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Fatty liver disease is associated with an increased risk of gastroesophageal reflux disease in Korean population : a retrospective study.

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Fatty liver disease is associated with an increased risk of gastroesophageal reflux disease in Korean population : a retrospective study.

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Disclosure

All authors declare that they have no conflict of interest.

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Abstract

Objectives: Gastroesophageal reflux disease (GERD) is related to obesity and metabolic syndrome. Fatty liver disease (FLD) emerges as the principal cause of liver disease worldwide, because the prevalence rates of obesity, diabetes, and dyslipidemia, which easily contribute to FLD development, are increasing. In this regard, we aimed to investigate the association between FLD and GERD in Korean population.

Design and setting The enrolled 14,723 subjects were examinees who underwent health check-up examination, including esophagogastroduodenoscopy in 2ndary hospital Korea, between 2004 and 2011. GERD was diagnosed in accordance with the Los Angeles classification and FLD with ultrasonography.

Primary outcome measures FLD is an independent risk factor of GERD.

Results: Among the 14,723 subjects, 4,232 (28.7%) patients were classified into the fatty liver group and 10,491 (71.3%) into the non-fatty liver group. In the univariate analysis, the incidence rate of GERD (10.4% [440/4,232] vs. 6.1% [637/10,491], P<0.0001) was significantly higher in the fatty liver group than in the non-fatty liver group. In the multivariate analysis, FLD was independently associated with GERD risk (odds ratio: 1.19, 95% confidence interval: 1.03-1.37, P=0.016).

Conclusion: FLD is an independent risk factor of GERD in Korean population. The mechanism and pathophysiology between fatty liver and erosive esophagitis should be further evaluated in future studies.

Key words: Gastroesophageal reflux disease, Fatty liver, Alcoholic, Non-alcoholic fatty liver disease

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Strengths and limitations of this study

- ► This study included all subjects for health check-up examination.
- ► This study has the largest sample size among studies in the literature to date.
- ► This study showed the relationship between fatty liver disease and GERD
- ► The study did not survey alcohol intake precisely.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a multifactorial disorder caused by a reflux of acidic gastric contents into the esophagus, leading to tissue damage and symptoms.[1, 2] GERD is related to obesity and metabolic syndrome and has a negative effect on the quality of life and everyday activities from troublesome symptoms and complications. In the general population, the prevalence rate of GERD was ~30%.[3-5]

Fatty liver disease (FLD) includes alcoholic FLD and non-alcoholic FLD (NAFLD). NAFLD is defined as built-up fat exceeding 5% of hepatocytes without significant alcohol intake and any other causes of liver disease.[2] NAFLD ranges from simple steatosis and fatty liver in the early stage to nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis in the progressive stage.[6] Recently, NAFLD has emerged as the principal cause of liver disease worldwide, because the prevalence rates of obesity, diabetes, and dyslipidemia, which easily contribute to NAFLD development, are increasing.

In Korea, increasingly westernized lifestyle and habits increase the prevalence rates of obesity, diabetes, dyslipidemia, GERD, and FLD. However, there were only few studies which investigated the relationship between GERD and FLD.[7-9] Therefore, we investigated the association between these two diseases in this study.

PATIENTS AND METHODS

Study populations

The 14,723 patients who underwent health check-up examination, including medical history, laboratory tests, abdominal ultrasonography, and esophagogastroduodenoscopy

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between 2004 and 2011 in Myongji Hospital, Goyang, Korea, were enrolled. The inclusion criteria were as follows: i) age of >18 years, ii) presence of fatty liver diagnosed using abdominal ultrasonography, and iii) no other liver diseases, such as viral disease, autoimmune liver disease, hemochromatosis, and Wilson's Disease. This study was approved by the Institutional Review Board of Myongji Hospital (IRB NO. 11-093).

Methods

All the patients answered the health questionnaire, including data on sex, age, height, weight, social habits, and medical history. Systolic blood pressure, diastolic blood pressure, fasting glucose level, serum lipid profile, and liver function test results were checked. Obesity was defined as a body mass index (BMI) of ≥25 kg/m^2. The criterion of high blood pressure was a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. A fasting blood glucose level ≥126 mg/dL was defined as a high fasting glucose. We evaluated GERD using the Los Angeles (LA) classification system by esophagogastroduodenoscopy.[10]

Patients and public involvement

Patients and/or public were not involved in present study.

Statistical analysis

The SPSS 18.0 software (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA) for MS Windows® was used for the statistical analysis. Categorical variables were presented as absolute numbers or percentages and continuous data as means (standard deviations). The two subgroups were compared using t-tests, and multivariable analyses for the risk factors of erosive esophagitis were conducted. Statistical analysis using two independent sample t-tests

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was performed. P-values <0.05 were considered statistically significant.

RESULTS

The characteristics of the 14,723 subjects are shown in Table 1. Among the 14,723 subjects, 4,232 (28.7%) patients were classified into the FLD group and 10,491 (71.3%) into the non-FLD group. The FLD and non-FLD groups included 3,078 (72.7%) and 4,766 (45.4%) men (P<0.0001), respectively. The mean age was 50.1 ± 12.2 years in the FLD group and 46.3 ± 12.9 years in the non-FLD group (P<0.0001). The mean BMI was 25.9 ± 2.8 kg/m^2 in the FLD group and 23.0 ± 2.9 kg/m^2 in the non-FLD group (P<0.0001). The mean systolic blood pressure was 126.0 ± 13.2 mmHg in the FLD group and 119.3 ± 14.2 mmHg in the non-FLD group (P<0.0001). The mean diastolic blood pressure was 76.8 ± 9.6 mmHg in the FLD group and 71.8 ± 10.4 mmHg in the non-FLD group (P<0.0001). The mean fasting glucose level was 102.7 ± 27.1 mg/dL in the FLD group and 92.3 ± 17.3 mg/dL in the non-FLD group (P<0.0001).

In the univariate analysis, BMI ≥25 kg/m^2 (61.2% [2,590/4,232] vs. 23.6% [2,476/10,491], P<0.0001), high blood pressure (20.3% [857/4,232] vs. 10.8% [1,133/10,491], P<0.0001), high fasting glucose (10.2% [431/4,232] vs. 2.7% [285/10,491], P<0.0001), and erosive esophagitis (10.4% [440/4,232] vs. 6.1% [637/10,491], P<0.0001) were significantly higher in the FLD group than in the non-FLD group.

