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ORIGINAL RESEARCH

Differences in Several Factors in the Development of Erosive Esophagitis Among Patients at Various Stages of Metabolic Syndrome: A Cross-Sectional Study

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Background: Erosive esophagitis (EE) is strongly associated with metabolic syndrome (MS), but is not always recognized in individuals with MS and the prevalence of EE in individuals with non-MS is not low.

Aim: To examine the differences in clinical factors associated with EE at various stages of MS, as well as the differences in metabolites between subjects with MS, with and without EE.

Methods: A total of 7,097 persons who underwent health checkups including esophagogastroduodenoscopy were analyzed. We examined the differences in clinical factors for EE among subjects with non-MS, pre-MS, and MS and compared metabolites between 34 subjects with MS, with and without EE.

Results: EE prevalence was significantly higher in the MS and pre-MS groups than in the non-MS group ($p < 0.001$). EE severity was higher in the MS group than in the pre-MS and non-MS groups ($p < 0.001$). In the non-MS group, there were significant differences between subjects with and without EE with respect to *Helicobacter pylori* (*H. pylori*) and smoking. In the pre-MS and MS groups, there were significant differences in *H. pylori*, hiatal hernia, and drinking in those with and without EE. The levels of glutamine, hypoxanthine, and lactic acid metabolites were significantly different between subjects with MS, with and without EE (all $p < 0.05$).

Conclusion: Although *H. pylori* and lifestyle factors such as smoking and drinking are important for EE, differences in these factors should be considered at various stages of MS. Additionally, several metabolites may be involved in the development of EE in MS.

Keywords: metabolic syndrome, erosive esophagitis, metabolite analysis

Introduction

The incidence of esophageal adenocarcinoma (EAC) has increased markedly in the last few decades.[1,2] Barrett's esophagus (BE), caused by long-standing pathologic exposure to gastroduodenal refluxate, is known to be a precursor lesion of EAC.[3–7] Therefore, preventing EE is important for suppressing the onset of BE and EAC. The prevalence of gastroesophageal reflux disease (GERD), including erosive esophagitis (EE), which is strongly associated with obesity and metabolic syndrome (MS), has been increasing in both developed and developing countries including Japan and western countries from 1970 to 1990.[8,9] Although obesity and MS are important for onset of EE,[10–12] EE is sometimes undiagnosed in individuals with

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MS and the prevalence of EE in the non-obese population is not low.[13] However, there are few reports about EE at various stages of MS and the difference between MS subjects with and without EE. This study aimed to measure the differences in clinical factors associated with EE among subjects with non-MS, pre-MS, and MS, and to measure the differences in metabolites between subjects with MS, with and without EE.

Methods

Study Population and Design

This single-center cross-sectional study was performed at the Shikoku Central Hospital of the Mutual Aid Association of Public School Teachers in Shikoku region, Japan. A total of 14,227 healthy subjects who underwent comprehensive medical surveys, including physical examinations, blood-test screening, and examination of the stomach (esophagogastroduodenoscopy or upper gastrointestinal series) between April 2017 and March 2019 were enrolled. Subjects with a history of digestive tract surgery, who took medications such as H2-receptor antagonists or proton pump inhibitors, or who were diagnosed with gastric or esophageal cancer at the time of esophagogastroduodenoscopy were excluded from this study. The study protocol was approved by our institutional ethics committee, and all procedures were performed in accordance with the Declaration of Helsinki. All subjects were informed that their clinical data might be analyzed retrospectively, and informed consent was obtained.

Diagnosis of MS

We used the Japanese diagnostic criteria for MS.[14] The criteria used for diagnosing MS in this study were as follows: waist circumference (WC) greater than 85 cm for males or 90 cm for females, and the presence of two or more of the following: (1) impaired glucose tolerance (IGT): fasting plasma glucose (FPG) ≥110 mg/dL or medication for diabetes; (2) dyslipidemia: triglycerides (TG) ≥150 mg/dl, and/or high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL or medication for dyslipidemia; and (3) hypertension: blood pressure ≥130/85 mmHg or medication for hypertension. In this study, we designated individuals who fulfilled these criteria as the MS group. Individuals who did not fulfill the MS criteria were divided into two groups as follows: the non-MS group was defined as individuals having no MS component; the pre-MS group was defined as individuals having a WC > 85 cm for males or 90 cm for females along with one other component of MS.

Evaluation of *H. pylori* Infection

Serological *Helicobacter pylori* (*H. pylori*) status was assessed using an enzyme-linked immunosorbent assay (Eiken Chemical, Tokyo, Japan). The seropositive antibody titer threshold for *H. pylori* infection was set at 3 U/mL. An increase in Δ13C values of >2.5‰ by urea breath test (UBT) indicated positive results. In this study, non-*H. pylori* infection was defined as follows: (1) subjects with *H. pylori* antibody seronegativity and/or UBT negativity, and no endoscopically atrophic gastritis (AG); (2) subjects who did not undergo a *H. pylori* antibody test in this study, had no history of eradication therapy, had endoscopically regular arrangement of collecting venules, and absence of AG; and (3) subjects with a history of eradication therapy and confirmed for the absence of *H. pylori* using UBT. We instituted a strict definition of non-*H. pylori* infection; therefore, individuals not fulfilling the above criteria were defined to have *H. pylori* infection in this study.

