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Original Article

Visceral fat thickness of erosive and non-erosive reflux disease subjects in Indonesia's tertiary referral hospital

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ABSTRACT

Background: There has been an increasing number of reports regarding the correlation between obesity and gastroesophageal reflux disease (GERD). Visceral fat thickness is thought to be a risk factor for GERD and its severity. Several studies have conflicting results, so this study aimed to determine visceral fat thickness difference between erosive and non-erosive reflux disease.
Methods: A cross-sectional study of 56 adult subjects with GERD symptoms was held at Cipto Mangunkusumo National General Hospital between April and November 2018. Gastroesophageal Reflux Disease Questionnaires (GERDQ) were utilized to determine the presence of GERD. Ultrasonography was used to determine visceral fat thickness. Esophageal erosions were diagnosed using upper gastrointestinal endoscopy. The difference in visceral fat thickness between esophagitis and non-esophagitis group was analysed using T-test.
Results: From 56 total subjects, 55.4% have erosive reflux disease (ERD), in which were dominated by subjects with grade A esophagitis (64.5%) based on Los Angeles Classification of Esophagitis (LA classifications). There was no significant difference of visceral fat thickness between non-erosive reflux disease (NERD) and ERD (p = 0,831). There was, however, an increasing trend of visceral fat thickness with the advancing severity of esophagitis, although statistical significance was not reached.
Conclusion: Visceral fat thickness as measured by ultrasonography has no significant difference between NERD and ERD.

1. Introduction

The prevalence of gastroesophageal reflux disease (GERD) is increasing globally. From one systematic review we found that there is an increasing prevalence between studies held before 1995 and after [1]. An observational study conducted by Syam et al. in Indonesia showed that 22,7% subjects who underwent upper gastrointestinal endoscopy had esophagitis [2].

GERD's primary manifestation is typical complaint of “heartburn” [2,3], and diagnosis is made based on GERDQ [4]. GERD is classified to non-erosive reflux disease, erosive reflux disease, and Barret's esophagus. This classification describes gradient of severity by findings on endoscopy. Many researches mainly from western countries have proven that obesity particularly abdominal obesity increase the risk of GERD and esophageal adenocarcinoma [5]. The mechanism is not fully understood. Obesity is initially thought to play a role in GERD by increasing the intragastric pressure and gastroesophageal pressure gradients, a similar mechanism found in pregnancy. However, there have been many other theories proposed in addition to mechanical factors; humoral factors such as

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adipocytokines and other proinflammatory cytokines are thought to play important role in the occurrence of GERD and its severity in obesity [6].

In Asia, this subject has been studied and the results are still conflicting. A study regarding BMI and GERD in Japan showed that the prevalence of GERD was significantly higher in obese subjects [7]. A study by *Chung* et al. in South Korea reported that suffering from the metabolic syndrome significantly increased the risk of GERD and the severity of esophagitis reflux [8]. In Japan, a study conducted by *Niigaki* et al. in health screening subjects, showed that waist circumference as a parameter of visceral fat accumulation was associated with an increased risk of GERD and significant esophagitis reflux when compared to other parameters such as dyslipidemia, hypertension, and hyperglycemia [9]. Nam et al. specifically measure the visceral adipose tissue volume in Korean subjects, and found that visceral fat tissue is associated with an increased risk of erosive esophagitis [10]. But study from Japan by Gunji et al. did not achieve a significance between visceral fat and erosive esophagitis. In Indonesia, study from Budiyani et al. have found that insulin resistance is significantly corelated with risk of erosive esophagitis [11]. Therefore, this study is aimed to determine the relationship between central obesity measured by visceral fat thickness and the risk of erosive esophagitis in GERD subjects.

2. Methods

2.1. Study subjects

This is a cross sectional study involving 56 subjects with GERD symptoms, conducted from April to November 2018 at Cipto Mangunkusumo National General Hospital in Jakarta, Indonesia. The inclusion criteria were: patients aged above 18 years old and suffering from GERD diagnosed through GERD questionnaires (GERDQ score 8 and above). Patients were excluded if; 1) refused to participate in research, 2) were known to be pregnant or using hormonal drugs (such as contraceptive pills), 3) were known to have esophageal malignancies or other structural abnormalities of the esophagus, 4) have ascites or intra-abdominal tumors, 5) long term use of proton pump inhibitors or H2 receptor antagonists, 6) long term use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs). Subjects were asked for their willingness to take part in this study and filled consent form. Ethical clearance was obtained from The Ethics Committee of the Faculty of Medicine, University of Indonesia.

