

Differences in the Insulin Resistance Levels Measured by HOMA-IR between Patients with Erosive and Non-Erosive Gastroesophageal Reflux Disease

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Abstract

Background. Insulin resistance is the core of Metabolic Syndrome which carries a high risk for cardiovascular events. Insulin resistance had been reported to be higher in GERD patients than subjects without GERD, specifically in erosive esophagitis. **Objective.** To compare the degree of insulin resistance, using HOMA-IR index, between erosive and non-erosive reflux disease.

Methodology. A cross-sectional study of 84 adult patients with GERD symptoms was conducted. The subjects were recruited consecutively between January 2017 and April 2017 at Cipto Mangunkusumo National Hospital in Jakarta. Gastroesophageal Reflux Disease Questionnaire (GERDQ) was used for subject recruitment. Homeostatic model assessment-insulin resistance (HOMA-IR) index was used to evaluate insulin sensitivity. Esophageal erosions were diagnosed using upper gastrointestinal endoscopy. Bivariate analysis was used to determine HOMA-IR difference between esophagitis and non-esophagitis group.

Results. The median of HOMA-IR in all subjects was 1.46 (0.32-13.85). Mann-Whitney test revealed that HOMA-IR index was higher in patients with erosive esophagitis [median 1.74 (0.35-13.85)] than those without erosive esophagitis [median 1.21 (0.32-10.78)] ($p=0.05$).

Conclusion. Insulin resistance is significantly higher in gastroesophageal reflux disease patients with esophageal erosions than in those without esophageal erosion.

Key words: *insulin resistance, erosive esophagitis, esophageal erosion, HOMA-IR*

INTRODUCTION

Insulin resistance is the disturbance of insulin action that needs higher levels to reach normal physiologic effects in regulating glucose.¹ In clinical context, insulin resistance may manifest as interrelated symptoms such as obesity, dyslipidemia, and hyperglycemia, which carry a high risk of cardiovascular events, called Metabolic Syndrome.² The prevalence of metabolic syndrome is increasing and has become a public health issue. According to National Health Survey of 2013, the proportion of high triglyceride, low HDL, and hypertension were 13%, 22.9% and 28.6%, respectively.³ Another survey in Jakarta revealed that the prevalence of metabolic syndrome in 2006 had reached 28.6%.⁴

Aside from cardiovascular events, insulin resistance is also associated with other conditions such as polycystic ovary syndrome, non-alcoholic fatty liver disease, and gastroesophageal reflux disease (GERD).¹ Gastroesophageal reflux disease is a common finding in daily practice. The prevalence of GERD in Jakarta in 2002 was 25.15%.⁵ This condition has a wide clinical spectrum from mild to severe that can be related to a low quality of life.^{6,7}

There were several studies conducted to learn the association between GERD and insulin resistance. Pointer et al., showed that insulin resistance was significantly higher in obese women with GERD than in non-GERD subjects.⁸ Insulin resistance was also reported to be higher in erosive esophagitis than those without erosive

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esophagitis in obese subjects in South Korea.⁹ Another study in Japan failed to show an association between insulin resistance and the severity of GERD.¹⁰

The high prevalence of the metabolic syndrome and its components in Indonesia has urged us to identify factors related to the pathogenesis, which is insulin resistance. Insulin resistance has been shown to be higher in GERD patients, particularly in those with erosive esophagitis. Nevertheless, data regarding insulin resistance in this population is scarce. Racial and lifestyle differences from previous studies emphasize the need to conduct the study in our country.

A cross-sectional study was conducted from January, 2017 to April, 2017 in the gastroenterology outpatient clinic of Cipto Mangunkusumo Hospital, Jakarta. This is a tertiary national referral hospital with a capacity of 900 beds. The general objective of this study was to analyze the difference of insulin resistance between erosive and non-erosive reflux disease in patients with GERD. The specific objective of this study was to compare the clinical characteristic associated with metabolic syndrome in patients with erosive esophagitis and without erosive esophagitis, to obtain the HOMA-IR index of patients with GERD, and the difference of HOMA-IR index between each group. It is hypothesized that insulin resistance, measured by HOMA-IR index, is higher in subjects with erosive esophagitis than in those without erosive esophagitis. This study was approved by the ethical board of Faculty of Medicine Universitas Indonesia (No: 982/UN2.F1/ETIK/2016).