Assessment of Esophagogastroduodenoscopy

Standard endoscopic examination of the esophagus, stomach, and duodenum was performed by endoscopy specialists from the Gastroenterology Department of our hospital. All examiners had more than 10 years of experience in endoscopy. Esophagogastroduodenoscopy was performed using a conventional single-channel endoscope (GIF-H290, -HQ290, or -H290Z; Olympus, Tokyo, Japan). A hiatal hernia was diagnosed by the presence of a gastric wall above the diaphragmatic hiatus unaccompanied by underlying longitudinally arrayed vessels.[15] EE was diagnosed according to the Los Angeles classification system.[16] In this study, EE higher than grade A was defined as EE. Endoscopic findings from each subject were validated independently by a double endoscopy specialist.

Serum Metabolomics

Assessments of metabolomics were performed for 34 subjects with MS during 2019 April. The method of liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) (Nexera UHPLC system with on-line LC-MS 8040, Shimadzu Corporation, Kyoto, Japan) was

adopted for the metabolomics. The levels of the target metabolites were determined from the peak areas in mass chromatography, monitoring each mass-to-charge ratio of the individual target, and represented as relative amounts (relative areas) after normalization based on the peak area of the internal standard. In all, 101 primary metabolites including amino acids, organic acids, and so on were measured, and a total of 52 metabolites were obtained from subjects with MS.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD), and categorical data were expressed as counts, with percentages shown in parentheses. Differences were considered to be statistically significant at P values of less than 0.05. Statistically significant differences in the quantitative data between the two groups were determined using the χ^2-test or Mann–Whitney *U*-test. Statistically significant differences among three groups were determined using the m × n χ^2-test or Kruskal–Wallis test. If the Kruskal–Wallis test revealed differences between groups, post hoc pairwise comparisons were performed using the Mann–Whitney *U*-test with Bonferroni correction. Factors with a significant influence on EE prevalence were determined using univariate analysis. All parameters with *P*-values <0.05 by univariate analysis were assessed using stepwise multivariate logistic regression analysis. Using a logistic regression model, both odds ratio (OR) and 95% confidence interval (CI) were calculated. Correlations between variables were assessed by calculating Spearman rank correlation coefficients. All statistical analyses were performed using MedCalc Statistical Software for Windows (MedCalc Software; Ostend, Belgium).

Results

Subject Description and Baseline Characteristics Among the Non-MS, Pre-MS, and MS Groups

Supplementary Figure 1 shows the flow diagram of subject enrollment in this study. Of the 14,227 subjects who underwent a regular health checkup between April 2017 and March 2019 at our hospital, we excluded 1,487 subjects referring to individuals who did not get evaluated for MS, 7,130 subjects who did not undergo esophagogastroduodenoscopy or selected the upper gastrointestinal series in substitution for esophagogastroduodenoscopy for the evaluation of the upper gastrointestinal tract, and 125 subjects who fulfilled the other exclusion criteria; the remaining 7,097 subjects were enrolled in the study. The baseline characteristics of the 7,097 subjects are summarized in Table 1. The prevalence of non-MS, pre-MS, and MS groups was 69.2%, 13.6%, and 17.2%, respectively.

Comparison of EE Prevalence and Severity Among Non-MS, Pre-MS, and MS Groups

A comparison of EE prevalence and severity among the non-MS, pre-MS, and MS groups is shown in Figure 1. EE prevalence in the non-MS, pre-MS, and MS groups was (722/4,910) 14.7%, (278/964) 28.8%, and (348/1,223) 28.5%, respectively (Figure 1A). There was a significant difference in the prevalence of EE among the three groups ($p < 0.001$). EE prevalence was significantly higher in the MS and pre-MS groups than in the non-MS group ($p < 0.001$ and $p < 0.001$, respectively). The prevalence of grade A, B, C, and D in the non-MS group with EE was 88.7%, 10.5%, 0.8%, and 0%, respectively (Figure 1B). The prevalence of grade A, B, C, and D in the pre-MS group with EE was 85.6%, 12.2%, 1.4%, and 0.7%, respectively. The prevalence of grade A, B, C, and D in the MS group with EE was 79.6%, 16.1%, 4.3%, and 0%, respectively. The ratio of high severity EE was higher in the MS group than in the pre-MS and non-MS groups ($p < 0.001$ and $p < 0.001$, respectively).

Factors Associated with EE in the Non-MS, Pre-MS, and MS Groups

The results of univariate and multivariate analyses for factors associated with EE in the non-MS, pre-MS, and MS groups are summarized in Tables 2–4. Multivariate analysis in the non-MS group showed that sex, age, *H. pylori*, and smoking were significant independent predictors of EE (Table 2). The odds ratios (ORs) (95% confidence interval (CI), *p*-value) for EE were as follows: males, 2.147 (1.716–2.687, $p < 0.001$); age, 1.011 (1.000–1.021, $p < 0.05$); smoking, 1.616 (1.305–2.001, $p < 0.001$); and positive for *H. pylori*, 0.281 (0.193–0.409, $p < 0.001$). Multivariate analysis in the pre-MS group showed that drinking, *H. pylori*, and hiatal hernia were significant independent predictors of EE (Table 3). The ORs (95% CI, *p*-value) for EE were as follows: drinking, 1.413 (1.029–1.940, $p < 0.05$); positive for *H. pylori*, 0.508 (0.311–0.829, $p < 0.01$); hiatal hernia, 1.480

Table 1 Baseline Characteristics Among Non-MS, Pre-MS, and MS Groups (n=7,097)

