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BRIEF ARTICLE

Erosive esophagitis associated with metabolic syndrome, impaired liver function, and dyslipidemia

Song-Seng Loke, Kuender D Yang, Kuang-Den Chen, Jung-Fu Chen

Song-Seng Loke, Department of Family Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung 833, Taiwan
Kuender D Yang, Department of Medical Research, Show Chwan Memorial Hospital, Taichung 40601, Taiwan
Kuang-Den Chen, Center for Translational Research in Biomedical Science, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung 833, Taiwan
Jung-Fu Chen, Division of Endocrinology and Metabolism, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung 833, Taiwan
Author contributions: Loke SS, Chen KD and Chen JF contributed to design the study. Loke SS wrote this manuscript and performed the research; Yang KD contributed to design the study and revised the paper critically; Chen KD analyzed the data; Chen JF performed the research.
Correspondence to: Song-Seng Loke, MD, Department of Family Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, 123, Dapi Road, Niaosong District, Kaohsiung 833, Taiwan. loke@adm.cgmh.org.tw
Telephone: +886-7-7317123 Fax: +886-7-7317123
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Abstract

AIM: To investigate whether erosive esophagitis is correlated with metabolic syndrome and its components, abnormal liver function, and lipoprotein profiles.

METHODS: We conducted a cross-sectional, case control study of subjects who underwent upper endoscopy during a health examination at the Health Management and Evaluation Center of a tertiary medical care facility located in Southern Taiwan. Metabolic syndrome components, body mass index (BMI), liver function, dyslipidemia, and cardiovascular risk factors, as defined by the ratio of total cholesterol to high-density lipoprotein cholesterol (HDL-C), and the ratio of low-density lipoprotein cholesterol to HDL-C were compared between individuals with and without erosive esophagitis. Risk factors for erosive esophagitis were evaluated by multivariate logistic regression.

RESULTS: Erosive esophagitis was diagnosed in 507 of 5015 subjects who were individually age and sex matched to 507 esophagitis-free control subjects. In patients with erosive esophagitis, BMI, waist circumference, blood pressure, fasting plasma glucose, triglyceride levels, aspartate aminotransferase, alanine aminotransferase, the ratio of total cholesterol to HDL-C, and the ratio of low-density lipoprotein cholesterol to HDL-C were significantly higher and HDL-C was significantly lower compared to patients without erosive esophagitis (all $P < 0.05$). In a multivariate analysis, central obesity (OR = 1.38; 95%CI: 1.0-1.86), hypertension (OR = 1.35; 95%CI: 1.04-1.76), hypertriglyceridemia (OR = 1.34; 95%CI: 1.02-1.76), cardiovascular risk factors as defined by a ratio of total cholesterol to HDL-C > 5 (OR = 1.45; 95%CI: 1.06-1.97), and aspartate aminotransferase (OR = 1.59; 95%CI: 1.08-2.34) were significantly associated with erosive esophagitis.

CONCLUSION: Metabolic syndrome, impaired liver function, and a higher ratio of total cholesterol to HDL-C were associated with erosive esophagitis.

Key words: Erosive esophagitis; Metabolic syndrome; Central obesity; Abnormal liver function; Dyslipidemia

Core tip: A cross-sectional, case control study of subjects who underwent upper endoscopy during a health examination was conducted. Metabolic syndrome components, body mass index, liver function, and dyslipidemia were compared between individuals with and without erosive esophagitis. Risk factors for erosive esophagitis were evaluated. Erosive esophagitis was diagnosed in 507 of 5015 subjects who were individually age- and sex-matched to 507 esophagitis-free control

subjects. In addition to metabolic syndrome, we also found that abnormal liver function and predictors of future coronary heart disease were associated with erosive esophagitis.