METHODOLOGY

Subjects

A minimum number of 82 subjects is needed to obtain the HOMA-IR index using the sample size formula for numerical descriptive data, $n = \left(\frac{Z\alpha S}{d}\right)^2$, ($Z\alpha=1.64$, $d=0.2$, $S=1.1$) A minimum of 36 subjects in each group is needed to determine the difference in HOMA IR index between non-erosive reflux disease and erosive reflux disease which was calculated using the unpaired categorical-numeric analysis formula, $n1 = n2 = 2 \left[\frac{(Z\alpha + Z\beta)S}{X1 - X2}\right]^2$, ($Z\alpha=1.64$, $\beta=80\%$, $Z\beta=0.84$, $S=1.7$, $X1-X2=0.7$)

The subjects with GERD were consecutively recruited using GERD-Q score greater than or equal to 8. The inclusion criteria were as follows: age greater than or equal to 18 years old, no intake of proton-pump inhibitor (PPI), or H2 receptor antagonist (H2RA), or had been off the drugs for at least two weeks. Subjects who were pregnant, had DM type 1, or other esophageal abnormalities such as malignancy were excluded for this study.

Methodology

Subjects identified by GERD-Q score greater than 8 were asked for written consent for every procedure taken in this study. Subjects using PPI or H2RA treatment longer than 8 weeks were excluded. For subjects on PPI (omeprazole or lansoprazole) or H2RA (ranitidine, 2 doses daily) for greater than or equal to 4 weeks, the PPI and H2RA were discontinued and replaced with antacids for 2 weeks. Data consisting of age, sex, comorbidities, smoking status and alcohol drinking status were obtained from subjects with informed consent. Physical examination measurements obtained were seated blood pressure (after a 5-min rest using a calibrated sphygmomanometer, waist circumference (using flexible measuring tape above the upper iliac crests through the umbilicus), height and weight (using a calibrated scale). A venous blood sample was drawn to assess fasting glucose and fasting insulin (for assessing HOMA-IR), and lipid profile. All samples were analyzed in the Clinical Pathology Laboratory in Cipto Mangunkusumo Hospital. All subjects underwent esophagogastroduodenoscopy procedure in the Digestive Endoscopy Center/*Pusat Endoskopi Saluran Cerna* Cipto Mangunkusumo Hospital. The procedure was performed by qualified gastroenterology staff in the center. The results of endoscopy were further categorized as erosive esophagitis or non-erosive disease.

Statistical analysis

Statistical analysis was carried out using SPSS© version 17.0 for windows. Bivariate analysis using Mann-Whitney was performed to evaluate the association between esophageal erosion and insulin resistance for non-parametric data. P value <0.05 was considered statistically significant.

RESULTS

A total of 84 subjects who fulfilled the inclusion criteria were accounted for analysis in this study. The median of HOMA-IR index in this study population is 1.46 (0.32-13.85). Characteristics of the subjects can be seen in Table 1.

The age of subjects in this population ranged from 17 to 40 years old. Majority of the subjects were female. The mean BMI was 23.3 kg/m², which is categorized as overweight. A total of 33.3% of the subjects were obese. Most of the subjects had normal lipid profile and fasting blood glucose.

Most of the subjects had minor esophageal erosion seen from the upper endoscopy, with 34 subjects (40.5%) having esophagitis grade A, and 10 subjects (11.9%) having esophagitis grade B. A total of 36 subjects (42.9%) had non-erosive reflux disease.

Table 1. Characteristics of the study subjects

Variable	Value (n= 84)
Age, median in years (min-max)	53 (18-76)
<40 (%)	19 (22)
≥40 (%)	65 (77.4)
Sex (female), n (%)	58 (69)
Habit	
Smoking (%)	5 (6)
Alcohol consumption (%)	1 (1.2)
Smoking and alcohol consumption (%)	3 (3.6)
Comorbidities (T2DM, Hypertension, Dyslipidemia)	
None (%)	50 (59.5)
1 comorbidity	24 (28.6)
≥2 comorbidities (%)	10 (11.9)
Body Mass Index, (kg/m ²), mean (SD)	23.3 (4.8)
Waist circumference (cm)	
Male, mean (SD)	86.4 (14.8)
Female, median (min-max)	84.5 (62-113)
Blood pressure	
Systolic Blood Pressure ≥140 and/or Diastolic Blood Pressure ≥90	24 (28.6)
Systolic Blood Pressure <140 and/or Diastolic Blood Pressure <90	60 (71.4)
Fasting blood glucose (mg/dL), median (min-max)	85.5 (68- 246)
Triglyceride, (mg/dL), median (min-max)	92.5 (40-494)
HDL, (mg/dL) median (min-max)	48 (23-95)
LDL, (mg/dL), mean (SD)	122.4 (34.4)
Total cholesterol (mg/dL), mean (SD)	184.3 (38.1)
HOMA-IR, median (min-max)	1.46 (0.32-13.85)
Endoscopic results, n (%)	
Non-erosive	36 (42.9)
Esophagitis grade A	34 (40.5)
Esophagitis grade B	10 (11.9)
Esophagitis grade C	3 (3.6)
Esophagitis grade D	1 (1.2)