The multivariate analyses were performed to evaluate the association between erosive esophagitis and FLD (Table 2). Fatty liver (odds ratio [OR], 1.19; 95% confidence interval [CI], 1.03-1.37; P=0.016), male sex (OR, 3.65; 95% CI, 3.11-4.29; P<0.0001), and obesity (OR, 2.02; 95% CI, 1.16-3.51; P=0.013) have been identified as significant risk factors for GERD. However, high blood pressure (OR, 1.04; 95% CI, 0.88-1.24; P=0.633) and high

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fasting glucose (OR, 1.20; 95% CI, 0.94-1.54; P=0.149) were not statistically significant.

DISCUSSION

GERD is a condition in which refluxed acidic gastric contents result in troublesome symptoms or complications.[11] In Korea, the prevalence of GERD has increased gradually.[12] GERD is related to a variety of symptoms, such as heartburn (most common), regurgitation, and difficulty of swallowing.[13] Therefore, GERD has a negative effect on the quality of life and everyday activities of patients. GERD develops when the anti-reflux barrier comprising the lower esophageal sphincter (LES) and the crucial portion of a hiatus do not function appropriately. LES function is associated with LES length (total and abdominal), intrinsic LES pressure (LESP), and duration and frequency of transient LES relaxation.[14] LES function is attenuated by several factors, such as an increased BMI, intra-abdominal pressure, intra-gastric pressure, inspiratory intra-thoracic pressure, and hiatal hernia. High fat diet and caloric intake increase weight and obesity, which reduce the intrinsic LESP and increase the frequency of transient LES relaxation; these consequently lead to GERD.[15, 16] Therefore, obesity is a risk factor of GERD. In addition, patients with GERD have overexpressed cytokines in the mucosa of the esophagus. Obesity triggers esophageal mucosal injury because a variety of cytokines are produced by adipose tissues and macrophages.[17, 18]

The prevalence of FLD ranges from 25% to 45% worldwide. FLD includes alcoholic FLD and NAFLD. The pathophysiology of NAFLD involves multifactorial mechanisms affected by environmental, genetic, and metabolic factors.[19] Visceral adipose tissues alter the metabolism of lipid and glucose. As a result, hepatocyte fat accumulates, inflammatory milieu injures the liver, and other tissues generate. Lipid toxicity, apoptotic process, oxidative

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stress, and endoplasmic reticular stress lead to liver damage and progressive fibrosis.[20] Increased BMI and obesity are documented risk factors of NAFLD.[19]

From previous studies, we have known that obesity was a risk factor of GERD and NAFLD. In this regard, the present study investigated whether FLD is a risk factor of GERD. In addition, a recent study reported that NAFLD was strongly associated with GERD.[9] However, this study has some limitations, including its small sample size; further, only patients with gastrointestinal problems were included, not the general population. Conversely, the present study included numerous patients for health check-up examination and reported that BMI $\geq$25 kg/m^2, high blood pressure, high fasting glucose, and erosive esophagitis were significantly higher in the FLD group than in the non-FLD group. In the multivariate analysis, the risk factors of GERD were FLD, male sex, and obesity. Therefore, our study suggests that FLD is a risk factor of GERD, which is consistent with those of previous studies.

There are some has some advantages in the present study. First, we included all subjects for health check-up examination. Second, this study has the largest sample size among studies in the literature to date. In this regard, this study may be more useful in the clinical practice. However, it is limited by its retrospective design, and we did not survey alcohol intake precisely.

In conclusion, the present study reports that FLD is an independent risk factor of GERD in Korean population. The mechanism and pathophysiology between fatty liver and erosive esophagitis should be further evaluated in future studies.

Acknowledgments None declare

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Conflicts of interest

There are no conflicts of interest.

Author contributions Ja Sung Choi, Seok-Hoo Jeong and Hee Man Kim were involved in study conception and design; Ki Jun Han and Sangheun Lee conducted statistical analyses; all authors were involved in the drafting and critical revision of the manuscript, and approved the final version, including the authorship list.

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Competing interests None declared.

Patient consent Not required.

Ethics approval This study was approved by the Institutional Review Board of Myongji Hospital (IRB NO. 11-093).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data are not available.

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Table 1. Characteristics of all subjects (n=14,723)

	Fatty liver		P-value
	Presence (n=4,232)	Absence (n=10,491)	
Age	50.1 ± 12.2	46.3 ± 12.9	<0.0001
Male sex	3,078 (72.7%)	4,766 (45.4%)	<0.0001
BMI	25.9 ± 2.8	23.0 ± 2.9	<0.0001
SBP	126.0 ± 13.2	119.3 ± 14.2	<0.0001
DBP	76.8 ± 9.6	71.8 ± 10.4	<0.0001
Fasting glucose	102.7 ± 27.1	92.3 ± 17.3	<0.0001
BMI			<0.0001
<18.5 kg/m^2	11 (0.3%)	460 (4.4%)	
18.5 to 25 kg/m^2	1,631 (38.5%)	7,555 (72.0%)	
≥25 kg/m^2	2,590 (61.2%)	2,476 (23.6%)	
High blood pressure	857 (20.3%)	1,133 (10.8%)	<0.0001
High fasting glucose	431 (10.2%)	285 (2.7%)	<0.0001
Erosive esophagitis	440 (10.4%)	637 (6.1%)	<0.0001
LA-A	317 (7.5%)	480 (4.6%)	

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LA-B	115 (2.7%)	149 (1.4%)
LA-C	8 (0.2%)	5 (0.05%)
LA-D	0 (0%)	3 (0.03%)

High blood pressure: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg

High fasting glucose: ≥126 mg/dL. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LA-A, Los Angeles classification A; LA-B, Los Angeles classification B; LA-C, Los Angeles classification C; LA-D, Los Angeles classification D;

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Table 2. Multivariable analysis for the risk factors of erosive esophagitis

	Erosive esophagitis	
	Odds ratio (95% CI)*	P-value
Fatty liver	1.19 (1.03-1.37)	0.016
Male sex	3.65 (3.11-4.29)	<0.0001
Obesity	2.02 (1.16-3.51)	0.013
High blood pressure	1.04 (0.88-1.24)	0.633
High fasting glucose	1.20 (0.94-1.54)	0.149

*Age was adjusted.

