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Is Metabolic Syndrome Considered to Be a Risk Factor for Gastroesophageal Reflux Disease (Non-Erosive or Erosive Esophagitis)?: A Systematic Review of the Evidence

Mohammad Mohammadi,[1] Nahid Ramezani Jolfaie,[2] Rooya Alipour,[1] and Mitra Zarrati[1,*]

[1]Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, IR Iran
[2]Department of Nutrition, School of Nutrition and Food Sciences, Isfahan University of Medical Sciences, Isfahan, IR Iran

[*]*Corresponding author*: Mitra Zarrati, Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, IR Iran. Tel: +98-2186704814, Fax: +98-2188622707, E-mail: zarrati_ms@yahoo.com

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Abstract

Context: The incidences of both gastroesophageal reflux disease (GERD) and metabolic syndrome (MetS) have increased in recent years, and it has been suggested that there is a probable association between the two. The aim of this review is to clarify whether or not MetS is a risk factor for the incidence of GERD.

Evidence Aquisition: We searched the PubMed, ProQuest, Ovid, Science Direct, and Google Scholar databases up to February 2015 regarding the relationship between GERD and MetS as found in observational studies. Any studies that evaluated the association between the components of MetS and GERD, as well as any studies examining the association of MetS with Barrett's esophagus or esophageal carcinoma, were excluded.

Results: Thirteen studies met the eligibility criteria. The results of nine studies suggested that there was a higher prevalence of MetS among patients with GERD ($P < 0.05$) and, thus, it could be considered as an independent risk factor for the incidence of GERD. However, in the one study was not observed significant association between GERD and MetS ($P = 0.71$). Two studies in which the prevalence of GERD was compared between individuals with and without MetS showed a higher prevalence of GERD in patients with MetS ($P < 0.05$). However, this finding was not observed in a similar study conducted among female participants, which reported that the different types of MetS were not important factors with regard to the prevalence of erosive esophagitis (P = Not significant).

Conclusions: It can be concluded that MetS may increase the risk of GERD. Consequently, there might be potential benefits to treating the metabolic abnormalities in these patients.

Keywords: Gastroesophageal Reflux, Metabolic Syndrome X, Obesity, Abdominal Obesity, Insulin Resistance

1. Context

Gastroesophageal reflux disease (GERD) is considered to be a common and chronic digestive disease in the United States and in Europe (1, 2). However, the prevalence of GERD has been increasing in Asian countries in recent decades (3, 4). An endoscopic survey conducted in Iran showed the overall prevalence of reflux esophagitis in subjects over 40-year-old with a general health status to be 37% (5).

GERD is commonly characterized by an abnormal backward flow of gastric contents into the esophagus, in which esophagitis can occur as a result of the chronic exposure of the esophagus epithelium to gastric acid, which can cause esophageal mucosal injury, bleeding or ulcers (6-8). GERD is generally considered to be classifiable into three categories: non-erosive esophagitis, erosive esophagitis, and Barrett's esophagus (9, 10). Aside from the most prevalent signs of GERD, namely heartburn and acid regurgitation, there are some other reported symptoms, such as eructation, nausea, sore throat, cough, and chest pain (2, 11). High intra-abdominal pressure, elevated gastric acid production, and abnormal relaxation of the esophageal sphincter can also play an important role in the development of the disease (1, 6). Several risk factors, including old age, male gender, race, family history, obesity, hiatal hernia, smoking, and alcohol consumption, have been identified for GERD (12-14). As the long-term complications of GERD can reduce patients' health-related quality of life and increase their healthcare costs (5, 15), more attention is needed to control the GERD-related risk factors.

On the other hand, metabolic syndrome (MetS) is considered to be a major metabolic disorder worldwide. The prevalence of MetS is estimated to be approximately 24% in the United States, 12% in Europe, and 10% to 40% in most

Asian countries (16, 17). MetS is diagnosed if three or more of the following five medical conditions are met: elevated waist circumference (WC) ($\geq$ 90 cm for men and $\geq$ 80 cm for women), high serum triglycerides (TG) ($\geq$ 150 mg/dL), low levels of high density lipoprotein cholesterol (HDL-C) (< 40 mg/dL in males and < 50 mg/dL in females), elevated blood pressure (BP)) systolic $\geq$ 130 mmHg and/or diastolic $\geq$ 85 mmHg, (and increased fasting blood glucose (FBG) ($\geq$ 100 mg/dL) (18, 19). It has been suggested that visceral adiposity, hypertension, hyperglycemia, and dyslipidemia can all lead to insulin resistance. Thus, patients with MetS are at risk of insulin resistance as well as GERD. As previously mentioned, obesity is one of the common risk factors for GERD (9, 20, 21). According to recent evidence, the incidences of both diseases have been rapidly increasing. Hence, a possible relationship has been hypothesized between MetS and GERD (22). Most studies focusing on the association of obesity with GERD have revealed that obesity can lead to a significant increase in the risk of developing GERD symptoms (23-27). Although several studies have indicated that each criterion of MetS (i.e., abdominal obesity, hyperglycemia, and hypertension) is a risk factor for reflux esophagitis, the relationship between MetS as a whole entity and the occurrence of GERD has not been extensively studied (28-32). Indeed, only a limited number of studies have been performed to determine whether or not MetS can be considered as a risk factor for GERD (20, 22, 33-39). Furthermore, the accumulated evidence regarding their association has not yet been comprehensively reviewed.

