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RAPID COMMUNICATION

Metabolic syndrome is associated with erosive esophagitis

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Abstract

AIM: To clarify whether insulin resistance and metabolic syndrome are risk factors for erosive esophagitis.

METHODS: A case-control study was performed using the database of the Kangbuk Samsung Hospital Medical Screening Center.

RESULTS: A total of 1679 cases of erosive esophagitis and 3358 randomly selected controls were included. Metabolic syndrome was diagnosed in 21% of the cases and 12% of the controls ($P < 0.001$). Multiple logistic regressions confirmed the association between erosive esophagitis and metabolic syndrome (Odds ratio, 1.25; 95% CI, 1.04-1.49). Among the components of metabolic syndrome, increased waist circumference, elevated serum triglyceride levels and hypertension were significant risk factors for erosive esophagitis (all $P < 0.01$). Furthermore, increased insulin resistance (Odds ratio, 0.91; 95% CI, 0.85-0.98) and fatty liver, as diagnosed by ultrasonography (Odds ratio, 1.39; 95% CI, 1.20-1.60), were also related to erosive esophagitis even after adjustment for a series of confounding factors.

CONCLUSION: Metabolic syndrome and increased insulin resistance are associated with an increased risk of developing erosive esophagitis.

Key words: Metabolic syndrome; Erosive esophagitis; Insulin resistance; Fatty liver

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INTRODUCTION

Metabolic syndrome is a cluster of metabolic abnormalities defined as the presence of an increased waist circumference and two of the following components: high blood pressure, hypertriglyceridemia, low levels of high density lipoprotein (HDL)-cholesterol, or diabetes/hyperglycemia. This syndrome helps to identify individuals at high risk for both cardiovascular disease and diabetes mellitus (DM); therefore, metabolic syndrome has become one of the major health problems worldwide.

Gastroesophageal reflux disease (GERD) and obesity are two of the most common diseases in Korea and the incidences of both have been increasing rapidly. Recently, GERD was shown to affect approximately 3.4%-3.8% of the Korean population[1,2] and in 1995 the prevalence of being overweight [body mass index (BMI) = 25-30 kg/m^2] or obese (BMI > 30 kg/m^2) was, respectively, reported as 11.7% and 2.1% in males, and 18.0% and 2.5% in females; in 2000 the prevalence of being overweight or obese was 33.1% and 3.2% in males, and 32.2% and 4.5% in females, respectively[3].

Several studies have shown the relationship between obesity, erosive esophagitis, and GERD symptoms[4-8]. Also, a recent study demonstrated that metabolic syndrome was associated with reflux esophagitis[9]. However, literature on whether metabolic syndrome and insulin resistance are risk factors for GERD is scant.

In this study, we therefore intended to determine whether metabolic syndrome and insulin resistance are associated with erosive esophagitis in a Korean population.

MATERIALS AND METHODS

Study population and selection of study participants

We conducted a cross-sectional case-control study. The study population consisted of subjects who visited the Medical Screening Center at Kangbuk Samsung Hospital from January to December 2006. Exclusion criteria

consisted of a history of prior gastric surgery, benign gastric or duodenal ulcer, gastric cancer or current proton pump inhibitor medication therapy.

Of the 83032 patients visited the Medical Screening Center, 44718 patients underwent upper gastrointestinal (UGI) endoscopic examination. However, only 28949 patients completed a questionnaire pertaining to their symptoms (heart burn and regurgitation) and provided weights, heights, and waist circumferences. The mean age of the participants was 45 ± 9.6 years and 11375 (39%) were females. After application of the exclusion criteria, 1679 (5.8%) subjects were included as patients with erosive esophagitis. Two controls for each case patient (3358 subjects) were randomly selected from the subjects with normal UGI endoscopic findings and no reflux symptoms.

Questionnaire

All participants completed a self-administered validated questionnaire that identified reflux symptoms, such as irritating heartburn and/or acid regurgitation experienced during the preceding year[6]. In addition, the questionnaire included questions about current smoking and other medical or surgical histories.