Obesity in Koreans: BMI ≥25 kg/m^2

High blood pressure: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg

High fasting glucose: ≥126 mg/dL

CI, confidence interval

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		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	1
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3
Study design	#4	Present key elements of study design early in the paper	3,4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3,4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale	3,4

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		for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	
	#6b	For matched studies, give matching criteria and the number of controls per case	3,4
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3,4
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for cases and controls.	3,4
Bias	#9	Describe any efforts to address potential sources of bias	3,4
Study size	#10	Explain how the study size was arrived at	3,4
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	4
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	4
	#12b	Describe any methods used to examine subgroups and interactions	N/A
	#12c	Explain how missing data were addressed	4
	#12d	If applicable, explain how matching of cases and controls was addressed	N/A
	#12e	Describe any sensitivity analyses	4
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	5
	#13b	Give reasons for non-participation at each stage	5
	#13c	Consider use of a flow diagram	5
Descriptive data	#14a	Give characteristics of study participants (eg demographic,	5

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		clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	
	#14b	Indicate number of participants with missing data for each variable of interest	5
Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	5
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
	#16b	Report category boundaries when continuous variables were categorized	5
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	5
Key results	#18	Summarise key results with reference to study objectives	6-7
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	6-7
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	6-7
Generalisability	#21	Discuss the generalisability (external validity) of the study results	6-7
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	7

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Fatty liver disease is associated with an increased risk of erosive esophagitis in Korean population: A cross-sectional study.

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Disclosure

All authors declare that they have no conflict of interest.

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Abstract

Objectives: To investigate an association between fatty liver disease (FLD) and erosive esophagitis.

Design and setting: This was a cross-sectional study of subjects selected from examinees who underwent health check-up, including esophagogastroduodenoscopy in one hospital between 2004 and 2011. Erosive esophagitis was classified according to the Los Angeles classification and FLD was diagnosed with ultrasonography. The anthropometric and laboratory data of the subjects were analyzed using chi-square test and multivariate logistic regression. Additionally, we have analyzed our data with two-stage least square estimation using the Baltagi-Chang one-way model to clarify unobserved confounding variable.

Primary outcome measure: The effect of FLD on erosive esophagitis.

Results: Among the 14,723 eligible subjects, 4,232 (28.7%) subjects diagnosed with FLD were classified into the fatty liver group, and 10,491 (71.3%) subjects without FLD were classified into the non-fatty liver group. The incidence rate of erosive esophagitis was significantly higher in the fatty liver group than in the non-fatty liver group (10.4% vs. 6.1%, P<0.0001). The multivariate analysis revealed that the fatty liver group was significantly associated with erosive esophagitis (odds ratio: 1.19, 95% confidence interval: 1.03-1.37, P=0.016).

Conclusion: FLD diagnosed by ultrasonography is an independent risk factor of erosive esophagitis. It suggests that FLD-related metabolic abnormality may be associated with erosive esophagitis.

Key words: Erosive esophagitis, Alcoholic, Fatty liver disease, Non-alcoholic fatty liver

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disease

Strengths and limitations of this study

► The sample size of 14,723 is quite large to have statistical power to clarify the relationship between fatty liver disease and erosive esophagitis.

► This study showed that fatty liver disease was strongly associated with erosive esophagitis.

► The limitation of this study was that alcohol intake of the subjects was evaluated precisely.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a multifactorial disorder caused by a reflux of acidic gastric contents into the esophagus, leading to tissue damage and symptoms.[1, 2] GERD is related to obesity and metabolic syndrome and has a negative effect on the quality of life and everyday activities from troublesome symptoms and complications. In the general population, the prevalence rate of GERD was ~30%.[1-3]

Fatty liver disease (FLD) includes alcoholic FLD and non-alcoholic FLD (NAFLD). NAFLD is defined as built-up fat exceeding 5% of hepatocytes without significant alcohol intake and any other causes of liver disease.[4,5] NAFLD ranges from simple steatosis and fatty liver in the early stage to nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis in the progressive stage.[6] Recently, NAFLD has emerged as the principal cause of liver disease worldwide, because the prevalence rates of obesity, diabetes, and dyslipidemia, which easily contribute to NAFLD development, are increasing.

In Korea, increasingly westernized lifestyle and habits induces the increased prevalence rates of obesity, diabetes, dyslipidemia, FLD as well as GERD. However, there were only few studies which investigated the relationship between GERD and FLD.[7-9] Therefore, we investigated the association between erosive esophagitis diagnosed by endoscopy and FLD diagnosed by ultrasonography in this study.

METHODS

Study populations

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The study subjects were examinee who underwent health check-up in Myongji Hospital (Goyang city, Korea) between 2004 and 2011. The examination of the health check-up included questionnaires of medical history, laboratory tests, abdominal ultrasonography, and esophagogastroduodenoscopy. The subjects with age of >18 years were included. The exclusion criteria were as follows: 1) history of liver diseases, such as acute or chronic viral hepatitis, autoimmune liver disease, hemochromatosis, and Wilson's Disease, 2) liver cirrhosis of any causes, and 3) history of past or current liver cancer. This study was approved by the Institutional Review Board of Myongji Hospital (IRB NO. 11-093).

Methods

This was designed as a cross-sectional study. All the subjects were divided into two groups: FLD group and non-FLD group, according to the presence or absence of FLD. The data were compared between two groups. The data for analysis were obtained from the medical records of the health check-up. The health questionnaire which all the subjects were requested to complete included data on sex, age, height, weight, social habits, and medical history. The anthropometric and laboratory data included systolic blood pressure, diastolic blood pressure, fasting glucose level, serum lipid profile, and liver function test.

Obesity was defined as a body mass index (BMI) of ≥25 kg/m^2. The criterion of high blood pressure was a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. A fasting blood glucose level ≥126 mg/dL was defined as a high fasting glucose. FLD was mainly diagnosed by abdominal ultrasonography. Erosive esophagitis was classified using the Los Angeles (LA) classification system by esophagogastroduodenoscopy.[10,11]

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Patients and public involvement

Patients and/or the general public were not involved in this study.