1.1. Objectives

We conducted the present systematic review in order to better understand the association between MetS and GERD by focusing on the prevalence of MetS among patients with GERD. With regard to the importance of this study, if it is determined that MetS is able to influence the severity and incidence of GERD, treating and relieving the factors potentially involved in MetS may prove a successful medical intervention for alleviating GERD. Finally, treating MetS and changing people's lifestyles may alleviate GERD and reduce the incidence of more serious complications such as Barrett's esophagus and esophagus cancer.

2. Evidence Aquisition

2.1. Search Strategy

We used the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement to review all articles assessing the association between MetS and the occurrence of GERD. We searched the PubMed, ProQuest, Ovid, Science Direct, and Google Scholar databases up to February 2015. As seen in Table 1, which presents the search strategy used to identify the included articles, keywords relevant to the MetS or GERD sections were linked using "OR" as a Boolean function, and the results of the two sections were combined by utilizing "AND". The search keywords were: ("gastroesophageal reflux" OR "gastro-esophageal reflux" OR "gastro-oesophageal reflux" OR "esophageal reflux" OR "reflux esophagitis" OR "non-erosive esophagitis" OR "erosive esophagitis") AND ("metabolic syndrome" OR "insulin resistance" OR "abdominal obesity" OR "hyperglycemia" OR "hyperlipidemia" OR "hypertension" OR "waist circumference"). We did not use any language or time restrictions in our literature search. The search results from the different databases were combined using EndNote X7 software and any duplicates were removed. An initial screening of the articles' titles and abstracts to exclude irrelevant studies was independently developed by two investigators in separate places so as to guarantee the blindness of the search. Then, the full texts of the remaining articles were examined to determine the eligible studies. A kappa coefficient of 0.78 was used as a measurement of the agreement between the identification and selection of articles. Finally, the results were merged and any differences were resolved by the third investigator. Furthermore, we screened the reference lists of the selected articles in order to identity additional relevant articles (Figure 1).

2.2. Eligibility Criteria

The inclusion criterion for articles selected for review were those studies that evaluated the association between MetS and the occurrence of GERD. Studies were excluded based on any of the following criteria: animal or in vitro studies; studies that only evaluated the relationship between the components of MetS and GERD and did not report any related data on the prevalence of MetS in patients with GERD; and studies that investigated the association of MetS with either Barrett's esophagus or esophageal adenocarcinoma.

2.3. Data Extraction and Quality Assessment

After the two independent researchers had assessed the details of the final eligible studies, a third assessment was performed by another investigator to ensure a final high quality evidence-based analysis. We abstracted the following data from the included papers: first author's name, publication year, place of publication, study design, definition of case and control subjects, sample size, mean age, results, and study quality.

Table 1. Search Strategy

Search Engines	Search Keywords	Number of Search Results
PubMed		
- Component 1: Gastroesophageal reflux	(gastro-esophageal reflux [tiab]) OR (gastroesophageal reflux [tiab]) OR (gastro-oesophageal reflux [tiab]) OR (esophageal reflux [tiab]) OR (reflux esophagitis [tiab]) OR (non-erosive esophagitis [tiab]) OR (erosive esophagitis [tiab])	21,358
- Component 2: Metabolic syndrome	(metabolic syndrome [tiab]) OR (insulin resistance [tiab]) OR (abdominal obesity [tiab]) OR (hyperglycemia [tiab]) OR (hyperlipidemia [tiab]) OR (hypertension [tiab]) OR (Waist Circumference [tiab])	399,827
- Component 1 and Component 2: Gastroesophageal reflux and Metabolic syndrome	(gastro-esophageal reflux [tiab]) OR (gastroesophageal reflux [tiab]) OR (gastro-oesophageal reflux [tiab]) OR (esophageal reflux [tiab]) OR (reflux esophagitis [tiab]) OR (non-erosive esophagitis [tiab]) OR (erosive esophagitis [tiab]) AND (metabolic syndrome [tiab]) OR (insulin resistance [tiab]) OR (abdominal obesity [tiab]) OR (hyperglycemia [tiab]) OR (hyperlipidemia [tiab]) OR (hypertension [tiab]) OR (Waist Circumference [tiab])	416
ProQuest		
- Component 1: Gastroesophageal reflux	ab((gastro-esophageal reflux) OR (gastroesophageal reflux) OR (gastro-oesophageal reflux) OR (esophageal reflux) OR (reflux esophagitis) OR (non-erosive esophagitis) OR (erosive esophagitis))	4739
- Component 2: Metabolic syndrome	ab((metabolic syndrome) OR (insulin resistance) OR (abdominal obesity) OR (hyperglycemia) OR (hyperlipidemia) OR (hypertension) OR (Waist Circumference))	100,258
- Component 1 and Component 2: Gastroesophageal reflux and Metabolic syndrome	ab((gastro-esophageal reflux) OR (gastroesophageal reflux) OR (gastro-oesophageal reflux) OR (esophageal reflux) OR (reflux esophagitis) OR (non-erosive esophagitis) OR (erosive esophagitis)) AND ab((metabolic syndrome) OR (insulin resistance) OR (abdominal obesity) OR (hyperglycemia) OR (hyperlipidemia) OR (hypertension) OR (Waist Circumference))	161
Ovid		
- Component 1: Gastroesophageal reflux	(Gastro-esophageal reflux OR gastroesophageal reflux OR gastro-oesophageal reflux OR esophageal reflux OR reflux esophagitis OR non-erosive esophagitis OR erosive esophagitis). ab.	26,941
- Component 2: Metabolic syndrome	(Metabolic syndrome OR insulin resistance OR abdominal obesity OR hyperglycemia OR hyperlipidemia OR hypertension OR Waist Circumference). ab.	502,592
- Component 1 and Component 2: Gastroesophageal reflux and Metabolic syndrome	((gastro-esophageal reflux OR gastroesophageal reflux OR gastro-oesophageal reflux OR esophageal reflux OR reflux esophagitis OR non-erosive esophagitis OR erosive esophagitis) and (metabolic syndrome OR insulin resistance OR abdominal obesity OR hyperglycemia OR hyperlipidemia OR hypertension OR Waist Circumference)). ab.	607
Science Direct		
- Component 1: Gastroesophageal reflux	TITLE((gastro-esophageal reflux) OR (gastroesophageal reflux) OR (gastro-oesophageal reflux) OR (esophageal reflux) OR (reflux esophagitis) OR (non-erosive esophagitis) OR (erosive esophagitis))	48,354
- Component 2: Metabolic syndrome	TITLE ((metabolic syndrome) OR (insulin resistance) OR (abdominal obesity) OR (hyperglycemia) OR (hyperlipidemia) OR (hypertension) OR (Waist Circumference))	41,946
- Component 1 and Component 2: Gastroesophageal reflux and Metabolic syndrome	TITLE ((gastro-esophageal reflux) OR (gastroesophageal reflux) OR (gastro-oesophageal reflux) OR (esophageal reflux) OR (reflux esophagitis) OR (non-erosive esophagitis) OR (erosive esophagitis)) and TITLE((metabolic syndrome) OR (insulin resistance) OR (abdominal obesity) OR (hyperglycemia) OR (hyperlipidemia) OR (hypertension) OR (Waist Circumference))	210