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INTRODUCTION

The prevalence of erosive esophagitis in Asian countries has dramatically increased during the last two decades[1-3]. The prevalence of erosive esophagitis in the Taiwanese adult population is estimated to be 10%-15%[1,4]. Although the mechanism underlying this increase in prevalence remains to be determined, several risk factors of erosive esophagitis have been identified, including male sex, hiatal hernia, smoking, alcohol consumption, and obesity[5-7]. Metabolic syndrome is a complex disorder comprising central obesity, high blood pressure (BP), hyperglycemia, hypertriglyceridemia, and a low concentration of high-density lipoprotein cholesterol (HDL-C). In addition to being associated with cardiovascular disease and diabetes mellitus, metabolic syndrome and its component elements have also been associated with various gastrointestinal diseases and abnormal liver function[7-12]. The correlation between erosive esophagitis and body mass index (BMI) is controversial[13,14], as is the association between erosive esophagitis and hypertriglyceridemia or hyperglycemia[5,13-15]. This study was undertaken to characterize the correlation between erosive esophagitis and metabolic syndrome and its components, abnormal liver function and abnormal lipoprotein profiles - that have been used to predict coronary heart disease.

MATERIALS AND METHODS

Subjects

This study was designed as a cross-sectional, case control study. From January 2008 to December 2008, 5981 subjects visited the Health Management and Evaluation Center of a tertiary medical care facility located in Southern Taiwan for routine health examinations. Our center offers a variety of healthcare tests and procedures, including upper gastrointestinal endoscopy. The majority of subjects underwent a self-paid physical check-up; others were employees coming for their regular medical check-up. Most of the subjects were free of symptoms and were not chronic alcohol drinkers. Of the 5031 subjects who underwent upper gastrointestinal endoscopy, 507 were diagnosed with erosive esophagitis. The severity of erosive esophagitis was graded from A-D according to the Los Angles classification[16]. We matched each case subject, according to age and gender, with one control selected from the 4508 subjects with normal upper endoscopic findings. The study was approved by the institutional review board of the hospital in which the study was conducted.

Definition of metabolic syndrome and obesity

In this study, metabolic syndrome was defined according to the modified National Cholesterol Education Program Adult Treatment Panel Ⅲ for Asian populations. The waist circumference cutoff measurement was altered according to the criteria of the Bureau of Health Promotion, Department of Health, because the absolute risk of diabetes and cardiovascular disease is greater in Asians with a lesser degree of obesity[17,18]. Metabolic syndrome was diagnosed when at least three of the following criteria were found: (1) waist circumference $\geqslant$ 90 cm for men and $\geqslant$ 80 cm for women; (2) systolic BP $\geqslant$ 130 mmHg, diastolic BP $\geqslant$ 85 mmHg, or current use of antihypertensive drugs; (3) triglyceride (TG) $\geqslant$ 150 mg/dL; (4) HDL-C $<$ 40 mg/dL for men and $<$ 50 mg/dL for women; and (5) fasting plasma glucose $\geqslant$ 110 mg/dL or current use of antihyperglycemic drugs. Subjects with a BMI $\geqslant$ 25 kg/m^2 were defined as obese according to the Steering Committee of the World Health Organization Regional Office for the Western Pacific[19]. Subjects with elevated serum alanine aminotransferase (ALT) (ALT $>$ 40 U/L) or aspartate aminotransferase (AST) (AST $>$ 37 U/L) levels were considered to have abnormal liver function. Cardiovascular risk, which is determined by a ratio of total cholesterol (TC)/HDL-C $>$ 5 and correlates significantly with the risk for cardiovascular events[20], was evaluated for its association with erosive esophagitis.

Statistical analysis

Statistical analysis were performed using SPSS (Statistical Package for the Social Sciences) 15 software (SPSS, Chicago, IL, United States). Continuous variables are expressed as the mean ± SD. Student's *t* test was used to compare continuous variables. Univariate analysis was performed using a χ^2 test for categorical variables. For each variable, the OR and 95%CI were calculated. A two-tailed *P* value of $<$ 0.05 was considered statistically significant. Multivariate analysis in the logistic regression model was conducted to examine the associations between erosive esophagitis and different risk factors.