	Total Subjects (n=7,097)	Non-MS Group (n=4,910)	Pre-MS Group (n=964)	MS Group (n=1,223)	*p*-value
Sex (M/F)	3,021/4,076	2,634/2,276	191/773	196/1,027	<0.001 (*<0.001, **<0.05, ***<0.001)
Age (years)	53.7 ± 9.2	53.0 ± 9.4[a]	54.2 ± 8.9[b]	56.0 ± 8.1[c]	<0.001
BMI (kg/m^2)	23.6 ± 3.7	22.0 ± 2.6[a]	26.6 ± 3.0[b]	27.6 ± 3.4[c]	<0.001
WC (cm)	83.7 ± 10.1	79.1 ± 7.2[a]	92.7 ± 6.6[b]	95.3 ± 7.6[c]	<0.001
Smoker, n (%)	1,166 (16.4%)	709 (14.4%)	199 (20.6%)	258 (21.1%)	<0.001 (*<0.001, ***<0.001)
Drinker, n (%)	4,141 (58.3%)	2,692 (54.8%)	621 (64.4%)	828 (67.7%)	<0.001 (*<0.001, ***<0.001)
SBP (mmHg)	125 ± 17	121 ± 16[a]	132 ± 15[b]	137 ± 15[c]	<0.001
DBP (mmHg)	80 ± 12	76 ± 11[a]	85 ± 11[b]	88 ± 11[c]	<0.001
Hypertension, n (%)	3,624 (51.1%)	1,788 (36.4%)	677 (70.2%)	1,159 (94.8%)	<0.001 (*<0.001, **<0.001, ***<0.001)
T-CHO (mg/dL)	211.5 ± 34.3	211.8 ± 34.0	210.2 ± 31.3	211.5 ± 37.2	NS
TG (mg/dL)	114.1 ± 88.8	96.5 ± 62.2[a]	120.2 ± 63.5[b]	180.3 ± 146.4[c]	<0.001
HDL-C (mg/dL)	66.7 ± 17.8	71.2 ± 17.7[a]	58.9 ± 13.4[b]	54.9 ± 13.6[c]	<0.001
LDL-C (mg/dL)	128.7 ± 30.5	127.0 ± 30.2[a]	133.8 ± 28.5[b]	131.2 ± 32.4[c]	<0.001
Dyslipidemia, n (%)	2,112 (29.8%)	924 (18.8%)	214 (22.2%)	974 (79.6%)	<0.001 (*<0.001, **<0.001, ***<0.05)
FPG (mg/dL)	101.9 ± 18.5	98.3 ± 13.7[a]	100.6 ± 11.0[b]	117.2 ± 29.0[c]	<0.001
HbA1c (%)	5.7 ± 0.6	5.6 ± 0.4[a]	5.6 ± 0.3[b]	6.1 ± 0.9[c]	<0.001
IGT, n (%)	1,313 (18.5%)	568 (11.6%)	73 (7.6%)	672 (54.9%)	<0.001 (*<0.001, **<0.001, ***<0.001)
UA (mg/dL)	5.4 ± 1.4	5.1 ± 1.3[a]	5.9 ± 1.4[b]	6.1 ± 1.3[c]	<0.001
ALT (IU/L)	24.1 ± 16.9	20.3 ± 13.5[a]	28.7 ± 16.2[b]	35.2 ± 23.0[c]	<0.001
AST (IU/L)	24.8 ± 11.2	23.5 ± 10.9[a]	25.7 ± 8.3[b]	29.1 ± 13.0[c]	<0.001
GGT (IU/L)	40.2 ±50.6	33.8 ± 48.5[a]	44.7 ± 39.5[b]	62.4 ± 59.6[c]	<0.001
Positivity of *H. pylori*, n (%)	869 (12.2%)	561 (11.4%)	122 (12.7%)	186 (15.2%)	<0.005 (*<0.001)
Hiatal hernia, n (%)	3,235 (45.6%)	2,087 (42.5%)	498 (51.7%)	650 (53.1%)	<0.001 (*<0.001, ***<0.001)

Notes: Data represent the mean ± standard deviation (SD) and number for categorical variables. *P*-values are based on the m × n χ^2-test or Kruskal Wallis test. If the Kruskal Wallis test revealed differences between the groups, then post hoc pairwise comparisons were performed using the Mann–Whitney *U*-test with Bonferroni correction. Different letters (a, b, c) indicate a significant difference at the 0.0166 (0.05/3) level. The χ^2-test was used for comparisons of number for categorical variables between the two groups (*MS group vs non-MS group, **MS group vs pre-MS group, ***pre-MS group vs non-MS group). Significant is at the 5% level.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; EE, erosive esophagitis; F, female; FPG, fasting plasma glucose; GGT, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; *H. pylori, Helicobacter pylori*; IGT, impaired glucose tolerance; LA, Los Angeles; LDL-C, low-density lipoprotein cholesterol; M, male; MS, metabolic syndrome; SBP, systolic blood pressure; T-CHO, total cholesterol; TG, triglyceride; UA, uric acid; WC, waist circumference.

(1.111–1.972, $p < 0.01$). Multivariate analysis in the MS group showed that age, drinking, TG, *H. pylori*, and hiatal hernia were significant independent predictors for EE (Table 4). The ORs (95% CI, *p*-value) for EE were as follows: age, 0.974 (0.957–0.992, $p < 0.005$); drinking, 1.468 (1.075–2.005, $p < 0.05$); TG, 1.001 (1.000–1.002, $p < 0.05$); positive for *H. pylori*, 0.283 (0.176–0.456, $p < 0.001$); and hiatal hernia, 1.504 (1.154–1.961, $p < 0.005$).