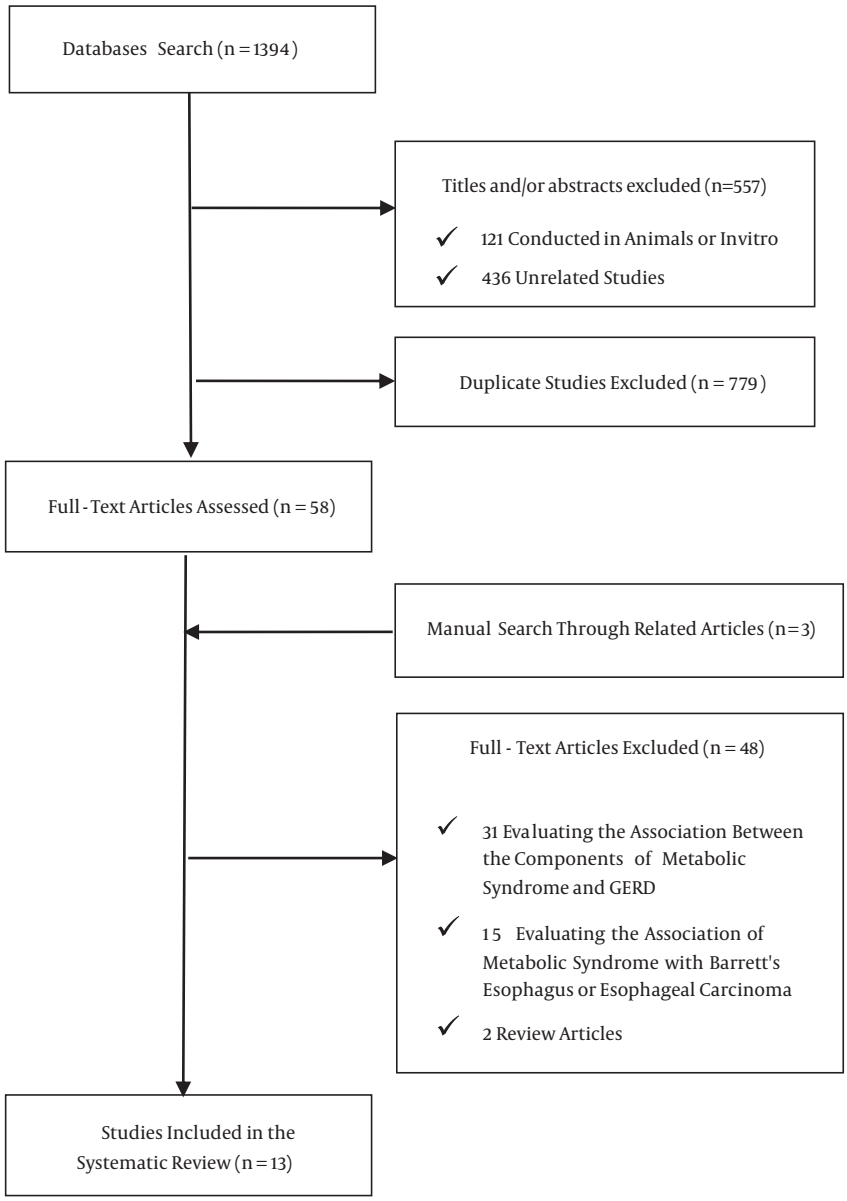

Figure 1. Flow Chart Representing the Study's Selection Process

We used the previously validated nine-point Newcastle-Ottawa scale (NOS), a method for elevating the methodological quality of non-randomized studies such as case-control and cohort studies, to score the included observational articles (40, 41). The three major components of the NOS scoring technique are: selection of participants (maximum score = 4*), comparability of study groups (maximum score = 2*), and measurement of the outcome or exposure (maximum score = 3*). High quality studies were considered to have a total of seven or more points, while low quality studies were considered to have less than seven points. The maximum score was nine points, which could represent the highest quality of study.