Statistical analysis

The SPSS 18.0 software (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA) for MS Windows® and STATA version 15.0 were used for the statistical analysis. Categorical variables were presented as absolute numbers or percentages and continuous data as means (standard deviations). The two subgroups were compared using t-tests, and multivariable analyses for the risk factors of erosive esophagitis were conducted. Additionally, we have analyzed our data with two-stage least square estimation using the Baltagi-Chang one-way model (STATA version 15) to clarify unobserved confounding variable. Statistical analysis using two independent sample t-tests was performed. P-values <0.05 were considered statistically significant.

RESULTS

The baseline characteristics of the 14,723 subjects are shown in Table 1. Among the 14,723 subjects, 4,232 (28.7%) patients were classified into the FLD group and 10,491 (71.3%) into the non-FLD group. The male proportion of the FLD group was higher than that of non-FLD group (72.7% [3,078] *vs.* 45.4% [4,766], P<0.0001). The mean age was higher in the FLD group than in the non-FLD group (50.1 ± 12.2 years *vs.* 46.3 ± 12.9 years, P<0.0001). The mean BMI was higher in the FLD group than in the non-FLD group (25.9 ± 2.8 kg/m^2 vs. 23.0 ± 2.9 kg/m^2, P<0.0001). The mean systolic blood pressure was higher in the FLD group than in the non-FLD group (126.0 ± 13.2 mm Hg *vs.* 119.3 ± 14.2 mm Hg,

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P<0.0001). The mean diastolic blood pressure was higher in the FLD group than in the non-FLD group (76.8 ± 9.6 mmHg *vs.* 71.8 ± 10.4 mmHg, P<0.0001). The mean fasting glucose level was higher in the FLD group than in the non-FLD group (102.7 ± 27.1 mg/dL vs. 92.3 ± 17.3 mg/dL, P<0.0001). In the univariate analysis, BMI ≥25 kg/m^2 (61.2% vs. 23.6%, P<0.0001), high blood pressure (20.3% vs. 10.8%, P<0.0001), and high fasting glucose (10.2% vs. 2.7%, P<0.0001) were significantly higher in the FLD group than in the non-FLD group. The prevalence rate of erosive esophagitis was 7.3% (1,077/14,723). The prevalence rate of erosive esophagitis was higher in FLD group than in non-FLD group (10.4% vs. 6.1%, P<0.001).

The multivariate analyses were performed to evaluate the association between erosive esophagitis and FLD (Table 2). FLD group (odds ratio [OR], 1.19; 95% confidence interval [CI], 1.03-1.37; P=0.016), male sex (OR, 3.65; 95% CI, 3.11-4.29; P<0.0001), and obesity (OR, 2.02; 95% CI, 1.16-3.51; P=0.013) have been identified as significant risk factors for erosive esophagitis. However, high blood pressure (OR, 1.04; 95% CI, 0.88-1.24; P=0.633) and high fasting glucose (OR, 1.20; 95% CI, 0.94-1.54; P=0.149) were not statistically significant.

Additionally regression analyses using Baltagi-Chang one-way model were performed to investigate the risk factors of erosive esophagitis (Table 3). In both sexes, fatty liver (Coefficient, 0.0496; 95% CI, -0.0050 – 0.1042; P=0.075), considering the confounding role of obesity, was not identified as a significant risk factor of erosive esophagitis. High blood pressure (Coefficient, -0.0426; 95% CI, -0.0624 – -0.0228; P<0.0001) showed a negative correlation and sex (male) (Coefficient, 0.0580; 95% CI, 0.0433 - 0.0727; P<0.0001) showed a positive correlation with erosive esophagitis. In males, fatty liver (Coefficient, 0.0876; 95%

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CI, 0.0091 – 0.1661; P=0.029), considering the confounding role of obesity, was identified as a significant risk factor of erosive esophagitis. High blood pressure (Coefficient, -0.0647; 95% CI, -0.0942 – -0.0351; P<0.0001) showed a negative correlation with erosive esophagitis. In females, fatty liver (Coefficient, -0.0014; 95% CI, -0.0791 – 0.0762; P=0.970), considering the confounding role of obesity, was not identified as a significant risk factor of erosive esophagitis.

DISCUSSION

Our study demonstrated that FLD group had higher prevalence of erosive esophagitis, and FLD group was significantly associated with the increased risk of erosive esophagitis.

GERD is a condition in which refluxed acidic gastric contents result in troublesome symptoms or complications.[11] In Korea, the prevalence of GERD has increased gradually from 4.6% to 7.3%.[12] In our study, the prevalence of erosive esophagitis was 7.3%. GERD is related to a variety of symptoms, such as heartburn (most common), regurgitation, and difficulty of swallowing.[13] Therefore, GERD has a negative effect on the quality of life and everyday activities of patients. GERD develops when the anti-reflux barrier comprising the lower esophageal sphincter (LES) and the crucial portion of a hiatus do not function appropriately. LES function is associated with LES length (total and abdominal), intrinsic LES pressure (LESP), and duration and frequency of transient LES relaxation.[14] LES function is attenuated by several factors, such as an increased BMI, intra-abdominal pressure, intra-gastric pressure, inspiratory intra-thoracic pressure, and hiatal hernia. High fat diet and caloric intake increase weight and obesity, which reduce the intrinsic LESP and increase the frequency of transient LES relaxation; these consequently lead to GERD.[15, 16] Therefore,

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obesity is a risk factor of GERD. In addition, patients with GERD have overexpressed cytokines in the mucosa of the esophagus. Obesity triggers esophageal mucosal injury because a variety of cytokines are produced by adipose tissues and macrophages.[17, 18]

The prevalence of FLD ranges from 25% to 45% worldwide. FLD includes alcoholic FLD and NAFLD. The pathophysiology of NAFLD involves multifactorial mechanisms affected by environmental, genetic, and metabolic factors.[19] Visceral adipose tissues alter the metabolism of lipid and glucose. As a result, hepatocyte fat accumulates, inflammatory milieu injures the liver, and other tissues generate. Lipid toxicity, apoptotic process, oxidative stress, and endoplasmic reticular stress lead to liver damage and progressive fibrosis.[20] Increased BMI and obesity are documented risk factors of NAFLD.[19]

From previous studies, we have known that obesity was a risk factor of GERD and NAFLD. In this regard, the present study investigated whether FLD is a risk factor of GERD. In addition, a recent study reported that NAFLD was strongly associated with GERD.[9] However, this study has some limitations, including its small sample size; further, only patients with gastrointestinal problems were included, not the general population. Conversely, the present study included numerous subjects for health check-up examination and reported that obesity (BMI $\geq$25 kg/m^2), high blood pressure, high fasting glucose, and erosive esophagitis were significantly higher in the FLD group than in the non-FLD group. In the multivariate analysis, the risk factors of erosive esophagitis were FLD group, male sex, and obesity. Therefore, our study suggests that FLD is a risk factor of GERD which is consistent with those of previous studies.