Comparison of Baseline Characteristics Between 34 Subjects with and without EE in the MS Group

A comparison of the baseline characteristics between 34 subjects with and without EE in the MS group is shown in Supplementary Table 1. There was no significant difference in the baseline factors between the subjects with and without EE.

Comparison of Metabolites Between 34 Subjects with and without EE in the MS Group

A comparison of 52 metabolites between 34 subjects with and without EE in the MS group is shown in Table 5. There were significant differences in three of the 52 metabolites between the subjects with and without EE. The mean glutamine levels in the subjects without EE were significantly higher than those in the subjects with EE ($p < 0.05$). The mean hypoxanthine and lactic acid levels

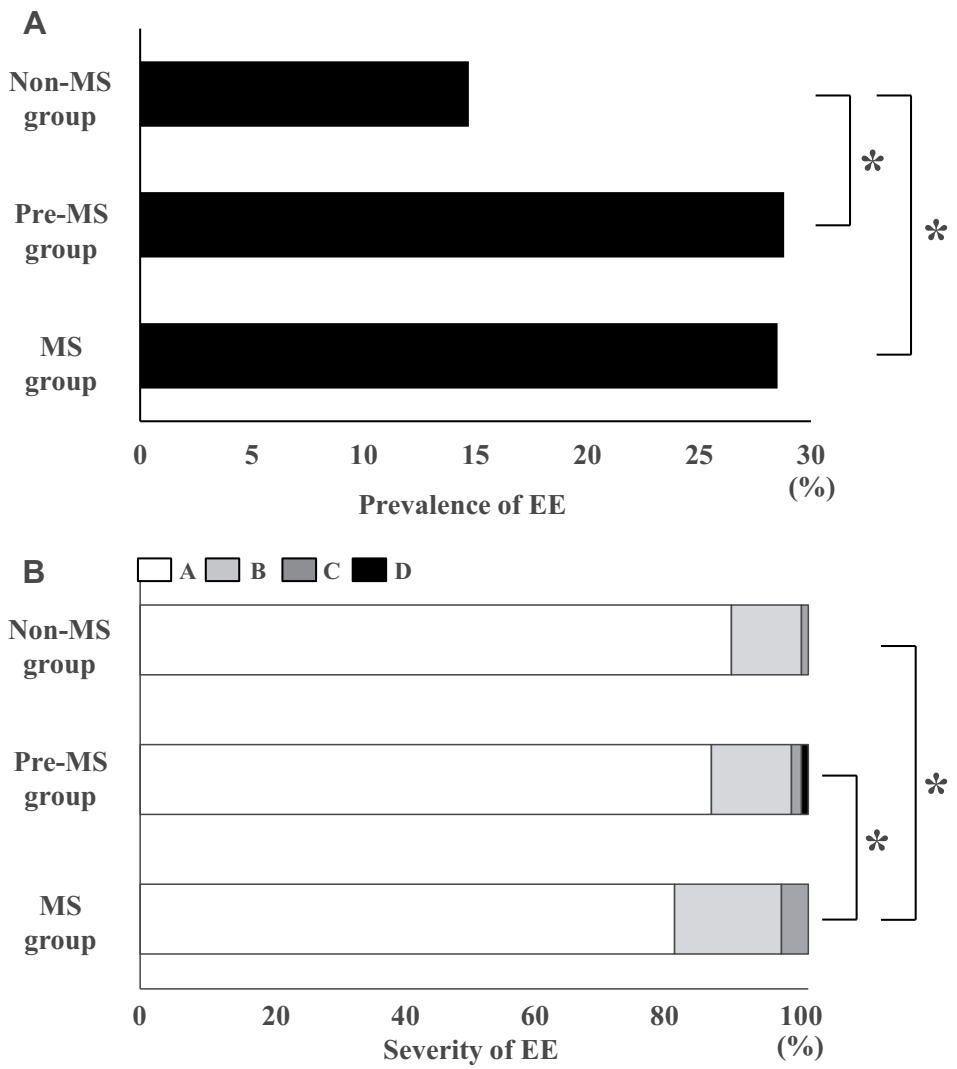

Figure 1 Comparison of EE prevalence and severity among the non-MS, pre-MS, and MS groups. (**A**) Comparison of EE prevalence among the non-MS, pre-MS, and MS groups. (**B**) Comparison of EE severity among the non-MS, pre-MS, and MS groups. The white bar indicates grade A of EE. The light gray bar indicates the grade B of EE. The dark gray bar indicates the grade C of EE. The black bar indicates the grade D of EE. EE, erosive esophagitis; MS, metabolic syndrome; *$P < 0.001$.

in the subjects with EE were significantly higher than those in the subjects without EE ($p < 0.01$ and $p < 0.05$, respectively).

Correlations Between Clinical Parameters and Metabolites Significantly Associated with EE

Spearman rank coefficients for clinical parameters and metabolites with statistically significant differences between subjects with and without EE in the MS group are shown in Table 6. Glutamine levels were significantly correlated with drinking and EE ($p < 0.05$). Hypoxanthine levels were significantly correlated with smoking, hiatal hernia, and EE ($p < 0.05$, $p < 0.005$, and $p < 0.05$, respectively). Lactic acid levels correlated significantly with EE ($p < 0.05$).

Discussion

This is the first study to clarify the differences in subjects with EE at various stages of MS as well as measuring the differences in metabolites with respect to EE in the context of medical checkups.