RESULTS

Prevalence of erosive esophagitis

Of the 5031 subjects who underwent upper gastrointestinal endoscopy, 16 were excluded from the analysis because of prior gastric surgery, gastric cancer, or peptic ulcer. Erosive esophagitis was diagnosed in 507 of 5015 subjects. The mean age of subjects with erosive esophagitis was 51.2 ± 11.2 years, and 82.6% were male.

Table 1 Comparison between subjects with and without erosive esophagitis

	With erosive esophagitis (n = 507)	Without erosive esophagitis (n = 507)	P value
Age (yr, mean ± SD)	51.2 ± 11.2	51.2 ± 11.2	-
Sex (M/F)	419/88	419/88	-
BMI (kg/m^2)	25.6 ± 3.6	24.9 ± 3.4	< 0.001
Waist circumference (cm)	87.3 ± 12.9	84.8 ± 11.9	< 0.001
Systolic BP (mmHg)	132.3 ± 18.1	129.2 ± 17.7	0.003
Diastolic BP (mmHg)	87.2 ± 11.7	84.2 ± 10.8	< 0.001
Fasting plasma glucose (mg/dL)	105.9 ± 36.5	101 ± 29	0.009
Triglycerides (mg/dL)	165 ± 107.4	137.1 ± 99.5	< 0.001
HDL-C (mg/dL)	50.4 ± 15	52.2 ± 14.5	0.025
TC/HDL-C	4.27 ± 1.26	4.04 ± 1.13	0.001
LDL-C/HDL-C	2.56 ± 0.96	2.46 ± 0.87	0.049
AST (U/L)	31 ± 28.7	27.3 ± 13.4	0.004
ALT (U/L)	37.1 ± 26.4	31.2 ± 21.6	0.005

The P values are based on Student's t test. M: Male; F: Female; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BP: Blood pressure; BMI: Body mass index; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol.

Characteristics of subjects with and without erosive esophagitis

The subject characteristics are summarized in Table 1. When compared with age- and sex-matched controls, BMI, waist circumference, systolic and diastolic BP, fasting plasma glucose, triglyceride levels, AST/glutamate-oxaloacetate transaminase (GOT) and ALT/glutamate-pyruvate transaminase (GPT) levels, the ratio of TC to HDL-C, and the ratio of low-density-lipoprotein cholesterol to HDL-C (LDL-C to HDL-C) were significantly higher and HDL-C was significantly lower in subjects with erosive esophagitis (all $P < 0.05$).

Univariate and multivariate analyses of the associations between erosive esophagitis and risk factors

The results from the univariate and multivariate logistic regression analyses are shown in Table 2. BMI ⩾ 25 kg/m^2 (OR = 1.72; 95%CI: 1.10-1.80), central obesity (OR = 1.60; 95%CI: 1.20-2.14), hypertension (OR = 1.43; 95%CI: 1.11-1.86), hyperglycemia (OR = 1.39; 95%CI 1.07-1.80), hypertriglyceridemia (OR = 1.50; 95%CI: 1.15-1.95), and cardiovascular disease risk factors of TC/HDL-C > 5 (OR = 1.57; 95%CI: 1.17-2.12), AST > 37 U/L (OR = 1.67; 95%CI: 1.14-2.45), and ALT > 40 U/L (OR = 1.40; 95%CI: 1.04-1.90) were significantly associated with erosive esophagitis, according to the univariate analyses. Furthermore, the multivariate logistic regression analysis confirmed the associations of central obesity, hypertension, hypertriglyceridemia, the ratio of TC/HDL-C > 5, and high AST levels with erosive esophagitis (all $P < 0.05$).

Association of erosive esophagitis with metabolic syndrome

Table 3 shows that the presence of metabolic syndrome (⩾ 3 metabolic criteria) was associated with a higher probability of erosive esophagitis than the presence of < 3 metabolic criteria (OR = 1.475; 95%CI: 1.149-1.895). The prevalence of metabolic syndrome was higher in subjects with erosive esophagitis than in those without (47.1% *vs* 37.7%, respectively; $P < 0.005$).

