechanism induces GERD

On the other hand, bronchoconstriction that occurs in asthma can induce GERD so that a vicious cycle occurs where GERD can trigger asthma symptoms, which then can turn to trigger GERD. Positive abdominal pressure is related to pleural and esophageal pressure. With air flow obstruction, negative pleural pressure can increase the pressure gradient between the chest and the abdominal cavity that causes GERD. In addition, excessive inflation and water trapping can cause the diaphragm to flatten, potentially damaging the anti-reflux barrier. Moote et al. reported that administration of methacholine which induces airflow obstruction is related to the length of the reflux period compared to controls (Harding & Richter, 1997).

Asthma treatment

Bronchodilators drugs can also reduce esophageal lower sphincter pressure (LES). Theophylline increases gastric acid secretion and decreases LES pressure (Yuksel, 2012). Ekstrom and Tibbling examined 25 asthma patients with GERD using a 24-hour esophageal pH test and found that asthma patients with theophylline therapy had a 24% increase in total exposure to esophageal acid and a 170% increase in symptoms of reflux. Patients with sub therapeutic theophylline did not have a significant increase in reflux parameters. Giving iv and oral β2 adrenergic agents also has the potential to reduce LES pressure (Parsons & Mastronarde, 2010).

Diagnosis

symptoms: heartburn, acid regurgitation, worsening in the supine or bent position, often after eating, especially large

meals or foods containing high fat containing food; (2) atypical manifestations: noncardiac chest pain, gastrointestinal symptoms (epigastric discomfort, nausea, dysphagia, etc.); (3) extra esophageal manifestations: pulmonary manifestations such as asthma, chronic cough, recurrent pneumonia; manifestations of larynx, and pharynx.

Some conditions can be the main cause for suspecting asthma associated with GERD, such as: (1) early onset of asthma that occurs during adulthood, (2) difficulty in controlling asthma, not responding to treatment without obvious causes; (3) asthma is resistant to steroids; (4) symptoms (heartburn, regurgitation) that occur when changing positions (from sitting, to the right to lie down or bend); (5) hoarseness; (6) the dominance of the nocturnal crisis; (7) coughing or wheezing after drinking or eating sour; (8) coughing or wheezing after a large meal; (9) asthma symptoms worsen after eating certain foods (eg chocolate, alcohol, peppermint, and coffee; symptoms (10) after vomiting asthma (Harding & Richter, 1997) (Naik & Vaezi, 2013) (Heidelbaugh et al., 2008).
Most asthma patients show typical symptoms of GERD, such as heartburn and regurgitation. Havemann et al. Found that the average prevalence of GERD in asthma was 59.2%, many patients may not show typical symptoms of reflux. Another study, Kiljander et al. found that although 35% of asthma patients in their study did not have typical reflux symptoms, there was reflux in the 24-hour monitoring test of esophageal pH (Naik & Vaezi, 2013). There is a tool to support in determining a diagnose namely GERD questionnaire (GERD-Q), a questionnaire to help establish a diagnosis of GERD, and measure therapeutic responses (Tjokroprawiro et al., 2007).

Diagnostic tests for GERD have developed rapidly nowadays. Common methods include endoscopy, barium esophagography, esophageal pH monitoring, esophageal manometry, and acid perfusion tests, PPI tests and new techniques used for the diagnosis of GERD, such as esophageal scintigraphy. All methods have limitations in sensitivity and specificity (Badillo & Francis, 2014).

Proton Pump Inhibitor Test (Acid Suppression Test)
Anti-reflux empirical treatment with twice-daily PPI without prior endoscopy seems to be the most useful and most effective approach possible for patients with GERD (WONG & FASS, 2004) (Indonesian Society of, 2014). If symptoms disappear with PPI and reappear if therapy is stopped, the diagnosis of GERD can be made. The test is said to be positive if there is clinical improvement in 1 week by as much as 50% (Tjokroprawiro et al., 2007).

Endoscopy
Endoscopy provides visualization directly from the esophageal mucosa and allows for a biopsy. Endoscopy combined with a more sensitive biopsy than barium esophagus in detecting esophagitis and esophageal barrel, has a sensitivity and specificity of 100% to identify esophagitis but the sensitivity is only 50% to 70% to identify GERD (Jiang & Huang, 2005) (Badillo & Francis, 2014). If mucosal break is not found in endoscopic examinations in patients with typical symptoms of GERD, this condition is referred to as non-erosive reflux disease (NERD). There are several classifications of esophagitis abnormalities in patients (Setyawati et al., 2008).