Metabolic characteristics were categorized based on esophageal erosion to determine the difference in insulin resistance in each group. Comparison of the metabolic characteristics showed that fasting blood glucose (FBG), proportion of Type 2 DM (T2DM) and body mass index

(BMI) were similar in each category. Other variables such as the proportion of hypertension, dyslipidemia, high triglyceride, high waist circumference, and low HDL were higher in subjects with esophageal erosion. There were significant differences in waist circumference and HDL level between erosive and non-erosive group. The comparison can be seen in Table 2.

The difference in HOMA-IR between erosive esophagitis and non-erosive disease can be seen in Table 3. Mann-Whitney test showed a significantly higher HOMA-IR index in subjects with esophageal erosion than in those without esophageal erosion (*p*=0.015). This result indicated a higher insulin resistance in these subjects.

DISCUSSION

Characteristics of subjects with GERD

Most of the subjects in this study were above 40 years old which is similar to several other studies which showed a tendency for patients with GERD to be above 40 years old.¹¹⁻¹⁵ Also, the higher prevalence of women in this population was similar to studies in Indonesia, Turkey, Albania, and Japan.¹¹⁻¹⁴ A study in Japan showed that older patients and women had higher psychologic stress scores than men and women tend to be older than men.¹³ Nevertheless, the association between age or sex and GERD was still controversial. Some studies showed positive correlation; others showed no significant correlation.¹¹⁻¹⁴ This finding indicates that the subjects' characteristics depend on the demographic data of the population.

Table 2. Comparison of clinical and metabolic characteristics of subjects with GERD based on presence or absence of esophageal erosion

Variable	Without esophageal erosion (n=36)	With esophageal erosion (n=48)	p
Hypertension			
No (%)	28 (78.8)	28 (58.3)	0.061a
Yes (%)	8 (22.2)	20 (41.7)	
Type 2 DM			
No (%)	31 (86.1)	42 (87.5)	1.00b
Yes (%)	5 (13.9)	6 (12.5)	
Dyslipidemia			
No (%)	20 (55.6)	22 (45.8)	0.378a
Yes (%)	16 (44.4)	26 (54.2)	
Body mass index			
<25 kg/m ² (%)	24 (66.7)	32 (66.7)	1.00a
≥25 kg/m ² (%)	12 (33.3)	16 (33.3)	
Fasting blood glucose			
<100 mg/dL (%)	32 (88.9)	42 (87.5)	1.00b
≥100 mg/dL (%)	4 (11.1)	6 (12.5)	
Triglyceride			
<150 mg/dL (%)	29 (80.6)	36 (75)	0.547a
≥150 mg/dL (%)	7 (19.4)	12 (25)	
HDL (mg/dL)			
Male ≥40, female ≥ 50 (%)	26 (72.2)	23 (47.9)	0.025a
Male <40, female < 50 (%)	10 (27.8)	25 (52.1)	
Waist circumference (cm)			
Male <90, female < 80 (%)	20 (55.6)	15 (31.3)	0.025a
Male ≥90, female ≥80 (%)	16 (44.4)	33 (68.7)	

a: chi square

Table 3. Difference in HOMA-IR index in erosive and non-erosive reflux disease

	HOMA-IR Median (Min-Max)	p*
Without esophageal erosion (n= 36)	1.21 (0.32-10.78)	0.015
With esophageal erosion (n= 48)	1.74 (0.35-13.85)	

*Mann-whitney test

The mean body mass index (BMI) in this study was 23.3 (SD 4.8) kg/m². This is similar to a study carried out among Indonesian medical doctors which showed that the mean BMI was 23.62 (SD 4.41) kg/m².¹⁵ On the other hand, the study in Albania showed a higher mean BMI of 26.2 kg/m².¹⁴ This difference may be due to racial or lifestyle difference of the study population.