There were some advantages in the present study. First, we included all subjects for health check-up examination. Second, this study has the largest sample size among studies in the

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literature to date. In this regard, this study may be more useful in the clinical practice. However, it is limited by its retrospective design, and we did not survey alcohol intake precisely. Future prospective studies are needed to elucidate the mechanism for the associations between FLD and erosive esophagitis.

In conclusion, the present study reports that FLD is an independent risk factor of erosive esophagitis in Korean population. The mechanism and pathophysiology between fatty liver and erosive esophagitis should be further evaluated in future studies.

Acknowledgments

None declares

Conflicts of interest

There are no conflicts of interest.

Author contributions

Ja Sung Choi, Seok-Hoo Jeong and Hee Man Kim were involved in study conception and design; Ki Jun Han, Sangheun Lee, and Yun-Jung Yang conducted statistical analyses; all authors were involved in the drafting and critical revision of the manuscript, and approved the final version, including the authorship list.

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Competing interests None declared.

Patient consent Not required.

Ethics approval This study was approved by the Institutional Review Board of Myongji Hospital (IRB NO. 11-093).

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Data sharing statement Data are not available.

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Table 1. Baseline characteristics of all subjects (n=14,723)

Variable	FLD group	Non-FLD group	P-value
n	4,232	10,491	
Age (year)	50.1 ± 12.2	46.3 ± 12.9	<0.0001
Male sex	3,078 (72.7%)	4,766 (45.4%)	<0.0001
BMI (kg/m^2)	25.9 ± 2.8	23.0 ± 2.9	<0.0001
SBP (mm Hg)	126.0 ± 13.2	119.3 ± 14.2	<0.0001
DBP (mm Hg)	76.8 ± 9.6	71.8 ± 10.4	<0.0001
Fasting glucose (mg/dL)	102.7 ± 27.1	92.3 ± 17.3	<0.0001
Obesity (BMI)			<0.0001
<18.5 kg/m^2	11 (0.3%)	460 (4.4%)	
18.5 to 25 kg/m^2	1,631 (38.5%)	7,555 (72.0%)	
≥25 kg/m^2	2,590 (61.2%)	2,476 (23.6%)	
High blood pressure	857 (20.3%)	1,133 (10.8%)	<0.0001
High fasting glucose	431 (10.2%)	285 (2.7%)	<0.0001
Erosive esophagitis	440 (10.4%)	637 (6.1%)	<0.0001
LA-A	317 (7.5%)	480 (4.6%)	
LA-B	115 (2.7%)	149 (1.4%)	
LA-C	8 (0.2%)	5 (0.05%)	
LA-D	0 (0%)	3 (0.03%)	

High blood pressure: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg

High fasting glucose: ≥126 mg/dL. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure;

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Table 2. Multivariable analysis for the risk factors of erosive esophagitis

Variable	Erosive esophagitis	P-value
	Odds ratio (95% CI)*	
Fatty liver disease group	1.19 (1.03-1.37)	0.016
Male sex	3.65 (3.11-4.29)	<0.0001
Obesity (BMI ≥25 kg/m^2)	2.02 (1.16-3.51)	0.013
High blood pressure	1.04 (0.88-1.24)	0.633
High fasting glucose	1.20 (0.94-1.54)	0.149

*Age was adjusted.

High blood pressure: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg; High fasting glucose: ≥126 mg/dL; CI, confidence interval

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Table 3. Regression analysis using Baltagi-Chang for the risk factors of erosive esophagitis

1) In both sexes

Variable	Erosive esophagitis	P-value
	Coefficient (95% CI)	
Fatty liver disease group	0.0496 (-0.0050, 0.1042)	0.075
Gender	0.0580 (0.0433, 0.0727)	<0.0001
High blood pressure	-0.0426 (-0.0624, -0.0228)	<0.0001
High fasting glucose	-0.0192 (-0.0547, 0.0162)	0.287

High blood pressure: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg; High fasting glucose: ≥126 mg/dL; CI, confidence interval

2) In male

Variable	Erosive esophagitis	P-value
	Coefficient (95% CI)	
Fatty liver disease group	0.0876 (0.0091, 0.1661)	0.029
High blood pressure	--0.0647 (-0.0942, -0.0351)	<0.0001
High fasting glucose	-0.0046 (-0.0524, 0.0432)	0.850

High blood pressure: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg; High fasting glucose: ≥126 mg/dL; CI, confidence interval

3) In female

Variable	Erosive esophagitis	P-value
	Coefficient (95% CI)	
Fatty liver disease group	-0.0014 (-0.0791, 0.0762)	0.970
High blood pressure	-0.0143 (-0.0411, 0.0124)	0.0293
High fasting glucose	-0.0423 (-0.0990, 0.0143)	0.143

High blood pressure: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg; High fasting

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glucose: ≥126 mg/dL; CI, confidence interval

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Objectives	#3	State specific objectives, including any prespecified hypotheses	3
Study design	#4	Present key elements of study design early in the paper	3,4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3,4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale	3,4

		for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	
	#6b	For matched studies, give matching criteria and the number of controls per case	3,4
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3,4
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for cases and controls.	3,4
Bias	#9	Describe any efforts to address potential sources of bias	3,4
Study size	#10	Explain how the study size was arrived at	3,4
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	4
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	4
	#12b	Describe any methods used to examine subgroups and interactions	N/A
	#12c	Explain how missing data were addressed	4
	#12d	If applicable, explain how matching of cases and controls was addressed	N/A
	#12e	Describe any sensitivity analyses	4
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	5
	#13b	Give reasons for non-participation at each stage	5
	#13c	Consider use of a flow diagram	5
Descriptive data	#14a	Give characteristics of study participants (eg demographic,	5

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		clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	
	#14b	Indicate number of participants with missing data for each variable of interest	5
Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	5
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
	#16b	Report category boundaries when continuous variables were categorized	5
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	5
Key results	#18	Summarise key results with reference to study objectives	6-7
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	6-7
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	6-7
Generalisability	#21	Discuss the generalisability (external validity) of the study results	6-7
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	7

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Fatty liver disease and the risk of erosive esophagitis in the Korean population: A cross-sectional study.