3. Results

Our initial database search retrieved 1394 reports. After an initial screening of titles and abstracts, 58 articles

were reviewed against the eligibility criteria. Eventually, ten observational studies were included in the final analysis, and three additional papers were selected by hand after screening the reference lists of the articles. We excluded the remainder of the articles, including the review articles (n = 2) and those that either evaluated the association between the individual components of MetS and GERD (n = 31) or the association of MetS with Barrett's esophagus or esophageal carcinoma (n = 15). All of the 13 included studies were conducted in Asian countries, and they were either case-control or cross-sectional studies. A total of 23,687 participants aged 37- to 60-year-old were included in these studies. The average quality score of the included articles was 6.5 points. Six of them were classified as high quality articles (22, 30, 31, 33, 34, 39), while the remaining seven studies were classified as low quality (20, 32, 37, 42-45). Information regarding the characteristics of the articles and the participants, the methodological quality of the articles, and the outcome measures of the articles is collected in Tables 2 and 3.

Most of the previous research studies focused on the various risk factors of GERD, including the components of MetS, obesity, and smoking. In some of these studies, the prevalence of MetS as a whole entity and as an independent risk factor for GERD, in addition to the assessment of the relationship between the individual components of MetS and GERD, were investigated. Further, in a few studies, the prevalence of GERD in patients with MetS was been compared with that in subjects without MetS. We reviewed all of the related studies that focused on the association between MetS and GERD. The outcomes of and differences between the selected studies will now be summarized in detail.

3.1. The Prevalence of MetS in Patients with GERD

Several studies were conducted in a Taiwanese population to evaluate the association between metabolic risk factors such as MetS rate, body mass index (BMI), WC, BP, lipid profile, and blood glucose and the severity of erosive esophagitis in patients with and without erosive esophagitis. Chua et al. (31) observed that there was a significant increase in the measurements of BMI, WC, BP, and TG, as well as a significant decrease in low density lipoprotein cholesterol (HDL-C) levels, among patients with erosive esophagitis ($P < 0.05$ for all). They reported that the prevalence of MetS in patients with erosive esophagitis was 27.8%, while in the control group it was 17.8%. Chua et al. (31) also revealed that MetS was significantly associated with a higher risk of reflux esophagitis (Odds ratio [OR]: 1.76, 95% confidence interval [CI]: 1.27 - 2.44, P = 0.001). Similar findings were also reported in a study by Hsu et al. (42). They found that there was a significant positive association between the prevalence of MetS and erosive esophagitis (OR: 1.6, 95% CI: 1.04 - 2.45, P = 0.03). Indeed, they showed that the prevalence of MetS was higher in patients with erosive esophagitis than in the control group (28.2% vs. 19.8%). In addition, certain risk factors such as old age, male sex, smoking, alcohol consumption, elevated FBG and BP, and higher levels of LDL-C and TG, led to an increasing prevalence of erosive esophagitis ($P < 0.05$ for all) (42). On the other hand, Tai et al. (45) compared the prevalence of MetS in obese patients with and without erosive esophagitis. They revealed that although obese patients with erosive esophagitis had a higher prevalence of MetS than patients without erosive esophagitis, no significant differences were observed between them (75.0% vs. 63.6%, P = 0.07). Indeed, they concluded that the presence of MetS was not associated with a higher prevalence of erosive esophagitis (OR: 1.13, 95% CI: 0.6 - 2.13, P = 0.71). However, increased WC ($P < 0.01$) and insulin resistance (P = 0.02), as well as the presence of reflux symptoms (P = 0.01), were independent risk factors associated with erosive esophagitis (45).

Chung et al. also assessed the association of MetS and visceral obesity with reflux esophagitis among 7078 Koreans who were referred for a health check-up (30). Following endoscopic examination, 3539 subjects with a diagnosis of erosive esophagitis were compared with individuals without erosive esophagitis as a control group. After adjustment for age and sex, the results suggested that smoking, alcohol consumption, and each of the components of MetS were significant risk factors for reflux esophagitis ($P < 0.001$ for all). Moreover, they reported that the prevalence of MetS in patients with reflux esophagitis was significantly higher than in those without reflux esophagitis (26.9% vs. 18.5%, $P < 0.001$), concluding that MetS could increase the risk of reflux esophagitis after a multivariate analysis (OR: 1.42, 95% CI: 1.26 - 1.60, $P < 0.001$).

On the other hand, Kallel et al. (32) used a 24-hour pH-metry monitoring method for GERD diagnosis, and they reported that 54 out of 100 individuals were diagnosed with pathological acid GERD. The multivariate regression analysis in their study revealed that higher measurements for WC (P = 0.002) and glucose levels (P = 0.001) were considered to be significant risk factors for GERD. In addition, despite the higher BMI ranges in patients with GERD compared to the control group, BMI could not be considered as an independent risk factor for GERD (P = 0.42). Moreover, the prevalence of MetS was higher in patients with GERD than in individuals without GERD (50% vs. 19.56%; P = 0.002), and after adjusting the age, sex, and BMI values, MetS was considered to be an independent factor associated with a 2.82-fold increase in risk of GERD (95%CI: 1.08 - 7.35, P = 0.03).