Measurement

BMI and metabolic syndrome components, such as waist circumference, lipid profile, blood pressure and fasting glucose level, were measured in all study participants. BMI was calculated as the ratio of weight (kg) to the square of height (kg/m^2) and abdominal obesity was defined as a waist circumference ≥ 80 cm in females and ≥ 90 cm in males[10]. Measurements were made at the World Health Organization (WHO) recommended site (the midpoint between the lower border of the rib cage and the iliac crest) by trained personnel[11]. The mean blood pressure was checked more than twice in the supine position with a sphygmomanometer after 10 min of rest. All blood testing was done after more than 12 h of fasting. Total cholesterol, triglycerides (TG), HDL-C and low-density lipoprotein (LDL)-C were measured with an automatic analyzer (Advia 1650, German). Total C and TG were analyzed by an enzymatic calorimetric test. A selective inhibition method was used in HDL-C measurement and a homogenous enzymatic calorimetric test was used in LDL-C measurement. Fasting glucose was measured by the hexokinase method with an automatic analyzer (Advia 1650) and fasting insulin was assayed *via* an immunoradiometric assay (Biosource, Belgium). The intraassay variation coefficients were 2.1%-4.5% and the interassay variation coefficients for the quality controls were 4.7%-12.2%. The degree of insulin resistance was evaluated by homeostasis model assessment (HOMA-IR) according to the following formula: (fasting insulin in μU/mL × fasting glucose in mmol/L)/22.5[12]. An experienced radiologist who was blind to the laboratory data performed ultrasonographic liver examinations. Fatty liver was defined as a bright liver on ultrasonography (USG). The diagnosis of bright liver was based on abnormally intense and high level echoes arising from the hepatic parenchyma with amplitudes similar to those of echoes arising from the diaphragm.

Participants were diagnosed with metabolic syndrome if they had an increased waist circumference and two of the following components: (1) high blood pressure (≥ 130 mmHg systolic or ≥ 85 mmHg diastolic), (2) hypertriglyceridemia (≥ 150 mg/dL), (3) low levels of HDL-C (≤ 40 mg/dL in males or ≤ 50 mg/dL in females), or (4) DM/hyperglycemia[10].

Upper gastrointestinal endoscopy

Standard endoscopic examination of the esophagus, stomach, and duodenum was performed in all subjects. The severity of erosive esophagitis was graded from A-D according to the LA classification[13]. We considered LA-A to be the cutoff for erosive esophagitis. We also considered a hiatal hernia to be present if diaphragmatic indentation was seen > 2 cm distal to the Z-line and the proximal margins of the gastric mucosal folds, which were observed with considerable air insufflation during inspiration. Distance was measured using the centimeter markings on the endoscope[14].

Statistical analyses

Statistical analysis was done using the χ^2 test for comparison of discrete variables and the *t*-test for comparison of continuous variables. The continuous variables measured in this study were expressed as the mean ± SD. Multivariate analysis was conducted using logistic regression. To examine the risks of potential confounders, including metabolic syndrome for erosive esophagitis, multivariate models included adjustments for age, gender, smoking, alcohol, and metabolic syndrome as categorical factors. For each variable, the odds ratio (OR) and 95% confidence interval (CI) were given. A two-tailed *P* value of < 0.05 was considered statistically significant.

RESULTS

Of the 28949 subjects, 1679 (5.8%) were confirmed to have erosive esophagitis; 1326 (78.9%) cases were classified as LA-A, 328 (19.5%) as LA-B, and 25 (1.6%) as LA-C or LA-D. The mean age was 45.19 ± 9.3 years and 86% of the subjects were men. The study characteristics are mentioned in Table 1. We found a significant increase in the mean BMI, waist circumference, systolic and diastolic blood pressure, fasting blood glucose, HbAlc, TG and HOMA in patients with erosive esophagitis as compared to the controls. Also, patients with erosive esophagitis were more likely to be male, obese, current smokers, regular consumers of alcohol, and more likely to have metabolic syndrome and fatty liver (as diagnosed by abdominal ultrasonography) and less than a college education.

Table 2 shows the results from the multivariate analysis examination of the association between erosive esophagitis and various risk factors. Male gender, current smoking, metabolic syndrome, reflux symptoms, regular

Table 1 Comparisons between participants with and without erosive esophagitis (n = 5037)