Table 1. Classification of Los Angeles (Makmun, 2014)

Degree of Damage	Description of Endoscopic
A	Minor erosion of the esophageal mucosa with a diameter of <5 mm
B	Mucosal erosion / mucosal folds with a diameter> 5 mm without interconnection
C	Lesions that are confluent but do not surround / surround the entire lumen
D	Esophageal mucosal lesions that are circumferential (surrounding the entire esophageal lumen)

Acid Perfusion Test (Bernstein Test)
The acid perfusion test aims to show the sensitivity of the mucosa to become acidic. The advantage of this test is able to see the relationship between the patient's symptoms and GERD. If the patient's symptoms are provoked by acid and lost by normal saline, this test is very specific for GERD. Richter et al. conducted 7 studies and found an overall sensitivity of 79% and specificity of 82% (Jiang & Huang, 2005).

pH monitoring of the esophagus
A 24-hour long-term esophageal pH test plays a key role in diagnosing GERD, especially in people with asthma without classic reflux symptoms or those who are difficult to treat. Irwin et al. In their study recommended a 24-hour test of esophageal pH in all asthma that was difficult to control or who received long-term prednisone therapy. A 24-hour test of esophageal pH is also useful in linking asthma symptoms with episodes of reflux (Harding & Richter, 1997) (Saritas Yuksel & Vaezi, 2012). The American Gastroenterology Association states that the use of esophageal pH testing is recommended in asthmatics triggered by reflux (Sontag et al., 2003).

Esophageal Manometry
Esophageal manometry is not sensitive in diagnosing GERD because there is still a large overlap between the value of LES pressure in GERD patients and controls (Amarasiri et al., 2013). The value of the pressure will have a diagnostic value which means that the extreme value is obtained. Richter et al. Showed that low LES pressure of less than 10 mmHg had poor sensitivity (58%) but good specificity (84%) in diagnosing reflux. At present, esophageal manometry is mainly used for evaluating GERD therapy, facilitating placement of esophageal pH probes, and guiding antireflux surgery (Badillo & Francis, 2014) (Indonesian Society of, 2014).
Esophagography of Barium

This examination can get rid of anatomic abnormalities, detect esophagitis, peptic ulcer, stricture and hiatus hernia, and provide information on the function of swallowing. Since this examination is not specific and not sensitive to GERD, normal results do not exclude GERD (Indonesian Society of, 2014).

Scintigraphy
This test is used to detect micro-aspirations in people with asthma with GERD. However, aspiration is proven only in a small number of people with asthma with GERD (Ravelli, Panarotto, Verdoni, Consolati, & Bolognini, 2006). The test is conducted by giving technetium 99m sulfur colloid liquid food and scanning the distal esophagus for 1 hour. More than 2 episodes of reflux within 1 hour are called abnormal. This test can also assess gastric emptying which is usually abnormal in

GERD patients. When showing the presence of isotopes in the lungs performed 12 hours later confirming aspiration (Falk et al., 2015).

Treatment

Treatment in GERD patients with asthma aims to treat GERD and asthma, reduce esophageal reflux, and protect the esophageal mucosa. The results of the treatment also showed improvement in asthma symptoms and a decrease in the use of asthma medications, although these improvements might not be proven by spirometry in all patients. Treatment of GERD includes lifestyle and dietary changes, administration of pharmacological, and surgical therapy (Naik & Vaezi, 2013).

Lifestyle changing

Lifestyle modification must begin and continue during GERD therapy. This modification is performed based on the severity of the disease. Many studies have shown that head elevation from beds is 6 inches high (15-20 cm), decreases fat intake, avoids eating large quantities, avoids lying down before 3 hours postprandial, quitting smoking, and losing weight can reduce esophageal reflux (Morehead, 2009). Certain foods such as chocolate, alcohol, peppermint, coffee, tomatoes, oranges, carbonated drinks can increase esophageal reflux and should be avoided. Patient education about factors that can trigger reflux is necessary even though randomized trials have not been conducted to test the efficacy of lifestyle modification. Patients who are not responsive to lifestyle modifications must receive medical care (Jiang & Huang, 2005).

Medication

Some drugs that are known to overcome the symptoms of GERD are antacids, prokinetics, H2 antagonist receptors, Proton Pump Inhibitors (PPI), and Baclofen. PPI is the most effective and proven to relieve symptoms, as well as cure esophagitis lesions in GERD (Indonesian Society of Gastroenterology, 2014). GERD patients with asthma are given initial PPI empirical therapy twice a day for 1-2 months. If there is a good response to heartburn symptoms and / or asthma, the dose is lowered to a minimum dose that can control the symptoms (Naik, 2013). PPI works directly on the proton pump of the parietal cell by affecting the H enzyme, K ATP-ase which is considered the final stage of the process of forming stomach acid. PPI doses that can be given to GERD are Omeprazole 2 x 20 mg, Lanzoprazole 2 x 30 mg, Pantoprazole 2 x 40 mg, Rabeprazole 2 x 10 mg, Esomeprazole 2 x 40 mg (Setyawati et al., 2008). In mild esophagitis therapy is given using the "therapy on demand" strategy, whereas in moderate-severe esophagitis therapy is given for 6 months (Indonesian Society of, 2014).