In another cross-sectional and case-control study (34),

Table 2. Basic Characteristics of the Included Studies (Prevalence of MetS)

Study (Year)	Country	Study Design	Time Period	Definition of Case and Control	Sample Size		Mean Age (Year)	Patients with MetS		P Value	OR (95% CI) P Value	Adjusted Factors	Study Score	Keywords
					Case (M/F)	Control (M/F)		Case, No. (%)	Control, No. (%)					
Chua et al. (2009) (31)	Taiwan	Retrospective case-control	2004-2006	Case: Patients with EE; Control: Healthy individuals without EE	427 (365/62)	427 (365/62)	48.3	118 (27.6)	76 (17.8)	NR	1.76 (1.27-2.44); P = 0.00	Age, gender	7	Erosive esophagitis, metabolic syndrome, reflux esophagitis
Chung et al. (2008) (30)	South Korea	Cross-sectional case-control	2004-2007	Case: Patients with RE; Control: Healthy individuals without RE	3539 (2810/729)	3539 (2810/729)	47.6	26.9 %	18.5%	P < 0.00	1.42 (1.26-1.60); P < 0.00	Age, gender smoking, alcohol, BMI	8	NM
Kallel et al. (2011) (32)	Tunisia	Cross-sectional	2009	Case: Patients with GERD; Control: Healthy individuals without GERD	54; Total: 3/67	46; Total: 33/67	Case: 44.5; Control 37.6	50%	19.56%	P = 0.00	2.82 (1.08-7.35); P = 0.03	Age, gender BMI	6	Body mass index, DeMeester score, gastroesophageal reflux,metabolic syndrome, pH-metry, waist circumference
Wu et al. (2011) (22)	China	Case-control	2010	Case: Patients with RE; Control: Healthy individuals without RE	182(82/100	190 (93/97)	Case: 46.2; Control47.2	55 (30.2)	40 (21.1)	P = 0.06	2.01 (1.15-3.50); P = 0.01	Age, gender	8	Metabolic syndrome, reflux esophagitis
Loke et al. (2013) (34)	Taiwan	Cross-sectional case-control	2008	Case: Patients with EE; Control: individuals without EE	507 (419/88)	507 (419/88)	51.2	239 (47.1)	191 (37/7)	P < 0.00	1.47 (1.14-1.89); P = 0.00	Age, gender	7	Erosive esophagitis, metabolic syndrome, central obesity, abnormal liver function, dyslipidemia
Park et al. (2008) (20)	South Korea	Cross-sectional case-control	2006	Case: Patients with EE; Control: Healthy individuals without EE	1679 (86% / 14%)	3358 (59%/41%)	45.2	353 (21)	433 (13)	P < 0.00	1.25 (1.04-1.49); P = 0.01	Age	6	Metabolic syndrome, erosive esophagitis, insulin resistance, fatty liver
Hsu et al. (2011) (42)	Taiwan	Cross-sectional	2007	Case: Patients with EO; Control: Healthy individuals without EO	131 (88/43)	612 (255/357)	Case: 53.6; Control 51.3	37 (28.2)	121 (19.8)	NR	1.60 (1.04-2.45); P = 0.03	None	5	NM
Tai et al. (2010) (45)	Taiwar	Cross-sectional	2007-2009	Case: Obese patients with EE; Control: Obese patients without EE	84 (41/43)	176 (56/120)	Case: 32.1; Control31.2	63 (75.0)	112 (63.6)	P = 0.07	1.13 (0.60-2.13); P = 0.71	Age	6	NM
Niigaki et al. (2013) (43)	Japan	Cross-sectional	2010-2011	Case: Patients with GERD or RE; Control: Healthy individuals without GERD or RE		3775	52	477 (12.6)		NM	RE: 2.21 (1.63-3.00); P < 0.00, GERD: 1.8 (1.46-2.39); P < 0.00	NM	5	Metabolic syndrome, obesity, reflux esophagitis, gastroesophageal reflux disease
Leeet al. (2009) (33)	Taiwar	Cross-sectional	2003-2006	Case: Patients with MetS, erosive or non-erosive reflux disease; Control: Patients without MetS and with erosive or non-erosive reflux disease		3669	56.3	498 (13.6)		NM	[a]1.75 (1.29-2.38); P < 0.05	Gender, smoking, short-term use of PPI or H2RA	7	NM

Abbreviations: BMI, body mass index; CI, confidence interval; EE, erosive esophagitis; EO, erosive oesophagitis; GERD, gastroesophageal reflux disease; F, female; M, male; MetS, metabolic syndrome; NM, not mentioned; NR, not reported; OR, odds ratio; RE, reflux esophagitis.
[a] Relative risk of progression from non-erosive to erosive state in patients with MetS.

5015 patients underwent an upper endoscopy. A total of 507 patients with erosive esophagitis and 507 normal individuals as the control group were selected and matched according to age and gender. Several factors such as BMI, liver enzymes, and the components of MetS were assessed. The levels of BMI, WC, BP, aspartate amino transferase/glutamate oxaloacetate transaminase (AST/GOT) and alanine amino transferase /glutamate pyruvate transaminase (ALT/GPT), FBG, BP, and TG, as well as the ratios of total cholesterol (TC)/HDL-C and LDL-C/HDL-C, were significantly higher in patients with erosive esophagitis compared with the controls, while the HDL-C levels were lower in the case group. Univariate and multivariate logistic regression analysis in this study showed that central obesity, hypertension, hyperglycemia, hypertriglyceridemia, TC/HDL-C > 5, AST > 37 U/L, and ALT > 40 U/L could be significantly associated with a higher probability of developing erosive esophagitis ($P < 0.05$ for all).

