Insulin Resistance in Gastroesophageal Reflux Disease

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ABSTRACT
Insulin resistance is the disturbance of glucose regulation characterized by higher insulin level. In clinical context, insulin resistance can manifest as abnormalities that are related with cardiovascular event risk, known as metabolic syndrome. Several studies had reported that insulin resistance was associated with erosive esophagitis in patients with gastroesophageal reflux disease (GERD).

Keywords: insulin resistance, GERD, metabolic syndrome, erosive esophagitis.

INTRODUCTION
Insulin sensitivity is the ability of insulin to exert normal physiologic effects in glucose regulation. In clinical context, insulin resistance may manifest as obesity, dyslipidemia, and hyperglycemia. These related abnormalities carry high risk of cardiovascular events, known as metabolic syndrome.1,2

The rising prevalence of metabolic syndrome carries a public health issue that needs attention. Based on Riskesdas 2013, the proportion of high triglyceride levels in Indonesia, low HDL, and hypertension had reached 13%, 22.9%, and 25.8%, respectively.3 A survey in Jakarta in 2006 showed that the prevalence of metabolic syndrome had reached 28.6%.4

In addition to the risk of cardiovascular events, insulin resistance may also be associated with other conditions such as polycystic ovary syndrome, non-alcoholic fatty liver disease, and gastroesophageal reflux disease.1 Gastroesophageal Reflux Disease (GERD) is quite common in daily practice. The prevalence of GERD in Jakarta in 2002 was 25.18%.5 This disease has a wide clinical spectrum and may cause complications related to gastric reflux to the esophagus, oral cavity, and / or lung and are associated with decreased quality of life.6,7 This paper will discuss the current understanding of the relationship between gastroesophageal reflux...
disease and insulin resistance.

**INSULIN RESISTANCE AND ITS MECHANISM**

Insulin sensitivity is the ability of insulin to work in glucose regulation, to increase glucose absorption, lower glucose levels and increase the conversion of glucose into a form that is stored by the body. Insulin resistance can be defined as decreased tissue responsiveness to insulin with an increased production of insulin to provide a normal biological response. Insulin resistance syndrome is a group of abnormalities and interrelated physical manifestations that occur in individuals with insulin resistance. Meanwhile, the metabolic syndrome represents a clinical diagnostic entity associated with insulin resistance that identifies an individual as having a high risk of cardiovascular morbidity.1

Under normal circumstances, insulin release from pancreatic β cells will induce the entry of glucose into cells when binding to insulin receptors on the cell surface. The insulin receptor will undergo autophosphorylation initiating a cascade in the translocation of glucose transporters types 1 and 4 (GLUT 1 and GLUT 4) to the membrane in facilitating the entry of glucose into the cell.8,9 The circumstances that cause insulin receptor disorders, both in activity and concentration, will affect the action of insulin. Molecular mechanism disturbances associated with glucose transport activity through insulin receptor substrate serine phosphorylation (IRS) -1 and mitochondrial disorders may cause insulin resistance.8

The mechanisms of insulin resistance in obesity begin with increased fatty acyl CoA and diacylglycerol in plasma and / or decreased oxidation due to mitochondrial dysfunction that activates protein kinase C in skeletal muscle. Furthermore, activation of serine residue on IRS-1 will decrease GLUT4 translocation. In the liver, elevated hepatic diacylglycerol content due to increased fatty acids from plasma will lead to decreased insulin kinase receptor activity and decrease IRS-2 tyrosine phosphorylase, resulting in decreased insulin stimulation of glycogen synthase activation and decreased phosphorylation of forkhead box protein O (FOXO) which may elevate hepatic gluconeogenesis.8-10

When there is an increase in adipocytes, especially abdominal visceral fat, the body’s insulin sensitivity decreases. The target tissue reduces the number of insulin receptors on the cell surface in response to prolonged high insulin levels. Adipose tissue can affect insulin sensitivity to other tissues by secreting adipokine molecules (TNFα, IL-6) that inhibit insulin signals locally or on remote target tissues.11

**Measurement of Insulin Resistance**

Insulin resistance is measured by two approaches, dynamic intervention and steady state assessment using mathematical calculations. The first approach includes examination of hyperinsulinemic glucose clamp, which is the gold standard. While the second approach includes assessment of Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI). This calculation is processed using a mathematical formula that represents fasting insulin kinetic and fasting glucose measurement.12