The present study showed that values of physical measurements such as body mass index (BMI) and WC, and almost all factors related to hypertension, dyslipidemia, and IGT were progressively greater in the non-MS, pre-MS, and MS groups, in accordance with previous reports that BMI, WC, blood

Table 2 Univariate and Multivariate Analyses for Factors Associated with EE in the Non-MS Group (n=4,910)

	Univariate Analysis			Multivariate Analysis		
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Sex (M/F)	2.947	2.500–3.488	< 0.001	2.147	1.716–2.687	< 0.001
Age (years)	1.010	1.002–1.019	< 0.05	1.011	1.000–1.021	< 0.05
BMI (kg/m^2)	1.096	1.065–1.129	< 0.001	1.041	0.984–1.101	0.163
WC (cm)	1.036	1.025–1.048	< 0.001	1.014	0.993–1.035	0.203
Smoking	2.210	1.823–2.680	< 0.001	1.616	1.305–2.001	< 0.001
Drinking	1.593	1.352–1.877	< 0.001	1.117	0.929–1.343	0.238
SBP (mmHg)	1.013	1.008–1.017	< 0.001	1.007	0.998–1.016	0.130
DBP (mmHg)	1.023	1.016–1.030	< 0.001	1.006	0.994–1.018	0.304
Hypertension	1.370	1.167–1.609	< 0.001	0.893	0.690–1.156	0.391
T-CHO (mg/dL)	1.000	0.998–1.002	0.999			
TG (mg/dL)	1.003	1.002–1.004	< 0.001	1.001	1.000–1.003	0.221
HDL-C (mg/dL)	0.989	0.984–0.993	< 0.001	1.003	0.998–1.009	0.272
LDL-C (mg/dL)	1.001	0.999–1.004	0.360			
Dyslipidemia	1.403	1.161–1.695	< 0.001	0.999	0.779–1.283	0.995
FPG (mg/dL)	1.010	1.005–1.015	< 0.001	1.000	0.993–1.008	0.943
HbA1c (%)	1.108	0.869–1.411	0.416			
IGT	1.314	1.044–1.655	< 0.05	1.008	0.731–1.389	0.963
UA (mg/dL)	1.357	1.277–1.442	< 0.001	1.069	0.990–1.154	0.090
AST (IU/L)	1.006	1.000–1.012	0.058			
ALT (IU/L)	1.013	1.007–1.018	< 0.001	1.001	0.995–1.007	0.732
GGT (IU/L)	1.004	1.002–1.005	< 0.001	1.001	0.999–1.002	0.526
H. pylori	0.321	0.223–0.463	< 0.001	0.281	0.193–0.409	< 0.001
Hiatal hernia	1.293	1.104–1.515	< 0.005	1.083	0.918–1.278	0.346

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; EE, erosive esophagitis; F, female; FPG, fasting plasma glucose; GGT, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; *H. pylori, Helicobacter pylori*; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; M, male; MS, metabolic syndrome; OR, odds ratio; SBP, systolic blood pressure; T-CHO, total cholesterol; TG, triglyceride; UA, uric acid; WC, waist circumference.

pressure, HOMA-IR, and other factors increased with the number of MS components.[17–19] EE prevalence in the pre-MS and MS-groups was about two times higher than that in the non-MS group. On the contrary, EE prevalence in the non-MS group was 14.7%; as this prevalence was not low,[13] this point cannot be ignored. In addition, the ratio of high EE severity increased progressively in non-MS group, pre-MS group, and the MS group; however, independent predictors of EE varied among the three groups. These findings imply that the prevalence, severity, and risk factors for EE differ at various stages of MS.

Smoking is known to decrease lower esophageal sphincter (LES) pressure and affect esophageal defense, which reduces esophageal clearance and saliva secretion, and a number of articles have reported that smoking is a risk factor for EE.[20–24] Although the prevalence of smoking in the non-MS group was lower than that in the pre-MS and MS groups in the present study, smoking was a significant factor for EE in the non-MS group. These results suggest that, even in non-obese individuals including the non-MS group, it is necessary to monitor smoking in the context of EE.

Several previous studies have shown that alcohol consumption is a risk factor for GERD. Drinking is considered to be associated with an increase in gastric acid secretion and a decrease in LES pressure.[23,25–27] The present study showed that drinking was not a significant factor for EE in the non-MS group whereas it was a significant factor for EE in the pre-MS and MS groups. These results suggest that the influence of alcohol consumption on EE may differ among the non-MS, pre-MS, and MS groups. For example, the difference in the calorie intake by drinking, motility of the digestive tract by IGT, and abdominal fat might have contributed to the results in the present study.[28–30]

The present study showed that the younger was a significant factor for EE in the MS group. The prevalence of smoking between the young subjects (age <50) and elder subjects (age ≥50) in the MS group was 26.4%

Table 3 Univariate and Multivariate Analyses for Factors Associated with EE in the Pre-MS Group (n=964)