Loke et al. (34) observed that the prevalence of MetS was significantly higher in patients with erosive esophagitis than in normal individuals (47.1% vs. 37.7%; $P < 0.005$), and also that they had a higher risk of reflux esophagitis (OR: 1.47, 95%CI: 1.14 - 1.89, $P = 0.003$).

One other study was conducted to determine whether MetS and insulin resistance were risk factors for the development of erosive esophagitis (20). Some 1679 individuals out of 4206 subjects who had been referred to the medical screening center in South Korea between January and De-

Table 3. Basic Characteristics of the Included Studies (Prevalence of GERD)

Study (Year)	Country	Study Design	Time Period	Definition of Case and Control	Sample Size		Mean age (Year)	Patients with GERD		P Value	OR (95% CI); P Value	Adjusted Factors	Study Score	Keywords
					Case (M/F)	Control (M/F)		Case, No. (%)	Control, No. (%)					
Hirata et al. (39) (2012)	Japan	Cross-sectional	2009-2011	Case: T2DM patients with MetS; Control: T2DM patients without MetS	28 (9/19)	38 (18/20)	Case: 67; Control 63	[a] 18/10	33/5	P = 0.03	NR	Age, gender	7	Gastroesophageal reflux symptom, metabolic syndrome, visceral fat, adiponectin
Sogabe et al. (37) (2014)	Japan	Cross-sectional	2008-2013	Case: Women with V-type MetS; Control: Women without S-type MetS	50 F	404 F	Case: 54.9; Control 58.7	6 (12)	45 (11.1)	P = NS	NR	NM	6	NM
Sogabe et al. (44) (2012)	Japan	Cross-sectional	2008-2009	Case: Men with V-type MetS; Control: Men without S-type MetS	145 M	120 M	Case: 56.1; Control 57.9	41 (28.3)	14 (11.7)	P < 0.01	3.80 (1.71-8.47); P < 0.00	NM	6	Erosive esophagitis, metabolic syndrome, subcutaneous fat-type, metabolic syndrome, ultrasonography, visceral fat-type metabolic syndrome

Abbreviations: CI, confidence interval; GERD, gastroesophageal reflux disease; F, female; M, male; MetS, metabolic syndrome; NM, not mentioned; NR, not reported; NS, not significant; OR, odds ratio; S-type, subcutaneous type; T2DM, type 2 diabetes mellitus; V-type, visceral type.
[a] Frequency scale for the symptoms of GERD (FSSG) scores < 8 / ≥ 8.

cember 2006 with erosive esophagitis were chosen as the case group, while 3358 subjects with normal endoscopy results and no reflux symptoms were selected for the control group. The groups were only matched for age. After comparing the levels of WC, BP, TG, and insulin resistance, as well as the rate of fatty liver, between the two groups, the results showed that all of these factors were significantly higher among patients with erosive esophagitis, which could be related to the increased risk of erosive esophagitis (P < 0.001, P = 0.047, P = 0.003, P = 0.011, P < 0.001, respectively). Moreover, the results of a multiple logistic regression analysis demonstrated that the prevalence of MetS was higher among patients with erosive esophagitis than in the control group (21% vs. 12%; P < 0.001), with a significant odds ratio for the risk of erosive esophagitis (OR: 1.25, 95% CI: 1.04 - 1.49, P = 0.01). Hence, there was a significant association between MetS and erosive esophagitis. In addition, comparing the severity of erosive esophagitis according to the Los Angeles (LA) classification suggested that MetS was significantly associated with a higher severity of erosive esophagitis. Thus, it could be considered as a predictive factor for erosive esophagitis (P for linear trend = 0.001).

In a study by Wu et al. (22), 182 patients with reflux esophagitis who were diagnosed by an upper endoscopy were selected as the case group, while 190 subjects with normal endoscopy results were randomly selected as the control group and then matched for age and gender with the cases. It was observed that the levels of FBG and WC and the waist to hip ratio (WHR) were significantly higher among patients with reflux esophagitis compared with the control group (P < 0.05 for all). A positive dose-response relationship was seen between the prevalence of reflux esophagitis and WHR (P < 0.01), TG (P = 0.02), and FBG (P = 0.02), while an inverse dose-response relationship was observed between reflux esophagitis and the levels of HDL-C (P = 0.02) in male individuals. The assessment of MetS rates revealed that although there were no significant differences in the prevalence of MetS between the two groups (30.2% vs. 21.1%; P = 0.06), there was a significant positive association between MetS and reflux esophagitis (OR: 2.01, 95% CI: 1.15 - 3.50, P = 0.01).

Another study, which was conducted in a Japanese population between April 2010 and March 2011, included 3775 adults who had been referred to a medical center for their routine annual health check-ups (43). 320 patients with reflux esophagitis and 604 patients with GERD were diagnosed by either endoscopic examination, the criterion of a QUEST score of ≥ 6, or their latest medical treatment for GERD. The presence of MetS was also observed in 477 of the study population. The multiple logistic regression analysis used to identify the independent risk factors associated with the presence of reflux esophagitis and GERD showed that specific factors such as male sex (P < 0.0001), the presence of hiatal hernia (P < 0.0001), gastric mucosal atrophy (P < 0.0001), visceral fat accumulation (P = 0.001), and dyslipidemia (P = 0.02) were significant predictive factors for the presence of both diseases. In addition, it was observed that the presence of MetS was considered to be a significant risk factor for the prevalence of both reflux esophagitis (OR: 2.21, 95% CI: 1.63 - 3.00, P < 0.0001) and GERD (OR: 1.871, 95% CI: 1.463 - 2.393, P < 0.0001), and it could also aggravate the reflux symptoms in patients with or without reflux esophagitis.