	With erosive esophagitis (n = 1679)	Without erosive esophagitis (n = 3358)	P
Age (yr, mean ± SD)	45.2 ± 9.3	45.2 ± 9.7	0.873
Gender (M/F, %)	86/14	59/41	< 0.001
BMI (kg/m^2)	24.8 ± 2.9	23.5 ± 3.0	< 0.001
Waist circumference (cm)	86.8 ± 8.7	81.5 ± 9.8	< 0.001
Current smoking	724 (43%)	786 (23%)	< 0.001
Alcohol use (≥ 3-4/wk)	360 (21%)	387 (12%)	< 0.001
Metabolic syndrome	352 (21%)	433 (13%)	< 0.001
Hiatal hernia	38 (2.2%)	24 (0.7%)	< 0.001
Reflux symptoms[1]	194 (12%)	265 (8.0%)	< 0.001
Systolic BP (mmHg)	118.3 ± 12.7	114.8 ± 13.5	< 0.001
Diastolic BP (mmHg)	77.7 ± 8.8	74.8 ± 9.5	< 0.001
Fatty liver on abdominal USG	809 (48%)	1014 30%)	< 0.001
Fasting plasma glucose	98.4 ± 20.5	95.2 ± 17.2	< 0.001
HbAlc	5.6 ± 0.7	5.5 ± 0.6	0.001
Triglycerides (mg/dL, mean ± SD)	158.9 ± 110.4	123.5 ± 78.6	< 0.001
HDL-C (mg/dL) (mean ± SD)	54.1 ± 12.0	56.4 ± 12.8	< 0.001
HOMA[2]	2.41 ± 1.10	2.18 ± 0.89	< 0.001
H pylori positive	211/555 (38%)	498/922 (54%)	< 0.001
Education (college and higher)	894/1184 (75%)	1639/2391 (69%)	< 0.001

[1]Reflux symptoms: Weekly heartburn and/or acid regurgitation; [2]HOMA: Homeostasis model assessment estimates steady state beta cell function and insulin sensitivity.

Table 2 Multivariate analyses of the risk for erosive esophagitis by gender, smoking, hiatal hernia, reflux symptoms, metabolic syndrome, fatty liver on abdominal USG and HOMA

	Adjusted odds ratio	95% CI	P
Gender	0.29	0.25-0.35	< 0.001
Current smoking	1.60	1.39-1.83	< 0.001
Alcohol use (≥ 3-4/wk)	1.80	1.53-2.14	< 0.001
Hiatal hernia	3.27	1.87-5.70	< 0.001
Reflux symptoms[1]	1.57	1.28-1.94	< 0.001
Metabolic syndrome	1.25	1.04-1.49	0.017
Fatty liver on abdominal USG	1.39	1.20-1.60	< 0.001
HOMA[2]	0.91	0.85-0.98	0.011

[1]Reflux symptoms: Weekly heartburn and/or acid regurgitation; [2]HOMA: Homeostasis model assessment estimates steady state beta cell function and insulin sensitivity.

Table 3 Risk of individual components of metabolic syndrome for erosive esophagitis

	OR (95% CI)[1]	P	OR (95% CI)[2]	P
Increased waist circumference	1.46 (1.28-1.67)	< 0.001	1.33 (1.15-1.54)	< 0.001
Hypertension	1.22 (1.06-1.40)	0.006	1.16 (1.00-1.35)	0.047
DM or elevated FBS	1.09 (0.77-1.54)	0.627	0.95 (0.66-1.38)	0.798
Increased TG	1.98 (1.74-2.26)	< 0.001	1.47 (1.14-1.90)	0.003
Low HDL-C	0.67 (0.56-0.80)	< 0.001	0.90 (0.74-1.09)	0.267

FBS: Fasting blood sugar; TG: Triglycerides; HDL-C: High-density lipoprotein-cholesterol. [1]Unadjusted; [2]Adjusted for gender, current smoking, hiatal hernia, reflux symptoms, alcohol use, fatty liver on abdominal USG, and HOMA.

alcohol use, HOMA and fatty liver (as diagnosed by abdominal ultrasonography) were significant independent risk factors for erosive esophagitis. Among the individual components of metabolic syndrome, increased waist circumference, hypertension, increased levels of TG, and low levels of HDL-C were significantly associated with erosive esophagitis. However, after adjusting for gender, smoking, hiatal hernia, reflux symptoms, regular alcohol use, HOMA and fatty liver (as diagnosed by abdominal ultrasonography), increased waist circumference, increased levels of TG, and hypertension were strongly associated with the development of erosive esophagitis (Table 3).

We also attempted to determine the relationship between the severity of erosive esophagitis, according to the LA classification, and various risk factors. Male gender, current smoking, regular alcohol use, hiatal hernia, metabolic syndrome, reflux symptoms, HOMA and fatty liver (as diagnosed by abdominal ultrasonography) were significantly associated with the severity of erosive esophagitis (Table 4). Among the individual components of metabolic syndrome, increased waist circumference and increased levels of TG were predictive factors for the severity of erosive esophagitis (Table 5).