	Univariate Analysis			Multivariate Analysis		
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Sex (M/F)	1.744	1.189–2.560	< 0.005	1.446	0.965–2.166	0.074
Age (years)	1.000	0.985–1.016	0.966			
BMI (kg/m^2)	1.028	0.983–1.075	0.231			
WC (cm)	1.000	0.979–1.022	0.983			
Smoking	1.333	0.954–1.861	0.092			
Drinking	1.539	1.138–2.081	< 0.01	1.413	1.029–1.940	< 0.05
SBP (mmHg)	0.999	0.990–1.008	0.827			
DBP (mmHg)	1.003	0.991–1.016	0.589			
Hypertension	1.070	0.787–1.453	0.667			
T-CHO (mg/dL)	1.001	0.996–1.005	0.703			
TG (mg/dL)	1.001	0.998–1.003	0.669			
HDL-C (mg/dL)	1.001	0.991–1.012	0.852			
LDL-C (mg/dL)	1.001	0.996–1.006	0.769			
Dyslipidemia	0.768	0.543–1.087	0.137			
FPG (mg/dL)	1.010	0.998–1.022	0.117			
HbA1c (%)	1.225	0.740–2.029	0.430			
IGT	1.497	0.910–2.460	0.112			
UA (mg/dL)	1.038	0.937–1.151	0.475			
AST (IU/L)	1.015	0.999–1.032	0.065			
ALT (IU/L)	1.009	1.001–1.017	< 0.05	1.007	0.998–1.015	0.114
GGT (IU/L)	1.000	0.996–1.003	0.928			
H. pylori	0.504	0.310–0.817	< 0.01	0.508	0.311–0.829	< 0.01
Hiatal hernia	1.580	1.191–2.097	< 0.005	1.480	1.111–1.972	< 0.01

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; EE, erosive esophagitis; F, female; FPG, fasting plasma glucose; GGT, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; *H. pylori, Helicobacter pylori*; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; M, male; MS, metabolic syndrome; OR, odds ratio; SBP, systolic blood pressure; T-CHO, total cholesterol; TG, triglyceride; UA, uric acid; WC, waist circumference.

and 19.8%, respectively. The prevalence of drinking between the young subjects (age <50) and elder subjects (age ≥50) in the MS group was 73.1% and 66.4%, respectively. Additionally, the prevalence of smoking and drinking in the young subjects (age <50) was significantly higher than in the elder subjects (age ≥50) (all, <0.05). Therefore, the age associated with EE in the MS group might be influenced by lifestyle such as smoking and drinking.

Although the mechanisms controlling the development of hiatal hernia are currently unclear, many studies demonstrated that obesity is an independent risk factor for the development of both hiatal hernia and GERD.[31] Additionally, EE was reported to be associated with hiatal hernia in several studies.[32,33] The present study, in accordance with previous reports, demonstrated that hiatal hernia was significant and independent risk factors for EE in the pre-MS group and the MS group.

In some previous reports, *H. pylori* infection in patients with EE was significantly less than that in patients without EE; further, *H. pylori* serostatus has shown an inverse association with GERD.[12,34] This may be caused by ammonia generation, decreased acid production due to gastric atrophy, and a neuroimmunological influence.[34] The present study showed that the prevalence of positive *H. pylori* infection in all subjects with EE (67/1,348, 5.0%) was significantly lower than in all subjects without EE (784/5,749, 13.6%), and that absence of *H. pylori* was a highly significant predictor of EE in the three groups.

Metabolomics involves the measurement of large numbers of low-molecular-weight metabolites including sugars, amino acids, and hormones. Although several studies have provided insight into the pathogenesis of several cancers,[35–41] few studies have investigated the association between metabolomics and GERD, including EE.[42] An increase of glutamine in glutaminolysis is a notable feature of tumor cells.[43] Under hypoxic conditions, glutamine is converted to glutamate and

Table 4 Univariate and Multivariate Analyses for Factors Associated with EE in the MS Group (n=1,223)

	Univariate Analysis			Multivariate Analysis		
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Sex (M/F)	1.798	1.231–2.624	< 0.005	1.269	0.824–1.954	0.280
Age (years)	0.961	0.946–0.976	< 0.001	0.974	0.957–0.992	< 0.005
BMI (kg/m^2)	1.034	0.998–1.071	0.067			
WC (cm)	1.018	1.002–1.034	< 0.05	1.015	0.997–1.033	0.097
Smoking	1.196	0.888–1.612	0.239			
Drinking	1.597	1.208–2.110	< 0.005	1.468	1.075–2.005	< 0.05
SBP (mmHg)	0.993	0.985–1.001	0.100			
DBP (mmHg)	1.015	1.004–1.027	< 0.05	1.002	0.990–1.015	0.708
Hypertension	0.939	0.541–1.629	0.822			
T-CHO (mg/dL)	1.002	0.999–1.006	0.189			
TG (mg/dL)	1.001	1.000–1.002	< 0.005	1.001	1.000–1.002	< 0.05
HDL-C (mg/dL)	0.997	0.988–1.006	0.477			
LDL-C (mg/dL)	1.001	0.997–1.005	0.609			
Dyslipidemia	1.254	0.912–1.724	0.164			
UA (mg/dL)	1.230	1.115–1.357	< 0.001	1.111	0.995–1.242	0.062
FPG (mg/dL)	0.998	0.993–1.002	0.288			
HbA1c (%)	0.948	0.799–1.124	0.537			
IGT	0.919	0.716–1.179	0.507			
AST (IU/L)	1.012	1.003–1.022	< 0.01	1.002	0.981–1.023	0.868
ALT (IU/L)	1.009	1.004–1.015	< 0.005	1.003	0.991–1.015	0.662
GGT (IU/L)	1.003	1.001–1.005	< 0.005	1.001	0.999–1.004	0.392
H. pylori	0.309	0.196–0.488	< 0.001	0.283	0.176–0.456	< 0.001
Hiatal hernia	1.635	1.269–2.107	< 0.001	1.504	1.154–1.961	< 0.005