The role of several metabolic risk factors in the development of GERD has been assessed among 19,812 normal

individuals (33). Subjects with MetS and non-erosive or erosive esophagitis were identified by repeated upper endoscopy and selected for the case group (n = 3669) based on the severity of their esophagitis (non-erosive or erosive) according to the LA classification. Within three consecutive study periods, 12.2%, 14.9%, and 17.9% of non-erosive cases, respectively, progressed to the erosive esophagitis stage, while 42.5%, 37.3%, and 34.6% of patients with erosive esophagitis, respectively, regressed to the non-erosive stage. The results obtained from the multivariate analysis revealed that particular factors such as male sex, BMI $\geq$ 27, smoking, and heavy drinking could independently increase the likelihood of progression from non-erosive to erosive esophagitis, along with reducing the likelihood of disease regression ($P < 0.05$ for all). Furthermore, it was shown that the short-term use of acid suppressants could increase the probability of regression of erosive esophagitis to the non-erosive stage ($P < 0.05$). Moreover, MetS was shown to be significantly associated with the progression of the disease to erosive esophagitis, which could indicate that patients with MetS have a significant risk of erosive esophagitis (relative risk [RR]: 1.75, 95% CI: 1.29 - 2.38, $P < 0.05$).

3.2. The Prevalence of GERD in Patients with MetS

Hirata et al. (39) conducted a cross-sectional study to determine the association of visceral fat accumulation, adiponectin, and MetS with GERD symptoms in 66 Japanese individuals with type 2 diabetes. The frequency scale for the symptoms of GERD (FSSG) questionnaire was used to evaluate the reflux symptoms in patients with GERD. Patients were considered to be positive if their FSSG scores were eight or above. Bioelectrical impedance analysis was used to measure the visceral fat area of the included patients. In addition, subjects with MetS were also diagnosed according to the Japanese guidelines for MetS. The results revealed that there were no significant differences in age and gender between the group with MetS (n = 38) and the without MetS (n = 28). Comparing the FSSG score, anthropometry, and laboratory outcomes between the two groups showed that the prevalence of the FSSG score $\geq$ 8 ($P = 0.03$), the mean values of the FSSG score ($P = 0.01$), BMI ($P = 0.002$), WC ($P = 0.016$), TG ($P = 0.011$), and BP ($P = 0.009$) were substantially higher among type 2 diabetic patients with MetS than in patients without MetS. Moreover, these findings indicated that there was a multiplicative effect on the GERD symptoms score followed by the coexistence of MetS and low levels of serum adiponectin ($P = 0.04$).

In two cross-sectional studies conducted by Sogabe et al. (37, 44), the association between the different types of MetS and erosive esophagitis in Japanese men and women with MetS was investigated. Indeed, a question was posed regarding whether or not there was a difference in the prevalence of erosive esophagitis between patients with the visceral fat type MetS (V-type MetS) and patients with the subcutaneous fat type MetS (S-type MetS). The studies' participants consisted of 454 women and 265 men with MetS who underwent a certain health check-up. Comparing the prevalence of erosive esophagitis between the women with V-type MetS and the women with S-type MetS showed that there were no significant differences between the two groups. More precisely, the logistic regression analysis illustrated that hiatal hernia ($P < 0.001$), hemoglobin A1c (HbA1c) ($P < 0.05$), and the presence of H. pylori ($P < 0.005$) could be considered as significant predictors of the prevalence of erosive esophagitis in women with MetS, whereas the types of MetS were not found to be important factors in the prevalence of erosive esophagitis. However, the study that was conducted among men showed that the frequency of erosive esophagitis was significantly higher in patients with V-type MetS than in patients with S-type MetS. Further, according to the logistic regression analysis, the V-type MetS (OR: 3.80, 95% CI: 1.71 - 8.47, $P < 0.005$) was found to be a remarkable predictor of the increased prevalence of erosive esophagitis, as was the presence of hiatal hernia ($P < 0.001$).

4. Discussion

The present systematic review was performed to provide a comprehensive overview of the evidence on the association between MetS and GERD occurrence. In this study, MetS has been considered and studied as a whole entity, which can be seen as an innovation.Regarding the association between MetS and GERD, only two studies failed to show any significant results (37, 45), while the rest of the studies reported a strong relationship between the two conditions (20, 22, 30-34, 39, 42-44). Generally, the results showed that there could be a bidirectional relationship between MetS and GERD, which means that a higher prevalence of MetS might lead to a higher prevalence of GERD and, conversely, that a higher prevalence of GERD might lead to a higher prevalence of MetS. However, the exact prevalence of MetS in patients with GERD varied in the reviewed studies, which might be due to differences in sex distribution, race, age, and the methods used to diagnose GERD and MetS. Moreover, the results demonstrated that the prevalence of erosive esophagitis in men with MetS was higher in patients with V-type MetS than in patients with S-type MetS, while no relationships were reported between erosive esophagitis and the types of MetS in women with MetS (37, 44), which could be due to the greater accumulation of visceral fat in men compared to the accumulation of subcutaneous fat in women (29). Many other studies