DISCUSSION

This cross-sectional study in a Korean population showed that metabolic syndrome was strongly associated with the development and severity of erosive esophagitis. Also, insulin resistance, independent of metabolic syndrome, was another significant risk factor for erosive esophagitis.

Recently, the prevalence of metabolic syndrome has rapidly increased in Korea. According to the International Diabetes Federation (IDF) criteria, the age-adjusted prevalence of metabolic syndrome in males was 10.9% in 1997 and 23.3% in 2003. In females, the age-adjusted prevalence of metabolic syndrome was 42.2% in 1997 and 43.4% in 2003[15]. In the current study,

Table 4 Associations of grade of erosive esophagitis, according to LA classification, with risk factors for erosive esophagitis *n* (%)

	Control (*n* = 3358)	A (*n* = 1326)	B (*n* = 328)	C or D (*n* = 25)	*P* for linear trend
Age (yr, mean ± SD)	45.2 ± 9.7	44.8 ± 9.7	46.4 ± 9.3	49.9 ± 10.7	0.094
Males	1991 (59)	1122 (85)	300 (92)	22 (88)	< 0.001
Current smoking	786 (23)	554 (42)	162 (49)	8 (32)	< 0.001
Alcohol use (≥ 3-4/wk)	387 (12)	251 (19)	101 (31)	8 (32)	< 0.001
Hiatal hernia	24 (0.2)	32 (2)	3 (1)	3 (12)	< 0.001
Reflux symptoms[1]	265 (8.0)	141 (11)	50 (15)	3 (12)	< 0.001
Metabolic syndrome	433 (13)	255 (19)	87 (27)	10 (40)	0.001
Fatty liver on Abdominal USG	1014 (30)	625 (47)	166 (51)	18 (72)	< 0.001
HOMA[2] (mean ± SD)	2.18 ± 0.89	2.39 ± 1.10	2.50 ± 1.10	2.70 ± 1.12	0.007

[1]Reflux symptoms: Weekly heartburn and/or acid regurgitation; [2]HOMA: Homeostasis model assessment estimates steady state beta cell function and insulin sensitivity.

Table 5 Associations of grade of erosive esophagitis, according to LA classification, with individual components of the metabolic syndrome *n* (%)

	Control (*n* = 3358)	A (*n* = 1326)	B (*n* = 328)	C or D (*n* = 25)	*P* for linear trend[1]
Increased waist circumference	942 (28)	504 (38)	159 (48)	19 (76)	< 0.001
Hypertension	722 (22)	378 (29)	103 (31)	8 (32)	0.244
DM or elevated FBS	84 (2.5)	49 (4)	11 (3)	0	0.346
Increased TG	850 (25)	561 (42)	138 (42)	11 (44)	0.004
Low HDL-C	497 (15)	164 (12)	37 (11)	5 (20)	0.582

[1]Adjusted for gender, current smoking, hiatal hernia, reflux symptoms, alcohol use, fatty liver on abdominal USG, and HOMA.

the prevalence of metabolic syndrome was lower than previously reported, especially for females. A possible explanation for this difference is that the participants in this study were much younger than those in previous studies. Because the prevalence of metabolic syndrome increases with age[16,17], younger subjects are more likely to have a lower prevalence of metabolic syndrome than older subjects. Additionally, the higher educational level and economic status of the subjects could be another reason for the lower than expected prevalence of metabolic syndrome. Higher income was protective against metabolic syndrome[18] and females in the lower economic group were more likely to be at risk for metabolic syndrome when compared with females in the higher economic group[19,20].

With the increased prevalence of metabolic syndrome, GERD has also become more prevalent in Korea. The overall prevalence of erosive esophagitis was 3.4% in 2001[21] and 6.6% in 2006[6]. In terms of reflux symptoms, 2.5% of adults experienced heartburn and reflux symptoms in 2000[22]. In contrast, 7.1% reported that GERD symptoms were present at least once a week in 2007[1]. This increase may be due to extended life expectancy, greater intake of Westernized food[2], and/or increasing rates of obesity[6]. Moreover, an increase in alcohol consumption[23,24] and a decrease in *Helicobacter pylori (H pylori)* infections[25] could be possible reasons for the increase in erosive esophagitis in Korea.