DISCUSSION

In this study, erosive esophagitis was identified in 10.1% of subjects who underwent routine health examinations. Central obesity, hypertension, hypertriglyceridemia, a high TC/HDL-C ratio (TC/HDL-C > 5), and AST > 37 U/L were significantly associated with erosive esophagitis. Previously, Chua *et al*[13] showed that an increase in BMI was related to an increase in erosive esophagitis, but Chung *et al*[14] did not find a significant association between BMI and erosive esophagitis. Our study showed that central obesity, but not BMI, was an independent risk factor for erosive esophagitis.

A possible reason for this finding is that BMI is not a good indicator of the percentage of body fat among Asian populations[21]. Only the visceral component of abdominal fat increases the risk for erosive esophagitis because visceral adipose tissue is strongly associated with elevated serum levels of proinflammatory adipokines, which may play a role in the development of erosive esophagitis[7,14,22]. In addition, central obesity may increase intra-abdominal pressure and decrease lower esophageal sphincter pressure, resulting in esophageal sphincter relaxation with acid reflux, which may lead to esophagitis[22-24].

Studies have also shown that hypertriglyceridemia is associated with erosive esophagitis[13-15], but contrasting results have also been reported[5]. The present study shows that hypertriglyceridemia is a potential risk factor for erosive esophagitis. Although the underlying mechanisms still need to be fully characterized, high dietary fat intake and delay in gastric emptying may increase the risk of erosive esophagitis[25,26].

The association of hyperglycemia and erosive esophagitis is controversial. Moki *et al*[5] demonstrated a positive relationship between erosive esophagitis and hyperglycemia. However, the majority of studies have found that hyperglycemia is not associated with erosive esophagitis[13-15,27]. Our results also indicate that hyperglycemia is not associated with erosive esophagitis. Gastric emptying can be delayed by diabetic autonomic neuropathy, which may promote erosive esophagitis. However, most individuals in our study population were in generally good health, without diabetic autonomic neuropathy, which may explain our finding that hyperglycemia is not associated with erosive esophagitis. The association of hypertension and erosive esophagitis is also controversial. Gudlaugsdottir *et al*[28] suggested that erosive esophagitis was associated with hypertension, but Wu *et al*[29] failed to establish a significant relationship between hypertension and erosive esophagitis. Our study showed that hyperten-

Table 2 Logistic regression analysis of risk factors for erosive esophagitis

	Univariate analysis OR (95%CI)	*P* value	Multivariate analysis OR (95%CI)	*P* value
Obesity[1]	1.72 (1.10-1.80)	< 0.05		0.606
Central obesity[2]	1.60 (1.20-2.14)	< 0.05	1.38 (1.00-1.86)	< 0.05
Hypertension	1.43 (1.11-1.86)	< 0.05	1.35 (1.04-1.76)	< 0.05
Hyperglycemia	1.39 (1.07-1.80)	< 0.05		0.143
Hypertriglyceridemia	1.50 (1.15-1.95)	< 0.05	1.34 (1.02-1.76)	< 0.05
Low HDL-C	1.24 (0.91-1.67)	0.192	-	-
TC/HDL-C > 5	1.57 (1.17-2.12)	< 0.05	1.45 (1.06-1.97)	< 0.05
AST > 37 (U/L)	1.67 (1.14-2.45)	< 0.05	1.59 (1.08-2.34)	< 0.05
ALT > 40 (U/L)	1.40 (1.04-1.90)	< 0.05		0.986

[1]Defined as body mass index ⩾ 25 kg/m^2; [2]Defined as waist circumference ⩾ 90 cm for men and ⩾ 80 cm for women. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HDL-C: High-density lipoprotein cholesterol; TC: Total cholesterol.