A total of 36 subjects (42.9%) did not have esophageal erosion and the other 48 (47.1%) patients had esophageal erosion. A study in Taiwan showed a larger proportion of subjects with GERD as having non-erosive disease (82%).¹⁶ A study in Egypt also revealed the proportion of non-erosive reflux disease (76%) to be higher than erosive esophagitis (24%).¹⁷ One study in China showed that there was a rise in esophagitis rates from 20.7% to 51% among subjects with GERD, which was similar to the esophagitis proportion in this study.¹⁸ This difference might be due to the difference in the questionnaire used to diagnose GERD, the smoking and alcohol drinking habit, or lifestyle. Nevertheless, the distribution of each Los Angeles (LA) grade esophagitis was similar to a study in South Korea.⁹

Most of the study subjects had normal fasting blood glucose and lipid profiles. According to a study in Egypt on patients with GERD, the level of triglyceride, total cholesterol and fasting blood glucose were higher than in this study.¹⁹ Hsien et al., showed that the mean HDL and LDL were in the normal range, 53.6 (SD16.1) kg/m² and 125.5 (SD 33.3) mg/dL respectively and most of their study subjects had similar BMI with this study.²⁰ The similarity of the subjects' characteristics signified that the difference of study characteristics might be due to the racial and lifestyle differences of the population.

The index of HOMA-IR is a mathematical model to represent insulin resistance in one population. The HOMA-IR index in patients with GERD in Indonesia has not been studied before. The index is affected by race, age, and metabolic disturbances. This study revealed that the median HOMA-IR was 1.46 (0.32-13.85). This index was lower than those found in other studies in Indonesia among obese and non-alcoholic fatty liver disease, and the geriatric population, which were 3.92 (SD 2.09) and 2.87 (SD 8.08), respectively.^{21,22} The difference was that the BMI and lipid profiles in those other studies were in the above normal range. This study involved subjects with relatively normal metabolic conditions as seen from the normal range of lipid profile and fasting blood glucose. Therefore, it is not surprising that the HOMA-IR index in this study was lower than those in other population. This finding was similar to the finding in a study in Iran which concluded that the cut-off for metabolic syndrome in a nondiabetic population was 1.77.²³ The study in Egypt showed the mean HOMA-IR index in subjects with GERD to be 2.86 (SD 2.189).¹⁹ The higher HOMA-IR index in that

study might be due to the higher BMI in that population, which was 2.8 (SD 6.5) kg/m².

Insulin resistance in erosive and non-erosive reflux disease in GERD patients

Insulin resistance in this study was calculated using HOMA-IR which had been validated with a good correlation with euglycemic clamp as the gold standard. Higher HOMA-IR index indicates higher insulin resistance. There is no cut-off in HOMA-IR that can be applied globally, because of the variance in each country and race.^{24,25} Therefore, it is important to understand the range of insulin resistance index in different populations. Gayoso-Diz et al., revealed that there was a tendency for the cut-off for insulin resistance to be higher in western countries than in Asian countries. In that study, the highest cut-off for insulin resistance was in France (3.8), and the lowest cut-off was in Thailand (1.55).²⁴

Mann Whitney analysis was performed to analyze comparative hypothesis of unpaired numeric variables with abnormal distribution. Through this analysis, the HOMA-IR index was significantly higher in esophageal erosive subjects compared with non-esophageal erosive subjects (p=0.015). There were several studies which had similar results. A study by Hsu et al., in Taiwan showed higher HOMA-IR in erosive esophagitis compared with non-erosive esophagus, which were 2.1 (SD 2.7) and 1.4 (SD1.4) respectively OR 1.19, 95% CI (1.08-1.30), p<0.00. In addition, the subjects in this study had similar BMI and age distributions.¹⁶ A study in an obese population in China also showed a significantly higher HOMA-IR in erosive esophagitis compared with subjects without esophageal erosion.²⁶ A study by Park et al., in Korea, which had similar characteristics in BMI, age, blood pressure and fasting blood glucose with this study, also revealed a significantly higher HOMA-IR in subjects with erosive esophagitis, compared with subjects with non-erosive disease, which were 2.41(SD 1.10) and 2.18 (SD 0.89) respectively (p <0.001). In addition, this study stated that higher grade of esophagitis was associated with higher HOMA-IR index.⁹ However, a study by Kamal et al., in a population with higher BMI and lipid profile level, revealed that the degree of esophagitis was not related to HOMA-IR.¹⁹ A study in Japan also showed no association between the severity of GERD, measured by Frequency Scale for the Symptoms of GERD (FSSG) score, and insulin resistance.¹⁰ The reliability of FSSG score was found to be lower than GERD-Q score to detect esophageal erosion.²⁷