Besides PPI, other therapies that can be given are antacids, H2 antagonist receptors and prokinetic agents. Antacids are quite effective and safe in relieving GERD symptoms but do not cure esophagitis lesions. Aside from being a HCl buffer, this drug can also strengthen the pressure of the lower esophageal sphincter. The dose given is 4 x 1 tablespoon. H2 antagonist receptors and prokinetic agents are the second choice if PPI is not available. The H2 antagonist receptor is effective in mild to moderate esophagitis and without complications. This group are included cimetidin 2 x 800 mg or 4 x 400 mg, ranitidine 4 x 150 mg, famotidine 2 x 20 mg, and nizatidine 2 x 150 mg (Setyawati et al., 2008).

Prokinetic agents increase gastric emptying and reduce acid contact with the esophageal mucosa so as do not yaffect acid secretion. The role of metoclopramide, domperidon, and cisapride is limited due to the side effects of this drug. Contraindicated prokinetic agents in patients with intestinal obstruction, perforation or gastrointestinal bleeding. Metoclopramide, dopamine antagonists, can trigger extrapyramidal reactions such as facial seizures, trismus, opistotonus, and parkinsonism in 1% of patients thus it is contraindicated in patients taking other dopamine receptor antagonists such as phenothiazide, tioxantin, and butyrofenon (Jiang & Huang, 2005). The dose of metoclopramide given is 3 x 10 mg. Domperidone is given at a dose of 3 x 10-20 mg. This side effect of domperidon is less frequent than metoclopramide because it is not through the blood brain barrier (Setyawati et al., 2008). Cisapride therapy can cause prolongation of QT, especially if given with P450 inhibiting drugs, such as ketoconazole, fluconazole, itraconazole, trolendomycin, erythromycin, and clarithromycin. The dosage that can be given is 3 x 5 mg (Jiang & Huang, 2005) (Setyawati et al., 2008). The study of Baclofen showed a reduction in the incidence of postprandial reflux and acid exposure and inhibits transient LES relaxation, but some further data is still needed to be recommended routinely (Badillo & Francis, 2014).

However, the principles of treating asthma patients are (1) achieving controlled asthma and maintaining normal activity, (2) reducing the risk of drug exacerbations, drug effects, and persistent airway obstruction. The drugs used consist of a controller and reliever (Health, 1995). Several studies showed the use of oral bronchodilator drugs such as theophylline, oral β2 agonists, can reduce lower esophageal sphincter pressure (LES) thereby increasing the incidence of acid reflux and total reflux time which causes a high risk of lesions or esophageal mucosal damage. Hence, the use of drugs from this group should be avoided.

Surgery

Patients who need a PPI to control GERD have an indication for surgery, especially in young patients. This is related to the existence of unanswered questions about the long-term security of PPIs. The optimal results can be achieved if surgery is performed in patients with normal esophageal motility and low LES pressure. Preoperative testing includes a 24-hour test of esophageal pH, esophageal manometry, and endoscopy. Laparoscopic fundoplication can be performed in patients with uncomplicated reflux disease. Whereas open procedures are recommended for patients with large hiatus hernias, short esophagus, peptic strictures, or second surgery (Jiang & Huang, 2005).

Although the major complaints of GERD can be successfully managed with medical therapy, patients with severe or refractory complications should be considered for surgical therapy (Badillo, 2014). Surgery needs to be considered in postmenopausal women with osteoporosis because calcium absorption is impaired due to PPI (Henry, 2014). The antireflux surgery tries to restore the sphincter's work by wrapping the stomach fundus around the esophagus, which is called fundoplication. When this technique is done well, this procedure will restore LES function, reduce reflux, and cure gastric esophagitis. The potential benefit of surgery compared to medical therapy is the reduction of greater esophageal acid exposure up to 98% (Jiang & Huang, 2005) (Henry, 2014). In a study of GERD, patients with respiratory complications, especially asthma, there was a significant increase in quality of life after fundoplication. Side effects that can occur are dysphagia, bloating, difficulty belching and intestinal disorders after surgery. Clinical therapy using full-dose PPI also shows results that are not much different from

fundoplication so that surgical therapy is rarely performed (Indonesian Society of, 2014) (Henry, 2014).

Summary

GERD and asthma can occur together in a patient without interconnectedness. Besides that, both can be mutually burdensome and can arise from the occurrence of each other by either triggering bronchoconstriction in asthma through a mechanism of vagal response, increased bronchial reactivity, micro-inspiration, or asthma worsening GERD through mechanisms that occur mechanically, or through the treatment of asthma. Methods for diagnosing GERD include: (1) PPI tests, (2) endoscopy, (3) acid perfusion tests (Bernstein test), (4) monitoring of esophageal pH, (5) esophageal manometry, (6) barium esophagography, and (7) scintigraphy. The main goal of treatment is to treat GERD and asthma, while reducing esophageal reflux and protecting the esophageal mucosa. It has been proven that treating GERD in patients with GERD and bronchial asthma will reduce asthma attacks which will improve the quality of life of patients. The use of oral bronchodilators in GERD patients with asthma needs to be avoided to reduce the risk of lesions or mucosal damage. Clinical therapy using full-dose PPIs shows results that are not much different from fundoplication so surgical therapy in patients with GERD with asthma is rarely performed.

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