2.2. Measurements

Subjects who met the research criteria were explained about the preparation of data collection such as interviews about age, sex, and history of illness, physical examination consisted of measuring blood pressure, body mass index, and waist circumference, abdominal ultrasonography examination, dan esophagogastroduodenal endoscopy. The visceral fat thickness was measured using ultrasonography, and defined by the distance between posterior surface of rectus abdominis muscle and anterior surface of aorta [12]. After 8 h fasting, the subject was placed on a flat bed and requested to be relax. The examination was performed by experienced medical staff using 3–5 MHz convex transducer placed without pressure at 1–5 cm above umbilical scar, and the measurement was taken at the end of expiration to eliminate pressure of the abdomen. The subjects underwent endoscopy for upper gastrointestinal tract which was performed by our experienced staff at our endoscopy center. Esophagitis was defined as mucosal break according to Los Angeles Classification of esophagitis [13].

2.3. Statistical analysis

Data tabulation used the Microsoft Excel © 2010 program. Nominal data were presented in percentage. Normally distributed numerical data presented as mean (standard deviation), while not normally distributed one presented as median (min, max). Bivariate analysis was carried out to assess the relationship between visceral fat thickness and the severity of GERD using unpaired T-test.

3. Results

This study involved 56 patients with GERD. The demographic and anthropometric characteristics of the research participants can be seen in Table 1.

More than half of the subjects of this study suffered from erosive reflux disease (55.4%), in which was dominated by the severity of class A esophagitis based on the Los Angeles Classification, affecting as many as 64,5% of all ERD patients. Male participants were more likely to experience ERD (64,3%) when compared to female participants (52,4%). In the age group less than 50 years old, the proportion between NERD and ERD was balanced out but in the older group there was an increase in the proportion of ERD (60.7% for ERD vs 39.3% for NERD) (Table 2).

The distribution data of visceral fat were normal, so an independent T-test was performed to determine the mean difference between the two groups and its significance (Table 3).

Furthermore, we found that there was a trend of increasing visceral fat thickness toward the greater severity of esophagitis (Table 4).

4. Discussions

In this study we found that 75% of the subjects were women. GERD generally affects women more frequently [1,3]. NERD

Table 1
Demographic and anthropometric characteristic of research participants.

Variable		Value
Female, n (%)		42 (75)
Age < 50 years, n (%)		28 (50)
BMI (median, min − max)		22,8 (11,2–36.0)
Waist circumference (cm, mean, SD)		75.3 (12.69)
Diabetes Mellitus, n (%)		5 (8.9)
Hypertension, n (%)		1 (1.8)
Visceral fat thickness (mm, mean, SD)		48.52 (19.53)
ERD, n (%)		31 (55.4)
Esophagitis severity	Grade A, n (%)	20 (35,7)
	Grade B, n (%)	6 (10.7)
	Grade C, n (%)	5 (8.9)

Data was presented in percentage. Mean (SD) was used for normally distributed data. BMI: body mass index, SD: standard deviation; ERD: erosive reflux disease.

Table 2
Characteristics of NERD and ERD participants.

Variables		NERD	ERD
Female, n (%)		20 (47,6)	22 (52,4)
Age < 50 years, n (%)		14 (50)	14 (50)
BMI	Underweight, n (%)	6 (60)	4 (40)
	Normal, n (%)	7 (36,8)	12 (63,2)
	Overweight, n (%)	12 (44,4)	15 (55,6)
	Risk of obesity, n (%)	5 (38,5)	8 (61,5)
	Obese grade I, n (%)	5 (41,7)	7 (58,3)
	Obese grade II, n (%)	2 (100)	0 (0)
Normal waist circumference, n (%)		15 (38,5)	24 (61,5)
DM, n (%)		3 (60)	2 (40)
Hypertension, n (%)		0 (0)	1 (100)

Data was presented in percentage. BMI: body mass index. NERD: non-erosive reflux disease; ERD: erosive reflux disease.