Table 3 Components of metabolic syndrome associated with erosive esophagitis *n* (%)

Metabolic factors	Erosive esophagitis (*n* = 507)	Matched normal control (*n* = 507)	OR (95%CI)	*P* value
Number of criteria				
⩾ 1 criterion	473 (93.3)	447 (88.2)	1.867 (1.203-2.899)	0.007
⩾ 2 criteria	391 (77.1)	335 (66.1)	1.731 (1.312-2.283)	< 0.001
⩾ 3 criteria	239 (47.1)	191 (37.7)	1.475 (1.149-1.895)	0.003
⩾ 4 criteria	112 (22.1)	64 (12.6)	1.963 (1.403-2.746)	< 0.001
5 criteria	28 (5.5)	20 (3.9)	1.423 (0.791-2.561)	0.301

sion is an independent risk factor for erosive esophagitis.

Several studies have reported that abnormal liver function is related to metabolic syndrome[10-12]. In addition to metabolic syndrome, high BMI, central obesity, and hyperlipidemia are associated with hepatic steatosis[30,31]. The severity of hepatic steatosis is significantly correlated with the results of hepatic enzyme tests[32]. Several studies have reported an association between gastroesophageal reflux disease (GERD) and chronic liver disease[33-36]. Suzuki *et al*[36] showed that more than 30% of patients with chronic liver disease had GERD. Ueda *et al*[34] showed a relatively higher incidence of GERD in patients with alcoholic liver disease. We found that abnormal liver function (higher AST level) was a risk factor for erosive esophagitis. Although the underlying mechanisms are not clear, hepatic steatosis related to metabolic syndrome, a risk factor of erosive esophagitis, may provide a potential explanation. The TC/HDL-C ratio has been used to predict the risk of future coronary heart diseases. This practice is supported by several studies that have demonstrated that the TC/HDL-C ratio is the most significant predictor of future coronary heart disease, along with smoking and diabetes mellitus[37-39]. Our study showed that subjects with erosive esophagitis might have a higher cardiovascular risk than those without erosive esophagitis. The present study has several limitations. First, only the association between abnormal liver function and erosive esophagitis was analyzed, and no further evaluation was conducted to determine the relationship between erosive esophagitis and hepatic steatosis or chronic hepatitis B or C. Second, this study had a cross-sectional design, and therefore, only the associations between erosive esophagitis and metabolic syndrome, abnormal liver function, and dyslipidemia could be determined. Further studies with a longitudinal design are required to evaluate their possible causal relationships.

In conclusion, metabolic syndrome and its components, such as central obesity, BP, and hypertriglyceridemia, are independent risk factors for erosive esophagitis. Abnormal liver function, including elevated AST, and cardiovascular risk factors were also found to be associated with erosive esophagitis. Further studies are needed to investigate the underlying mechanisms responsible for the relationship between abnormal liver function, cardiovascular risk, and erosive esophagitis.

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COMMENTS

Background

Erosive esophagitis is becoming more prevalent in Asia, but the underlying mechanism remains unknown. Obesity has been associated with erosive esophagitis. However, the associations of metabolic syndrome, its components, and liver function with erosive esophagitis are controversial.

Research frontiers

Several previous studies have identified the risk factors of erosive esophagitis, including male sex, hiatal hernia, smoking, alcohol consumption, and obesity. This study further determined the associations between erosive esophagitis and metabolic syndrome, its components, and liver function.

Innovations and breakthroughs

The present study demonstrated that metabolic syndrome, impaired liver function, and dyslipidemia were associated with erosive esophagitis.

Applications

Individuals with metabolic syndrome and high cardiovascular risk, as defined by

a higher ratio of total cholesterol to high-density lipoprotein cholesterol (HDL-C), are at higher risk for erosive esophagitis. This finding may suggest that treating metabolic disorders can prevent or reduce the risk of erosive esophagitis. However, further studies are needed to confirm this finding.

Terminology

Metabolic syndrome is a complex disorder comprising central obesity, high blood pressure, hyperglycemia, hypertriglyceridemia, and a low concentration of HDL-C. Cardiovascular risk, which is determined by a total cholesterol/HDL-C ratio > 5, correlates with the risk of cardiovascular events.

Peer review

Authors undertook to characterize the correlation between erosive esophagitis and metabolic syndrome and its components, abnormal liver function, and abnormal lipoprotein profiles. This case-controlled study is well organized and has enough potential for publication.

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