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; EE, erosive esophagitis; F, female; FPG, fasting plasma glucose; GGT, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; *H. pylori, Helicobacter pylori*; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; M, male; MS, metabolic syndrome; OR, odds ratio; SBP, systolic blood pressure; T-CHO, total cholesterol; TG, triglyceride; UA, uric acid; WC, waist circumference.

further to α-ketoglutarate by glutaminase and other enzymes to enable adenosine triphosphate (ATP) production through the tricarboxylic acid cycle.[44,45] The present study showed that glutamine levels were significantly lower in subjects with EE than in those without EE. Hypoxic conditions may advance further in subjects with EE than in those without EE in MS. However, there may be no association between hypoxic conditions and the developing from EE to EA because in fact, most patients with EE do not progress to EA. The association between cancer and hypoxanthine varies with the kind of cancer. Hypoxanthine levels were significantly higher in subjects with EE than in those without EE in MS in the present study. Several studies have reported that enzymes associated with the purine biosynthetic pathway are enhanced in tumor cells because purine nucleotides are essential for tumor cell proliferation,[46] and an increase in hypoxanthine is thought to most likely reflect an upregulation in purine metabolism due to hypoxia and oxidative stress. We found that the lactic acid levels were significantly higher in subjects with EE than in those without EE. Lactic acid is a known component of the Warburg effect and aerobic glycolysis, and dysregulated lactate metabolism is thought to be one of the hallmarks of carcinogenesis.[47] Lactate can serve as an energy source in several cancers, inducing glycolytic enzymes, which leads to an increase in ATP supply. Our results suggest elevation of lactate produced by the aerobic or anaerobic glycolysis pathway in subjects with EE. The metabolomic analysis in the present study identified three metabolites that were significantly correlated with EE in MS. Our results suggest metabolomics should be further investigated as a useful tool during medical checkup.

Several limitations exist in the present study that should be acknowledged. First, the present study is an observational single-center study. Multi-center studies are needed to validate our findings. Second, there was a possibility of selection bias because most of the participants in the present study were healthy individuals without symptoms. Whether hospitalized patients for EE would produce similar results to the present study is not clear. Thirds, the definition of non-*H. pylori* infection in the present study was strict. Therefore, there was

Table 5 Comparison of 52 Metabolites Between 34 Subjects with and without EE in the MS Group

Compound Name	Relative Area				
	EE (-) (n = 7)		EE (+) (n = 27)		*p*-value
	Mean	SD	Mean	SD	
Cystine	1.04E-03	1.84E-04	1.05E-03	1.62E-04	0.624
Asparagine	9.62E-05	3.76E-05	8.05E-05	3.63E-05	0.277
Aspartic acid	4.57E-04	6.65E-05	4.12E-04	1.14E-04	0.194
Serine	7.25E-04	1.49E-04	7.31E-04	1.41E-04	0.565
Alanine	2.23E-02	2.76E-03	2.14E-02	6.18E-03	0.882
4-Hydroxyproline	3.50E-04	1.38E-04	3.96E-04	1.55E-04	0.431
Glycine	4.75E-04	1.11E-04	4.38E-04	8.36E-05	0.431
Citicoline	3.38E-06	8.95E-06	1.03E-05	1.83E-05	0.318
Glutamine	3.37E-02	3.49E-03	2.98E-02	3.70E-03	< 0.05
Threonine	3.82E-03	1.22E-03	3.46E-03	7.40E-04	0.317
Dimethylglycine	4.82E-03	6.05E-04	4.69E-03	1.04E-03	0.782
Methionine sulfoxide	7.99E-05	4.33E-05	1.02E-04	3.90E-05	0.277
Glutamic acid	4.01E-03	1.17E-03	3.47E-03	1.55E-03	0.562
Citrulline	7.43E-03	8.67E-04	6.92E-03	1.16E-03	0.194
Guanosine monophosphate	0	NA	2.22E-06	1.07E-05	0.545
Proline	2.83E-01	8.20E-02	2.66E-01	7.49E-02	0.717
Ornithine	4.78E-03	1.28E-03	4.07E-03	8.58E-04	0.077
2-Aminobutyric acid	1.95E-02	4.34E-03	2.00E-02	6.49E-03	0.949
Lysine	3.55E-02	4.89E-03	3.18E-02	3.85E-03	0.110
Histidine	1.09E-02	1.34E-03	1.01E-02	1.95E-03	0.166
Adenosine monophosphate	5.31E-04	1.67E-04	5.97E-04	3.54E-04	0.983
Uracil	3.89E-04	1.27E-04	3.26E-04	1.06E-04	0.233
Argininosuccinic acid	0	NA	3.67E-06	1.33E-05	0.424
Thymidine monophosphate	3.69E-04	7.17E-05	3.83E-04	6.52E-05	0.456
Arginine	5.68E-02	1.00E-02	5.60E-02	1.07E-02	0.949
Creatine	3.64E-02	1.87E-02	3.67E-02	1.38E-02	0.717
Cytosine	1.62E-05	1.95E-05	1.68E-05	2.88E-05	0.689
Hypoxanthine	3.84E-04	1.67E-04	6.38E-04	2.38E-04	< 0.01
Uridine	6.82E-03	6.89E-04	5.89E-03	1.32E-03	0.074
Niacinamide	3.28E-04	1.28E-04	3.47E-04	1.27E-04	0.949
Adenosine 3′,5′-cyclic monophosphate	1.89E-05	2.41E-05	1.43E-05	2.46E-05	0.609
Guanosine	0	NA	4.54E-06	1.44E-05	0.424
Inosine	5.87E-06	1.55E-05	1.61E-05	3.84E-05	0.695
Pantothenic acid	2.10E-04	7.04E-05	1.53E-04	7.79E-05	0.077
Adenine	4.05E-05	2.09E-05	4.64E-05	3.17E-05	0.882
Tyrosine	8.42E-02	1.04E-02	8.64E-02	1.72E-02	0.882
Adenosine	4.23E-06	1.12E-05	1.53E-05	2.91E-06	0.426
Epinephrine	9.60E-05	2.63E-05	9.51E-05	2.85E-05	0.949
Asymmetric dimethylarginine	0	NA	1.27E-06	6.62E-06	0.715
Phenylalanine	7.22E-01	8.36E-02	7.36E-01	8.58E-02	0.717
Kynurenine	4.58E-03	9.01E-04	4.41E-03	8.82E-04	0.509
Acetyl-L-carnitine	9.12E-02	1.60E-02	9.40E-02	2.06E-02	0.915
Tryptophan	3.01E-01	4.62E-02	2.92E-01	4.93E-02	0.456
2-Ketoglutaric acid	4.22E-04	7.63E-05	3.73E-04	1.08E-04	0.131
Malic acid	6.76E-04	1.73E-04	6.20E-04	1.52E-04	0.406
Isocitric acid	3.86E-03	5.37E-04	4.24E-03	8.15E-04	0.180
Pyruvic acid	1.59E-04	7.60E-05	2.23E-04	1.22E-04	0.148
Lactic acid	1.52E-02	3.06E-03	1.97E-02	4.86E-03	< 0.05