The association between erosive esophagitis and insulin resistance may involve inflammatory mechanisms which influence each other. The exposure of the esophagus to refluxate stimulates esophageal epithelial cells to secrete chemokines which later activate immune cellular mechanism to exacerbate cell injury. Acid reflux causes the formation of platelet activating factor (PAF) by the

esophageal mucosa. This leads to the production of IL-6, H₂O₂, and IL-1 β that can reduce neurogenic muscle contraction by inhibiting acetylcholine release.²⁸ These proinflammatory cytokines are abundantly found in the esophageal mucosa and serum. A study in Japan revealed that IL-6 levels and IL-1 β levels were higher in reflux esophagitis compared with control.²⁹ Conditions that produce significant level of proinflammatory cytokines such as TNF α , IL-1, and IL-6, may cause insulin resistance.³⁰ Porwal et al., showed that there was a positive correlation between IL-6 and HOMA-IR.³¹

The prevalence of certain clinical metabolic characteristics based on the presence or absence of esophageal erosions can be seen in Table 2. Through the comparison, the proportion of hypertension, low HDL-cholesterol, high triglyceride, and high waist circumference were higher in subjects with esophageal erosion, with a distinctive difference in HDL and waist circumference. This finding was consistent with several previous studies. According to the studies carried out by Hsu et al., in Taiwan, and Park et al., in South Korea, there were higher proportion of metabolic profile abnormalities such as low HDL-cholesterol, high triglycerides, and high waist circumference in subjects with esophageal erosion.^{9,16} Those conditions were components of metabolic syndrome and are signs of insulin resistance. These findings are in concordance to the results of this study, which revealed a higher HOMA-IR index in subjects with esophageal erosion.

The proportion of obesity based on BMI in subjects with and without esophageal erosion was equal. This finding was consistent with other study in non-alcoholic fatty liver disease population, which described that the severity of GERD was positively correlated with insulin resistance, but not with BMI.³³ Although the obesity proportion based on BMI was equal, there was a prominent difference of waist circumference between groups. Waist circumference is more sensitive than BMI in predicting insulin resistance. Body mass index is an indicator of over-all obesity. However, waist circumference is a measurement of central obesity that consists of visceral and subcutaneous fat. Fox et al., described that visceral fat correlates more with metabolic abnormalities compared with subcutaneous fat.³⁴ Other studies have shown that visceral fat is positively correlated to HOMA-IR index in the next 10 years. Visceral fat is associated with more potent lipolysis and produces inflammatory mediators that can cause insulin resistance.³⁵

This is the first study to investigate insulin resistance in GERD patients in Indonesia. This study was designed to confirm findings from previous studies in other countries. This study showed that insulin resistance is higher in patients with erosive reflux disease. Therefore, patients with erosive reflux disease should have a thorough evaluation for clinical insulin resistance syndrome and the patients' management should target both diseases.

There are several limitations that warrant mention. The cross-sectional method used in this study was not able to determine the causal relationship between erosive esophagitis and insulin resistance. This study only aimed to compare the HOMA-IR index (insulin resistance) between non-erosive and erosive gastroesophageal reflux disease patients. Therefore, further studies with longitudinal design and paired controls are required to learn possible causal relationships between insulin resistance and esophageal erosion. In addition, the pathophysiology and interactions of other factors are complicated; therefore, further studies to evaluate these related factors are required. Lastly, the diagnosis of GERD in this study only used GERD-Q questionnaire which is not as good as using pH-metry for diagnosis.

CONCLUSION

In summary, our data demonstrate that subjects with esophageal erosion have higher insulin resistance as measured by HOMA-IR index, compared with subjects without esophageal erosion. This finding suggests an early detection of insulin resistance in patients with esophageal erosion.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

The authors declared no conflict of interest.

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