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Disclosure

All authors declare that they have no conflict of interest.

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Abstract

Objectives: To investigate an association between fatty liver disease (FLD) and erosive esophagitis.

Design and setting: This was a cross-sectional study of subjects selected from examinees who underwent health check-up, including esophagogastroduodenoscopy in one hospital between 2004 and 2011. Erosive esophagitis was classified according to the Los Angeles classification and FLD was diagnosed with ultrasonography. The anthropometric and laboratory data of the subjects were analyzed using chi-square test and multivariate logistic regression. Additionally, we have analyzed our data with two-stage least square estimation using the Baltagi-Chang one-way model to clarify unobserved confounding variable.

Primary outcome measure: The effect of FLD on erosive esophagitis.

Results: Among the 14,723 eligible subjects, 4,232 (28.7%) subjects diagnosed with FLD were classified into the fatty liver group, and 10,491 (71.3%) subjects without FLD were classified into the non-fatty liver group. The incidence rate of erosive esophagitis was significantly higher in the fatty liver group than in the non-fatty liver group (10.4% vs. 6.1%, P<0.0001). The multivariate analysis revealed that the fatty liver group was significantly associated with erosive esophagitis (odds ratio: 1.19, 95% confidence interval: 1.03-1.37, P=0.016).

Conclusion: FLD diagnosed by ultrasonography is an independent risk factor of erosive esophagitis. It suggests that FLD-related metabolic abnormality may be associated with erosive esophagitis.

Key words: Erosive esophagitis, Alcoholic, Fatty liver disease, Non-alcoholic fatty liver

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disease

Strengths and limitations of this study

► The sample size of 14,723 is quite large to have statistical power to clarify the relationship between fatty liver disease and erosive esophagitis.

► This study showed that fatty liver disease was strongly associated with erosive esophagitis.

► The limitation of this study was that alcohol intake of the subjects was evaluated precisely.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a multifactorial disorder caused by a reflux of acidic gastric contents into the esophagus, leading to tissue damage and symptoms.[1, 2] GERD is related to obesity and metabolic syndrome and has a negative effect on the quality of life and everyday activities from troublesome symptoms and complications. In the general population, the prevalence rate of GERD was ~30%.[1-3]

Fatty liver disease (FLD) includes alcoholic FLD and non-alcoholic FLD (NAFLD). NAFLD is defined as built-up fat exceeding 5% of hepatocytes without significant alcohol intake and any other causes of liver disease.[4,5] NAFLD ranges from simple steatosis and fatty liver in the early stage to nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis in the progressive stage.[6] Recently, NAFLD has emerged as the principal cause of liver disease worldwide, because the prevalence rates of obesity, diabetes, and dyslipidemia, which easily contribute to NAFLD development, are increasing.

In Korea, increasingly westernized lifestyle and habits induces the increased prevalence rates of obesity, diabetes, dyslipidemia, FLD as well as GERD. However, there were only few studies which investigated the relationship between GERD and FLD.[7-9] Therefore, we investigated the association between erosive esophagitis diagnosed by endoscopy and FLD diagnosed by ultrasonography in this study.

METHODS

Study populations

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The study subjects were examinee who underwent health check-up in Myongji Hospital (Goyang city, Korea) between 2004 and 2011. The examination of the health check-up included questionnaires of medical history, laboratory tests, abdominal ultrasonography, and esophagogastroduodenoscopy. The subjects with age of >18 years were included. The exclusion criteria were as follows: 1) history of liver diseases, such as acute or chronic viral hepatitis, autoimmune liver disease, hemochromatosis, and Wilson's Disease, 2) liver cirrhosis of any causes, and 3) history of past or current liver cancer. This study was approved by the Institutional Review Board of Myongji Hospital (IRB NO. 11-093).

Methods

This was designed as a cross-sectional study. All the subjects were divided into two groups: FLD group and non-FLD group, according to the presence or absence of FLD. The data were compared between two groups. The data for analysis were obtained from the medical records of the health check-up. The health questionnaire which all the subjects were requested to complete included data on sex, age, height, weight, social habits, and medical history. The anthropometric and laboratory data included systolic blood pressure, diastolic blood pressure, fasting glucose level, serum lipid profile, and liver function test.

Obesity was defined as a body mass index (BMI) of ≥25 kg/m^2. The criterion of high blood pressure was a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. A fasting blood glucose level ≥126 mg/dL was defined as a high fasting glucose. FLD was mainly diagnosed by abdominal ultrasonography. Erosive esophagitis was classified using the Los Angeles (LA) classification system by esophagogastroduodenoscopy.[10,11]

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Patients and public involvement

Patients and/or the general public were not involved in this study.

Statistical analysis

The SPSS 18.0 software (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA) for MS Windows® and STATA version 15.0 were used for the statistical analysis. Categorical variables were presented as absolute numbers or percentages and continuous data as means (standard deviations). The two subgroups were compared using t-tests, and multivariable analyses for the risk factors of erosive esophagitis were conducted. Additionally, we have analyzed our data with two-stage least square estimation using the Baltagi-Chang one-way model (STATA version 15) to clarify unobserved confounding variable. Statistical analysis using two independent sample t-tests was performed. P-values <0.05 were considered statistically significant.