(*Continued*)

Table 5 (Continued).

Compound Name	Relative Area				
	EE (-) (n = 7)		EE (+) (n = 27)		*p*-value
	Mean	SD	Mean	SD	
Uric acid	1.10E-02	1.88E-03	1.20E-02	2.60E-03	0.180
Citric acid	5.27E-02	4.82E-03	5.08E-02	6.37E-03	0.360
Succinic acid	1.24E-04	1.63E-04	2.15E-04	1.39E-04	0.221
Xanthine	5.07E-06	1.15E-05	5.40E-05	2.39E-04	0.588

Notes: P-value is based on Mann–Whitney *U*-test. Significant is at the 5% level. Peak areas of individual metabolites were normalized against the peak area of the internal standards, and the resulting values were represented as relative areas.
Abbreviations: EE, erosive esophagitis; MS, metabolic syndrome; NA, not applicable; SD, standard deviation.

Table 6 Spearman Rank Coefficients for Clinical Parameters and Metabolites with Statistically Significant Differences Between Subjects with and without EE in the MS Group

	Glutamine	Hypoxanthine	Lactic Acid
BMI	0.210	−0.114	−0.039
WC	−0.004	0.058	−0.109
Smoking	−0.051	−0.397*	−0.067
Drinking	−0.357*	−0.057	0.069
Hypertension	−0.208	0.106	0.028
Dyslipidemia	−0.256	0.015	−0.015
IGT	−0.192	−0.109	0.237
ALT	0.151	−0.278	−0.102
AST	0.637	−0.234	−0.098
GGT	0.102	−0.115	0.065
UA	−0.100	0.058	−0.008
H. pylori	−0.122	0.005	0.026
Hiatal hernia	−0.192	0.499**	0.192
EE	−0.412*	0.463*	0.374*

Notes: *$p < 0.05$, **$p < 0.005$.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; EE, erosive esophagitis; GGT, gamma-glutamyl transpeptidase; *H. pylori, Helicobacter pylori*; IGT, impaired glucose tolerance; MS, metabolic syndrome; UA, uric acid; WC, waist circumference.

a possibility of false positives for *H. pylori* infection. Finally, the number of subjects who were investigated with metabolomics was small because metabolomics is not usually included in medical checkups. Therefore, it was difficult to analyze for the severity of EE using these subjects. Further large-scale clinical studies on EE in both patients and healthy individuals will be required in the future.

Conclusion

We demonstrated that the prevalence of EE in the pre-MS and MS groups was higher than that in the non-MS group. The ratio of high EE severity increased progressively in the non-MS, pre-MS, and MS groups. Although *H. pylori* is a common significant independent predictor of EE, other independent EE predictors were different among the three groups. Lifestyle factors such as smoking and drinking are important for EE, and several metabolites may help identify the risk of EE in individuals with MS.

Abbreviations

AG, atrophic gastritis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BE, Barrett's esophagus; BMI, body mass index; DBP, diastolic blood pressure; EAC, esophageal adenocarcinoma; EE, erosive esophagitis; F, female; FPG, fasting plasma glucose; GERD, gastroesophageal reflux disease; GGT, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; *H. pylori, Helicobacter pylori*; IGT, impaired glucose tolerance; LA, Los Angeles; LES, lower esophageal sphincter; LDL-C, low-density lipoprotein cholesterol; M, male; MS, metabolic syndrome; SBP, systolic blood pressure; T-CHO, total cholesterol; TG, triglyceride; UA, uric acid; UBT, urea breath test; WC, waist circumference.

Ethics and Consent

All subjects were informed that their clinical data might be analyzed retrospectively, and informed consent was obtained. The study protocol was approved by the Ethics Committee in Shikoku Central Hospital of the Mutual Aid Association of Public School Teachers (H28-49), and all procedures were performed in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare.

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