have also reported some significant positive associations between GERD and its other risk factors, including the individual components of MetS, obesity, hiatal hernia, insulin resistance, smoking, and alcohol consumption (20, 22, 30-34, 37, 39, 42-45). It is believed that MetS and GERD might have a common pathogenesis (22). Although the precise mechanism of the higher prevalence of GERD among patients with MetS remains unclear (43), several mechanisms showed a few associations between each component of MetS and the prevalence of GERD. Results have shown that elevated WC, expressed as central, abdominal or visceral obesity, could independently increase the risk of GERD (20, 30, 31, 33, 34, 42, 43, 45). Indeed, as abdominal obesity significantly caused metabolic abnormalities, it could also contribute to the development of GERD (29, 46). Previous meta-analysis studies corroborated this finding, reporting that central adiposity could be strongly associated with esophageal inflammation and reflux esophagitis (47). Moreover, several studies observed that high BMI ranges, representing obesity, could increase the risk of GERD (31, 33, 34, 42). However, conflicting results have been reported in other studies, suggesting that no significant differences were observed in BMI ranges among patients with or without GERD (22, 30, 32, 45). Regarding the relationship between GERD and high BMI ranges, most of the studies have reported that a significant association might exist between the two (23, 25, 48, 49), although some studies have revealed that BMI status could not be a predictive factor for the development of GERD, but abdominal obesity could be a risk factor for erosive esophagitis, independently of BMI status (50-54). According to the meta-analysis by Corley et al., there was a significant relationship between BMI status and GERD among the American population (overweight OR = 1.57, 95%CI = 1.36 - 1.80 and obese OR = 2.15, 95%CI = 1.89 - 2.45), but not in Asian countries (55). One could suggest that BMI was not a proper indicator for evaluating the percentage of body fat among Asian populations, which might explain this conflicting result (56). Indeed, elevated BMI ranges are generally considered as overweight or obesity and do not specify visceral fat or subcutaneous fat (29). In particular, as visceral fat plays an important role in the incidence of GERD, elevated BMI ranges without the presence of visceral obesity will not definitely predict the presence of GERD. Studies have shown that visceral obesity, as the main criterion of MetS, could increase either transient lower esophageal sphincter (LES) relaxation, the incidence of hiatal hernia, or even intra-abdominal pressure and acid reflux (22, 57). Moreover, adipose tissue, especially visceral adipocytes, is the major source of adiponectin and pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, which may play important roles in the pathogenesis of GERD (20, 28, 58). It has been shown that IL-6 decreases the contraction of the circular muscles of the esophagus, which can facilitate the backward flow of intragastric contents into the esophagus. In addition, these cytokines were over-expressed in patients with GERD, which might cause a disruption in insulin action and might also stimulate the secretion of hepatic TG (9, 29, 59). Consequently, insulin resistance can lead to other metabolic disorders such as dyslipidemia and hyperglycemia that might play a role in GERD pathogenesis (60, 61).

Dyslipidemia, another component of MetS, can be associated with the development of GERD through disrupting the function of LES, which might cause an increase in the esophagus' exposure to gastric acid (43, 62, 63). Hyperglycemia may also affect the anti-reflux barrier mechanism by modulating the transient LES relaxation (63). Hyperglycemia is usually accompanied by autonomic neuropathy, which can delay gastric depletion and consequently lead to the increased development of GERD (29, 34). Moreover, hypertension is usually diagnosed in patients with MetS, and calcium antagonists are widely used to treat hypertension in such patients. Hence, these calcium-based medications may reduce the LES pressure and inhibit muscle contraction in the esophagus (29). Above all, each component of MetS can somehow affect the incidence of GERD, indicating that the co-occurrence of three or more of the five above-mentioned components might be associated with the incidence of GERD (28).

The main strength of the present systematic review is the large sample sizes examined in the included studies. Also, in all of the studies, the existence of both GERD and MetS was proven by established tests and evaluations rather than relying on the previous registrations, which might have contained errors. Additionally, we tried to perform a systematic and comprehensive search to identify all the relevant published papers, which can lead to an absence of publication bias. However, this review has several limitations. Meta-analysis statistical tests were not performed in this study, which limited the potential to identify more exact and definite results. Also, the designs of all the included studies were either case-control or cross-sectional, meaning that the results may not be completely reliable. There might be several possible discrepancies such as confounding variables, different methods of sampling or observation bias in these studies (64). For instance, no adjustment was made for the amounts of dietary components in the selected studies, which can affect the development of GERD (65, 66). On the other hand, despite the various adjustments for potential confounders, residual confounders related to other factors might be associated with the incidence of GERD. Moreover, it is difficult to specify the temporal sequence between ex-

posure and outcome, since the assessments of MetS and GERD were taken at exactly the same time, which provides weaker evidence of causality than a cohort study. Hence, cohort studies are better able to assess causality by evaluating the exposure predicting outcomes (64, 67). Further studies with a longitudinal design, including cohort studies, are hence needed to reach stronger conclusions.

In conclusion, it was shown that MetS and each component of that condition, especially central obesity, can be considered as independent risk factors for the incidence of GERD, and they can be significantly associated with the increased severity of erosive esophagitis. Therefore, since MetS is a reliable predictive factor for the prevalence of GERD, alleviating the metabolic abnormalities in patients with GERD might cause significant potential benefits in the treatment of GERD. Nonetheless, it is still unclear whether these associations imply a causal relationship between MetS and GERD. Hence, further studies with a longitudinal design, including cohort studies and clinical trials, are needed to reach stronger conclusions and better elucidate these complexities.

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Footnote

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