RESULTS

The baseline characteristics of the 14,723 subjects are shown in Table 1. Among the 14,723 subjects, 4,232 (28.7%) patients were classified into the FLD group and 10,491 (71.3%) into the non-FLD group. The male proportion of the FLD group was higher than that of non-FLD group (72.7% [3,078] *vs.* 45.4% [4,766], P<0.0001). The mean age was higher in the FLD group than in the non-FLD group (50.1 ± 12.2 years *vs.* 46.3 ± 12.9 years, P<0.0001). The mean BMI was higher in the FLD group than in the non-FLD group (25.9 ± 2.8 kg/m^2 vs. 23.0 ± 2.9 kg/m^2, P<0.0001). The mean systolic blood pressure was higher in the FLD group than in the non-FLD group (126.0 ± 13.2 mm Hg *vs.* 119.3 ± 14.2 mm Hg,

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P<0.0001). The mean diastolic blood pressure was higher in the FLD group than in the non-FLD group (76.8 ± 9.6 mmHg *vs.* 71.8 ± 10.4 mmHg, P<0.0001). The mean fasting glucose level was higher in the FLD group than in the non-FLD group (102.7 ± 27.1 mg/dL vs. 92.3 ± 17.3 mg/dL, P<0.0001). In the univariate analysis, BMI ≥25 kg/m^2 (61.2% vs. 23.6%, P<0.0001), high blood pressure (20.3% vs. 10.8%, P<0.0001), and high fasting glucose (10.2% vs. 2.7%, P<0.0001) were significantly higher in the FLD group than in the non-FLD group. The prevalence rate of erosive esophagitis was 7.3% (1,077/14,723). The prevalence rate of erosive esophagitis was higher in FLD group than in non-FLD group (10.4% vs. 6.1%, P<0.001).

The multivariate analyses were performed to evaluate the association between erosive esophagitis and FLD (Table 2). FLD group (odds ratio [OR], 1.19; 95% confidence interval [CI], 1.03-1.37; P=0.016), male sex (OR, 3.65; 95% CI, 3.11-4.29; P<0.0001), and obesity (OR, 2.02; 95% CI, 1.16-3.51; P=0.013) have been identified as significant risk factors for erosive esophagitis. However, high blood pressure (OR, 1.04; 95% CI, 0.88-1.24; P=0.633) and high fasting glucose (OR, 1.20; 95% CI, 0.94-1.54; P=0.149) were not statistically significant.

Additionally regression analyses using Baltagi-Chang one-way model were performed to investigate the risk factors of erosive esophagitis (Table 3). In both sexes, fatty liver (Coefficient, 0.0496; 95% CI, -0.0050 – 0.1042; P=0.075), considering the confounding role of obesity, was not identified as a significant risk factor of erosive esophagitis. High blood pressure (Coefficient, -0.0426; 95% CI, -0.0624 – -0.0228; P<0.0001) showed a negative correlation and sex (male) (Coefficient, 0.0580; 95% CI, 0.0433 - 0.0727; P<0.0001) showed a positive correlation with erosive esophagitis. In males, fatty liver (Coefficient, 0.0876; 95%

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CI, 0.0091 – 0.1661; P=0.029), considering the confounding role of obesity, was identified as a significant risk factor of erosive esophagitis. High blood pressure (Coefficient, -0.0647; 95% CI, -0.0942 – -0.0351; P<0.0001) showed a negative correlation with erosive esophagitis. In females, fatty liver (Coefficient, -0.0014; 95% CI, -0.0791 – 0.0762; P=0.970), considering the confounding role of obesity, was not identified as a significant risk factor of erosive esophagitis.

DISCUSSION

Our study demonstrated that FLD group had higher prevalence of erosive esophagitis, and FLD group was significantly associated with the increased risk of erosive esophagitis.

GERD is a condition in which refluxed acidic gastric contents result in troublesome symptoms or complications.[11] In Korea, the prevalence of GERD has increased gradually from 4.6% to 7.3%.[12] In our study, the prevalence of erosive esophagitis was 7.3%. GERD is related to a variety of symptoms, such as heartburn (most common), regurgitation, and difficulty of swallowing.[13] Therefore, GERD has a negative effect on the quality of life and everyday activities of patients. GERD develops when the anti-reflux barrier comprising the lower esophageal sphincter (LES) and the crucial portion of a hiatus do not function appropriately. LES function is associated with LES length (total and abdominal), intrinsic LES pressure (LESP), and duration and frequency of transient LES relaxation.[14] LES function is attenuated by several factors, such as an increased BMI, intra-abdominal pressure, intra-gastric pressure, inspiratory intra-thoracic pressure, and hiatal hernia. High fat diet and caloric intake increase weight and obesity, which reduce the intrinsic LESP and increase the frequency of transient LES relaxation; these consequently lead to GERD.[15, 16] Therefore,

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obesity is a risk factor of GERD. In addition, patients with GERD have overexpressed cytokines in the mucosa of the esophagus. Obesity triggers esophageal mucosal injury because a variety of cytokines are produced by adipose tissues and macrophages.[17, 18]

The prevalence of FLD ranges from 25% to 45% worldwide. FLD includes alcoholic FLD and NAFLD. The pathophysiology of NAFLD involves multifactorial mechanisms affected by environmental, genetic, and metabolic factors.[19] Visceral adipose tissues alter the metabolism of lipid and glucose. As a result, hepatocyte fat accumulates, inflammatory milieu injures the liver, and other tissues generate. Lipid toxicity, apoptotic process, oxidative stress, and endoplasmic reticular stress lead to liver damage and progressive fibrosis.[20] Increased BMI and obesity are documented risk factors of NAFLD.[19]

From previous studies, we have known that obesity was a risk factor of GERD and NAFLD. In this regard, the present study investigated whether FLD is a risk factor of GERD. In addition, a recent study reported that NAFLD was strongly associated with GERD.[9] However, this study has some limitations, including its small sample size; further, only patients with gastrointestinal problems were included, not the general population. Conversely, the present study included numerous subjects for health check-up examination and reported that obesity (BMI $\geq$25 kg/m^2), high blood pressure, high fasting glucose, and erosive esophagitis were significantly higher in the FLD group than in the non-FLD group. In the multivariate analysis, the risk factors of erosive esophagitis were FLD group, male sex, and obesity. Therefore, our study suggests that FLD is a risk factor of GERD which is consistent with those of previous studies.