This mathematical equation was often used in epidemiology study due to the practical and easy method using one blood sample. Nevertheless, this simple method could not be used in determining insulin resistance in certain population, such as in elderly and type 1 diabetes. This is due to insulin levels that will not accurately represent insulin resistance because β cells do not secrete sufficient insulin.12 Nevertheless, in one multivariate study in patients with hypertension and type 2 diabetes mellitus comparing HOMA-IR, QUICKI and McAulay index against insulin resistance using clamp technique, HOMA IR and QUICKI had good validity in estimating insulin resistance, with HOMA IR was being the most appropriate value.13 In addition, there was a good correlation between the estimated value of insulin resistance from HOMA and from the Clamp technique.8

The model of insulin resistance homeostasis (HOMA-IR) is used to estimate insulin resistance and β cell function using plasma insulin and fasting glucose concentration. The relationship between glucose and insulin in the basal state
reflects the balance between liver glucose output and insulin secretion maintained by the feedback mechanism between the liver and β cells. There is no cut off value that applied globally to determine insulin resistance. The higher the HOMA-IR index, the higher the insulin resistance in one individual. One study in Japan determined the value of HOMA-IR > 1.7 as a reference point for identifying subjects with a high risk of the presence of the metabolic syndrome. Indonesia does not have data on the average value of insulin resistance in the general population, but study in obese adolescents revealed HOMA-IR mean was 3.92 and in elderly women had a mean HOMA-IR level of 2.87.

GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD) is defined as symptoms of reflux or mucosal damage due to reflux of gastric contents into the esophagus or higher, to the oral or lung cavity, causing symptoms or related complications. This gastroesophageal reflux disease may be classified as a non-erosive reflux disease (NERD) or erosive reflux disease (ERD) based on the presence or absence of esophageal mucosal damage seen in endoscopy.

Epidemiological studies in western countries show that the prevalence of GERD was higher (10-20%) than Asian countries (3-5%). Disturbing heartburn symptoms were seen in about 6% of the population and regurgitation reached 16% of the population above. Indonesia does not have national epidemiological data on the disease. Endoscopic studies at RSCM / FKUI involving 1718 dyspepsia patients from 1997 to 2002 found an increase in esophageal prevalence of 5.7% in 1997 to 25.18% in 2002. Another study in the general population in Depok in 2012 showed the prevalence of GERD using a GERD-Q questionnaire was 9.35%. However, recent study in 2016 among population of physicians in Indonesia, showed that the prevalence of GERD was 27.4%. Reflux is a normal physiologic incident and is caused by the transient relaxation of the lower esophageal sphincter (LES). Under normal circumstances, there is an endogenous defense mechanism, the action of LES that inhibit irritating substance entering the esophagus, and the mechanism of excreting irritating materials through normal esophageal motility. If there is a disturbance in this defense mechanism, the esophagus will be irritated by prolonged acidic liquids, resulting in GERD conditions. In patients with GERD, temporary relaxation of LES occurs more frequently than normal conditions. Defects in LES, such as hypotonicity in LES, and the effects of a hiatal hernia can cause the condition.

INSULIN RESISTANCE AND GASTROESOPHAGEAL REFLUX DISEASE

There are many studies that linking gastroesophageal reflux disease with metabolic syndrome. A study by Park et al. showed an association between erosive esophagitis and metabolic syndrome. Another study by Wu et al. showed that the prevalence of metabolic syndrome in patients with reflux esophagitis was significantly higher than that of the control group and parameters associated with reflux esophagitis were peripheral circumference, and fasting blood glucose.

Hyperglycemia is a consequence of insulin resistance. It is known that the mechanism of GERD is primarily caused by a disturbance in the lower esophageal sphincter (LES). The relationship between fasting blood glucose and GERD symptoms can be explained by the presence of interference from the sensory and motor function of the esophagus. Changes in motility resulting from hyperglycemia include increased duration of peristaltic waves and decreased peristaltic velocity in the distal esophagus, decreased LES pressure, and deceleration of gastric emptying. In diabetic patients, hyperglycemia is associated with prolonged LES relaxation period compared with euglycemic patients. In normal individuals, hyperglycemia will decrease the lower esophageal sphincter pressure and esophageal peristalsis acceleration. In addition, the amount of temporary sphincter relaxation increases in hyperglycemic conditions.