Table 3
Mean difference of visceral fat thickness between the group of NERD and ERD subjects.

	Visceral fat thickness (mm), average (SD)	
NERD (n = 25)	47,9 (17,67)	p = 0.831
ERD (n = 31)	49,0 (21,19)	

T-test analysis of visceral fat thickness between ERD and NERD group. P value < 0.05 was considered significant; SD: standard deviation; NERD: non-erosive reflux disease; ERD: erosive reflux disease.

Table 4
Differences in mean visceral fat thickness between each esophagitis severity groups.

	Visceral fat thickness (mm. Average, SD)
Grade A (n = 20)	47,6 (22,96)
Grade B (n = 6)	50,0 (18,56)
Grade C (n = 5)	53,5 (19,56)

P value < 0.05 was considered significant; SD: standard deviation; NERD: non-erosive reflux disease; ERD: erosive reflux disease.

commonly affects women whereas ERD and Barret's esophagus usually affects men, this is thought to be caused by higher symptoms perception in women compare to men [14]. As seen in this study, men was more likely to experience ERD (64,3%), while the amount of NERD and ERD women are not markedly different. One trial involving model rats showed that estrogen has protective effect against esophageal mucosal damage [15]. Estrogen has anti-inflammatory effect by targeting the tissue factors so the recovery of the wound is faster [16]. These explained the reason behind the propensity of men to have ERD. Other study by Nam et al. in Korea which studied GERD subject from a large number of medical check-up patients also found that women have the propensity to have NERD and men to have reflux esophagitis [17].

The prevalence of GERD increases with age [18]. The complication rate is also increased as the age increased. This is due to increased gastric acid exposure in older age compare to younger age, and it is also caused by diminished esophageal clearance and damage to esophagogastric junction [19]. In our study the proportion of NERD and ERD subjects are balanced in under 50 years old group, but in older age group there is an increase in ERD frequency.

In this study almost half of the research participants (48,2%) were overweight. This is in accordance with the higher prevalence of GERD in overweight subjects. As many as 21,4% of the research participants belonged to the category grade I obesity. In addition, 17,9% of the research participants belonged to the classification of underweight. In contrast, in a study by Arie et al., in 2017 in Tebet District General Hospital, Jakarta as one of the secondary healthcare facilities, the largest proportion of the research participants (63,7%) were obese and only 3,3% were underweight [20]. A study conducted to morbidly obese patients (BMI > 35) who will undergo bariatric surgery found more esophageal manometry abnormalities that were associated with GERD [21], which BMI is extremely more severe than the mean BMI of our study. Underweight GERD subjects have been studied in Japan where it was found that these subjects have more severe symptoms and lower quality of life compare to normoweight GERD subjects [22].

Although the population of this study was dominated by overweight patients, based on the waist circumference measurements, most of the research participants (69,6%) had normal waist circumference. Indeed, although most of the subjects included in the category of overweight, only a portion of those were grade I obese (21,4%) and only 3,6% were grade II obese. It can be concluded that only few of the subjects in this study were having metabolic syndrome profile, even though we cannot conclude whether there were subclinical changes toward metabolic syndrome. This finding is different from Budiyani et al. in which although the GERD subjects' mean BMI was categorized as normoweight, the mean waist circumference was higher compare to our subjects' mean waist circumference. In Budiyani et al. study, the waist circumference and HOMA-IR gave significant mean difference between NERD and ERD subjects.

Unlike the epidemiological data which states that most cases of GERD are NERD [23], in this study ERD subjects were slightly more numerous than NERD subjects (55,4% vs 44,6% respectively), although most ERD subjects were still in the very mild or grade A category (80% of all ERD subjects). A systematic review by Sharma et al. highlighted Asia continent where the esophagitis prevalence was increasing between 1992 and 2001, and this increase remained significant after adjusting sex, race, age, and hiatal hernia existence [24]. In the report, they mentioned the higher prevalence of GERD in Japan and Malaysia, which the latter has similar geographical characteristics with Indonesia. The dominance of ERD subjects is estimated to be caused by the condition of the population in tertiary hospitals as a place of research, where patients who seek treatment are the final reference after treatment from various previous hospitals. This allows patients who come to our facilities in the more severe spectrum of the disease.