There were some advantages in the present study. First, we included all subjects for health check-up examination. Second, this study has the largest sample size among studies in the

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literature to date. In this regard, this study may be more useful in the clinical practice. However, it is limited by its retrospective design, and we did not survey alcohol intake precisely. Future prospective studies are needed to elucidate the mechanism for the associations between FLD and erosive esophagitis.

In conclusion, the present study reports that FLD is an independent risk factor of erosive esophagitis in Korean population. The mechanism and pathophysiology between fatty liver and erosive esophagitis should be further evaluated in future studies.

Acknowledgments

None declares

Conflicts of interest

There are no conflicts of interest.

Author contributions

Ja Sung Choi, Seok-Hoo Jeong and Hee Man Kim were involved in study conception and design; Ki Jun Han, Sangheun Lee, and Yun-Jung Yang conducted statistical analyses; all authors were involved in the drafting and critical revision of the manuscript, and approved the final version, including the authorship list.

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Competing interests None declared.

Patient consent Not required.

Ethics approval This study was approved by the Institutional Review Board of Myongji Hospital (IRB NO. 11-093).

Provenance and peer review Not commissioned; externally peer reviewed.

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Data sharing statement Data are not available.

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Table 1. Baseline characteristics of all subjects (n=14,723)

Variable	FLD group	Non-FLD group	P-value
n	4,232	10,491	
Age (year)	50.1 ± 12.2	46.3 ± 12.9	<0.0001
Male sex	3,078 (72.7%)	4,766 (45.4%)	<0.0001
BMI (kg/m^2)	25.9 ± 2.8	23.0 ± 2.9	<0.0001
SBP (mm Hg)	126.0 ± 13.2	119.3 ± 14.2	<0.0001
DBP (mm Hg)	76.8 ± 9.6	71.8 ± 10.4	<0.0001
Fasting glucose (mg/dL)	102.7 ± 27.1	92.3 ± 17.3	<0.0001
Obesity (BMI)			<0.0001
<18.5 kg/m^2	11 (0.3%)	460 (4.4%)	
18.5 to 25 kg/m^2	1,631 (38.5%)	7,555 (72.0%)	
≥25 kg/m^2	2,590 (61.2%)	2,476 (23.6%)	
High blood pressure	857 (20.3%)	1,133 (10.8%)	<0.0001
High fasting glucose	431 (10.2%)	285 (2.7%)	<0.0001
Erosive esophagitis	440 (10.4%)	637 (6.1%)	<0.0001
LA-A	317 (7.5%)	480 (4.6%)	
LA-B	115 (2.7%)	149 (1.4%)	
LA-C	8 (0.2%)	5 (0.05%)	
LA-D	0 (0%)	3 (0.03%)	

High blood pressure: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg

High fasting glucose: ≥126 mg/dL. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure;

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Table 2. Multivariable analysis for the risk factors of erosive esophagitis

Variable	Erosive esophagitis	P-value
	Odds ratio (95% CI)*	
Fatty liver disease group	1.19 (1.03-1.37)	0.016
Male sex	3.65 (3.11-4.29)	<0.0001
Obesity (BMI ≥25 kg/m^2)	2.02 (1.16-3.51)	0.013
High blood pressure	1.04 (0.88-1.24)	0.633
High fasting glucose	1.20 (0.94-1.54)	0.149

*Age was adjusted.

High blood pressure: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg; High fasting glucose: ≥126 mg/dL; CI, confidence interval

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Table 3. Regression analysis using Baltagi-Chang for the risk factors of erosive esophagitis

1) In both sexes

Variable	Erosive esophagitis	P-value
	Coefficient (95% CI)	
Fatty liver disease group	0.0496 (-0.0050, 0.1042)	0.075
Gender	0.0580 (0.0433, 0.0727)	<0.0001
High blood pressure	-0.0426 (-0.0624, -0.0228)	<0.0001
High fasting glucose	-0.0192 (-0.0547, 0.0162)	0.287

High blood pressure: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg; High fasting glucose: ≥126 mg/dL; CI, confidence interval

2) In male

Variable	Erosive esophagitis	P-value
	Coefficient (95% CI)	
Fatty liver disease group	0.0876 (0.0091, 0.1661)	0.029
High blood pressure	--0.0647 (-0.0942, -0.0351)	<0.0001
High fasting glucose	-0.0046 (-0.0524, 0.0432)	0.850

High blood pressure: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg; High fasting glucose: ≥126 mg/dL; CI, confidence interval

3) In female

Variable	Erosive esophagitis	P-value
	Coefficient (95% CI)	
Fatty liver disease group	-0.0014 (-0.0791, 0.0762)	0.970
High blood pressure	-0.0143 (-0.0411, 0.0124)	0.0293
High fasting glucose	-0.0423 (-0.0990, 0.0143)	0.143

High blood pressure: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg; High fasting

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glucose: ≥126 mg/dL; CI, confidence interval

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Reporting checklist for case-control study.

Based on the STROBE case-control guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE case-control reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	1
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3
Study design	#4	Present key elements of study design early in the paper	3,4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3,4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale	3,4

		for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	
	#6b	For matched studies, give matching criteria and the number of controls per case	3,4
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3,4
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for cases and controls.	3,4
Bias	#9	Describe any efforts to address potential sources of bias	3,4
Study size	#10	Explain how the study size was arrived at	3,4
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	4
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	4
	#12b	Describe any methods used to examine subgroups and interactions	N/A
	#12c	Explain how missing data were addressed	4
	#12d	If applicable, explain how matching of cases and controls was addressed	N/A
	#12e	Describe any sensitivity analyses	4
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	5
	#13b	Give reasons for non-participation at each stage	5
	#13c	Consider use of a flow diagram	5
Descriptive data	#14a	Give characteristics of study participants (eg demographic,	5

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		clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	
	#14b	Indicate number of participants with missing data for each variable of interest	5
Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	5
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
	#16b	Report category boundaries when continuous variables were categorized	5
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	5
Key results	#18	Summarise key results with reference to study objectives	6-7
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	6-7
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	6-7
Generalisability	#21	Discuss the generalisability (external validity) of the study results	6-7
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	7

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