This study demonstrated that metabolic syndrome and insulin resistance were also risk factors for erosive esophagitis. A recent study verified that elevated triglyceride levels, a component of metabolic syndrome, is an independent predictor for reflux esophagitis and suggested that humoral compounds might alter the lower esophageal sphincter pressure or affect esophageal clearance of refluxate[9]. In fact, human adipose tissue is a major site of IL-6 secretion[26]. IL-6 stimulates hepatic triglyceride secretion in rats[27] and plays an important role in insulin resistance in humans[28]. Moreover, IL-6 reduces esophageal circular muscle contraction[29]. Therefore, cytokines may play important roles in the pathogenesis of reflux esophagitis. However, given that very complex relationships exist among the risk factors for erosive esophagitis[23,30,31], we should be careful when interpreting the clinical significance of these relationships.

An interesting finding of this study was that among the individual components of metabolic syndrome, an elevated level of serum TG was a significant predictive factor not only for the presence of erosive esophagitis, but also for the severity of erosive esophagitis. This result is consistent with a recent study about metabolic syndrome and erosive esophagitis[9] as well as previous studies[32,33]; however, other reports did not find such a relationship between elevated serum TG and erosive esophagitis[34,35]. There are several possible explanations for this association. First, in view of the results of this study, insulin resistance and fatty liver may be responsible for increased serum TG levels because liver fat is a significant correlate of fasting glucose and triglyceride levels[36]. Also, hypertriglyceridemia is associated with increased insulin resistance[37]. Second, considering that *H pylori* infection has been suggested to be a protective factor for erosive esophagitis[38,39] and chronic *H pylori* infections can modify the serum lipid profile, including the increment of total C and TG[40,41], elevated serum TG levels could be just an epiphenomenon accompanying *H pylori* infection. Further studies are needed in order to

verify that point.

There were several limitations to our study. First, *H pylori* infections were not included in the multivariate analysis. *H pylori* infections in this study were diagnosed by histologic analysis of biopsy specimens. However, most of the subjects did not undergo the historical examination for *H pylori* because tissue biopsies were performed only when suspicious lesions were found by UGI endoscopic examination. Therefore, the prevalence of *H pylori* infection was lower in our subjects in comparison with the normal population. Nevertheless, patients undergoing a biopsy were randomly allocated to each comparison group; thus the rate of positive *H pylori* infection in patients with erosive esophagitis was significantly lower than in patients without erosive esophagitis, which is consistent with the result of a previous study[38]. Moreover, the result that metabolic syndrome was a significant risk factor for erosive esophagitis was still persistent after multivariate analysis, including *H pylori* infection ($P < 0.05$). Second, there is a possibility of selection bias because only one-half of the subjects who visited the health care center underwent UGI endoscopy and only a portion of them responded to the questionnaire regarding their symptoms. However, although subjects with reflux symptoms were more likely to participate in this study, the prevalence of patients with reflux symptoms was consistent with that of a recent study[1] and when the limited effects of reflux symptoms on erosive esophagitis are considered, this bias did not seem to affect the primary results of this study.

In conclusion, our study demonstrates that metabolic syndrome is an independent risk factor for erosive esophagitis. In addition, metabolic syndrome is significantly associated with the severity of erosive esophagitis. Therefore, we should take into account not only acid suppression, but also metabolic factors when consulting with patients who have erosive esophagitis.

COMMENTS

Background

Gastroesophageal reflux disease (GERD) and obesity are two of the most common diseases in Korea and the incidences of both have been increasing rapidly.

Research frontiers

Several studies have reported the relationship between obesity, erosive esophagitis, and GERD symptoms. A recent study demonstrated that metabolic syndrome was associated with reflux esophagitis. However, literature on whether metabolic syndrome and insulin resistance, suggested causes of metabolic syndrome, are risk factors for GERD remains scant.

Innovations and breakthroughs

One of the major findings of this study was that metabolic syndrome was strongly associated with the development and severity of erosive esophagitis. Moreover, insulin resistance, independent of metabolic syndrome, was a significant risk factor for erosive esophagitis.

Applications

This study should help to identify patients with particular risk for erosive esophagitis. An early identification of patients at risk for erosive esophagitis would allow more timely treatment and symptom relief.

Peer review

The present study showed a significant correlation between metabolic syndrome and erosive esophagitis and may be helpful for identifying the cause of erosive esophagitis. This study is interesting and valuable.

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