The component of metabolic syndrome that has been extensively studied in relation to GERD is obesity. The point that needs to be emphasized is that obesity is not a consequence of insulin
resistance, but a variable that can decrease insulin action against glucose regulation. Obesity is an independent risk factor for GERD, particularly esophageal erosion. The main mechanism is related to temporary relaxation in LES. There are several factors that cause GERD in obese patients, including increased gastroesophageal sphincter gradient, hiatal hernia incidence, intraabdominal pressure, and pancreatic and bile enzyme output. Hiatal hernia is the protrusion of the stomach through the diaphragm gap that can increase GERD incidence through weak LES tone and lower LES pressure at rest, as well as slower acid emptying than individuals without hiatal hernia. In addition to mechanical mechanisms, an increased metabolic activity in adipose tissue, especially visceral adipose tissue, increases adipokine secretion including IL-6 and TNFα which play a role in esophageal motility.

The mechanism of esophageal reflux associated with cytokines is a cycle that aggravates one another. Proinflammatory cytokines such as IL-6 and IL-1 produced by adipose tissue can decrease esophageal muscle contraction. The presence of reflux can lead to further esophagitis through the production of cytokines from the refluxate that stimulates esophageal epithelial cells to produce chemokines that may cause damage to the esophageal tissue. Activation of the inflammatory system will lead to increased production of adhesion molecules and other cytokines thereby increasing inflammation. In addition, endothelial cell activation also increases the progression of inflammation. Acid reflux will lead to platelet-activating factor (PAF) formation which is then released from the mucosa to activate circular muscle causing the production of IL-6, H_2O_2, and IL-1β, which is known to decrease

![Figure 1. Proposed mechanism for the association of GERD and insulin resistance](image-url)
neurogenic muscle contraction by inhibiting the release of acetylcholine.\textsuperscript{29,30}

Insulin resistance can be directly related to GERD events. A study by Ming et al. showed that insulin resistance had a significant association with erosive gastritis, but metabolic syndrome was not associated with GERD. This is probably due to those conditions which do not always coincide.\textsuperscript{31} There were several studies about the association of GERD with insulin resistance. One study in Europe reported that patients with Barretts esophagus, a result of long-term GERD, had higher insulin resistance than those without Barretts esophagus.\textsuperscript{32} Higher insulin resistance was reported to be higher in erosive esophagitis than non-erosive esophagitis obese population in South Korea.\textsuperscript{32} Another study in the general population in Taiwan also reported that insulin resistance was correlated with severe reflux disease, based on a validated questionnaire in Taiwan.\textsuperscript{33} In addition, there is a study which showed that GERD symptoms and HOMA-IR values can be improved with lifestyle improvement.\textsuperscript{34} However, Japanese studies have shown that insulin sensitivity is negatively correlated with GERD symptoms, but insulin resistance has no significant relationship with GERD severity.\textsuperscript{35}

The association of insulin resistance and gastroesophageal reflux disease are complex and the relationship between them can be explained by correlating inflammatory mediators. Gastroesophageal reflux disease has been shown to produce both localized esophageal and systemic inflammatory mediators.\textsuperscript{30,36} Based on studies on GERD patients in Moscow, it was found that proinflammatory cytokines levels such as IL-8 and TNFα in serum patients with erosive esophagitis were higher than those without esophagitis or normal subjects.\textsuperscript{36} Proinflammatory cytokines, such as IL-6 and TNFα, have been associated with insulin resistance through increased serine phosphorylation of Insulin Receptor Substrate-1 (IRS-1) which will eventually inhibit the action.
of Glucose Transporter Type 4 (GLUT-4). Proinflammatory cytokines have been associated with insulin resistance, through the inhibitory effect on insulin transport pathways in Tlr-4 related cells, although the exact mechanism is unclear. A study conducted by Fernandez et al showed a positive correlation between IL-6 levels and insulin resistance. Systemic inflammatory conditions may cause disruption of insulin sensitivity through cellular pathways of JNK, and IKKβ / NFκB in adipocytes, hepatocytes, and macrophages.

CONCLUSION

The literature review has consistently shown an association between gastroesophageal reflux disease, particularly erosive reflux disease, and insulin resistance. Their relationship is associated with interrelated inflammatory mediators. However, the pathophysiology involved is so complicated that many possible related factors may not be identified yet, such as the cellular mechanism associated with inflammatory mediators. Therefore, further research and literature study are needed to understand the relationship between both of them. Given the link between GERD and insulin resistance, it is recommended that clinical characteristics of insulin resistance syndrome or metabolic syndrome should be sought in patients with GERD, particularly erosive reflux disease, and the management given to the patient should involve both of these aspects.

REFERENCES