To date, there is no report on the relationship between the visceral fat thickness measured by ultrasonography and the severity of GERD. A previous study in South Korea by Nam et al. measured the visceral fat thickness using CT scans and the occurrence of erosive esophagitis. Subjects in that study had a higher BMI, which was 23.7 ± 2.9 kg/m2 for the normal group and 25.1 ± 2.9 kg/m2 for the erosive esophagitis group and had a higher mean waist circumference (85.2 ± 8.2 cm and 88.8 ± 7.5 cm respectively) [25]. In this study, Nam proved that visceral adiposity was related to increasing risk of erosive esophagitis in men and women.

In another study by Gunji et al. in male Japanese population found that other factors such as alcohol consumption, heavy smokers, metabolic changes, and hiatal hernia increased the risk of erosive esophagitis, while visceral fat adiposity measured by CT scan did not make a significant correlation [26]. Study by Gunji, which has numerous study subjects, has normal mean BMI, similar to our study. They also made more adjustments to confounding factors. Other study by Chung et al. in Korean population also found that the severity of esophagitis was dominated by LA grade A and B [8], similar to our study. Lower obesity rate and severity of esophagitis shown by these studies showed possibilities that the relationship between obesity and esophagitis will appear in more severe cases.

Differences in these characteristics are estimated to be influenced by the diversity in cultural background [1,24], diet [27–29], and lifestyle [30]. Many studies have reported demographical difference in GERD, but the underlying pathophysiology have not been fully understood. One of the proposed explanation other than genetics is understanding each society about GERD [24]. The term "heartburn" itself as one of the most common symptoms of GERD is not a common term in Asian countries especially in Indonesia, although nowadays as technology raises to be more accessible to the people so that it can help towards GERD understanding. Other than that, *H. pylori* eradication conversely related to the prevalence of GERD [26], though the data about this statement were still conflicting. Consumption of specific kinds of food also have related to GERD in some populations [27–29]. Inactive physical activity has been linked to obesity. But rigorous physical activity is also thought to increase the risk of GERD [30].

The difference in mean visceral fat thickness in NERD subjects was only slightly lower than ERD subjects (4.79 cm vs 4.9 cm respectively). This is not in accordance with the results of the difference in the mean visceral fat thickness measured using the same technique between patients with various degree of liver steatosis by Eifler et al. in Brasilian population [12]. They came up with a cut point of 9 cm for women and 10 cm for men, higher than the mean visceral fat thickness from our study. Further studies are indicated to assess appropriate mean visceral fat thickness in Indonesian population.

Visceral fat thickness is also subjected to individual body frame size, such as height, weight, waist circumference, and body mass index. Visceral fat thickness cannot fully describe the propensity of fat storage in each individual. In a study by Oh et al. in Korea showed that visceral-to-subcutaneous fat ratio (VSR) correlated with at least to 2 metabolic risk factors better compared to visceral or subcutaneous fat area [31].

Though in this study there's no significant correlation between mean visceral fat thickness and erosive esophagitis, we found a trend of increasing mean visceral fat thickness as esophageal erosion progress, similar to mean visceral fat thickness between NERD and ERD. Some studies have explored factors related to the severity of esophagitis. Gastric acid exposure, hiatal hernia, and male sex increase the risk of more severe esophageal erosion [32,33]. In our study, the mean visceral fat thickness increase consistently as esophageal erosion progress. To our knowledge, there has been no study that compares the thickness of visceral fat with the severity of esophagitis but it should be noted that the number of acquired subjects with GERD within our period of study is small and the subjects have normal mean BMI as well as waist circumference. Further study with more samples is needed to reflect Indonesian population, and the use of VSR is needed to be considered to better reflect individual fat storage.

5. Conclusions

This study showed no significant visceral fat thickness difference between NERD and ERD, but there is a trend of increasing visceral fat thickness along with the advancing of the disease severity.

Conflicts of interest

There is no conflict of interest in this study.

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