Systematic Review/Meta-analysis

Association between gastroesophageal reflux disease and nonalcoholic fatty liver disease: A meta-analysis

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Abstract

Background/Aim: The relationship between gastroesophageal reflux disease (GERD) and nonalcoholic fatty liver disease (NAFLD) has been demonstrated in recent epidemiologic studies although the results were inconsistent. This meta-analysis was conducted to summarize all available data and to estimate the risk of NAFLD among patients with GERD.

Materials and Methods: Comprehensive literature review was conducted using MEDLINE and EMBASE database from inception through November 2016, to identify studies that compared the risk of NAFLD among patients with GERD versus those without GERD. Effect estimates from each study were extracted and combined using the random-effect, generic inverse variance method of DerSimonian and Laird.

Results: Eight studies (four cross-sectional studies and four case–control studies) with 31,322 participants met the eligibility criteria and were included in the meta-analysis. The risk of NAFLD among patients with GERD was significantly higher than those without GERD with the pooled odds ratio of 2.07 (95% confidence interval, 1.54–2.79). The statistical heterogeneity was high with an I^2 of 87%.

Conclusions: A significantly increased risk of NAFLD among patients with GERD was observed in this meta-analysis.

Keywords: Erosive esophagitis, gastroesophageal reflux, meta-analysis, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a common hepatic disorder characterized by macrovesicular fat accumulation in the liver of individuals with no history of excessive alcohol consumption.[1] Insulin resistance and chronic inflammation are closely linked to the pathogenesis of NAFLD[2] and are often considered as the liver manifestation of metabolic syndrome.[3] With the pandemic of obesity, NAFLD is estimated to affect over 64 million people in the United States.[3-5] Risk factors of NAFLD include obesity, hypertension, dyslipidemia, hyperuricemia, lack of sleep, and physical inactivity.[2,6-9]

Gastroesophageal reflux disease (GERD) is one of the common gastrointestinal ailments characterized

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by the reflux of stomach contents into esophagus causing symptoms of heartburn, regurgitation, and dysphagia.[10] It is more common in Western countries with the estimated prevalence of 20% compared with <5% in Asian countries.[11] GERD is a risk factor for esophageal adenocarcinoma and several extraesophageal diseases including laryngitis, reflux asthma syndrome, interstitial lung disease, and recurrent otitis media.[10]

Recent studies have suggested that GERD could also be a risk factor for NAFLD although the results were inconsistent.[12-20] To summarize all available data, we conducted this systematic review and meta-analysis of observational studies, which compared the risk of NAFLD among patients with GERD versus those without GERD.

MATERIALS AND METHODS

Information sources and search strategy

A systematic literature search of MEDLINE and EMBASE database was carried out from inception to November 2016 to identify all original studies that investigated the association between GERD and NAFLD. The systematic literature review was independently conducted by three investigators (K.W., P.P., and P.U.) using the search strategy that included the terms for "gastroesophageal reflux" and "nonalcoholic fatty liver disease" as described in online supplementary data 1. No language limitation was applied. A manual search for additional potentially relevant studies using references of selected included articles was also performed. This study was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement, which is provided as online supplementary data 2.

Selection criteria

Eligible studies were required to be cross-sectional, case–control, or cohort studies that investigated the relationship between GERD and NAFLD. They were also required to provide the effect estimates [odds ratios (OR), relative risks (RR), hazard ratios (HR) or standardized incidence ratio (SIR)] with 95% confidence intervals (CI). Inclusion was not restricted by study size. When more than one article using the same database/cohort was available, the study with the most comprehensive data/analyses was included.

Retrieved articles were independently reviewed for their eligibility by the same three investigators (K.W., P.P., and P.U.). Disagreement was resolved by conference with all investigators. Newcastle-Ottawa quality assessment scale was used to appraise the quality of the study in three areas, including the recruitment of cases and controls, the comparability between the groups, and the ascertainment of the outcome of interest for cohort study and the exposure for case–control study.[21] The modified Newcastle-Ottawa scale as described by Herzog *et al*. was used for cross-sectional study.[22]

Data abstraction

A structured data collection form was used to extract the following data from each study: title of the study, name of the first author, publication year, year of the study, country where the study was conducted, number of subjects, demographics of subjects, methods used to identify and verify GERD and NAFLD, adjusted effect estimates with 95% CI, and covariates that were adjusted in the multivariable analysis.

To ensure the accuracy, this data extraction process was independently performed by two investigators (K.W. and P.P.) and was reviewed by the senior investigator (P.U.).

Statistical analysis

Data analysis was performed using the Review Manager 5.3 software from the Cochrane Collaboration (London, UK). Adjusted point estimates from each study were combined by the generic inverse variance method of DerSimonian and Laird, which assigned the weight of each study for the pooled analysis based on its variance.[23] As the outcome of interest was relatively uncommon, we planned to use RR and HR of cohort study as an estimate for OR to calculate the pooled effect estimates with OR of case–control study and cross-sectional study. In light of the high likelihood of between-study variance because of different study designs, populations, and methodologies, random-effect model was used. Cochran's Q test and I^2 statistic were used to determine the between-study heterogeneity. A value of I^2 of 0–25% represents insignificant heterogeneity, 26–50% represents low heterogeneity, 51–75% represents moderate heterogeneity, and >75% represents high heterogeneity.[24]

RESULTS

Using our search strategy, 962 potentially eligible articles were identified (350 articles from MEDLINE and 612 articles from EMBASE). After the exclusion of duplicated 320 articles, 642 articles underwent title and abstract review; 624 articles were excluded at this stage because they were case reports, case series, correspondences, review articles, *in vitro* studies, animal studies, or interventional studies, leaving 25 articles for full-text review. Twelve of them were excluded after the full-length review as they did not report the outcome of interest, while three articles were excluded as they were descriptive studies without

comparative analysis. Ten studies met the eligibility criteria. However, four studies utilized the same database.[16,17,19,25] The Choi *et al*.[25] and the Lee *et al*.[19] studies used the same cohort of employees of three Korean universities from 2007 to 2009. Similarly, the studies by Kang *et al*.[16] and Kim *et al*.[17] used the same cohort recruited from Myongji Hospital, Goyang, Korea from 2004 to 2011. To avoid double-counting of the same data, only the studies by Lee *et al*.[19] and Kang *et al*. were included. Those two studies were chosen over the studies by Choi *et al*.[25] and Kim *et al*.[17] as they provided more comprehensive data in the articles. Therefore, eight studies (four cross-sectional studies[15,16,19,26] and four case–control studies[12,14,18,20]) with 31,322 participants were included in the final analysis. The literature retrieval, review, and selection process are shown in Figure 1. The characteristics and quality assessment of the studies are shown in Table 1. It should be noted that the inter-rater agreement for the quality assessment using the Newcastle-Ottawa scale was high with the kappa statistics of 0.85.

We found a significantly increased risk of NAFLD among patients with GERD with the pooled OR of 2.07 (95% CI, 1.54–2.79), as demonstrated in Figure 2. The between-study heterogeneity was high with an I^2 of 87%. Subgroup analysis according to study design showed a significantly elevated risk in both cross-sectional (pooled OR 1.52; 95% CI, 1.15–2.00; I^2 86%) and case–control subgroup (pooled OR 3.04; 95% CI, 2.27–4.06; I^2 0%).

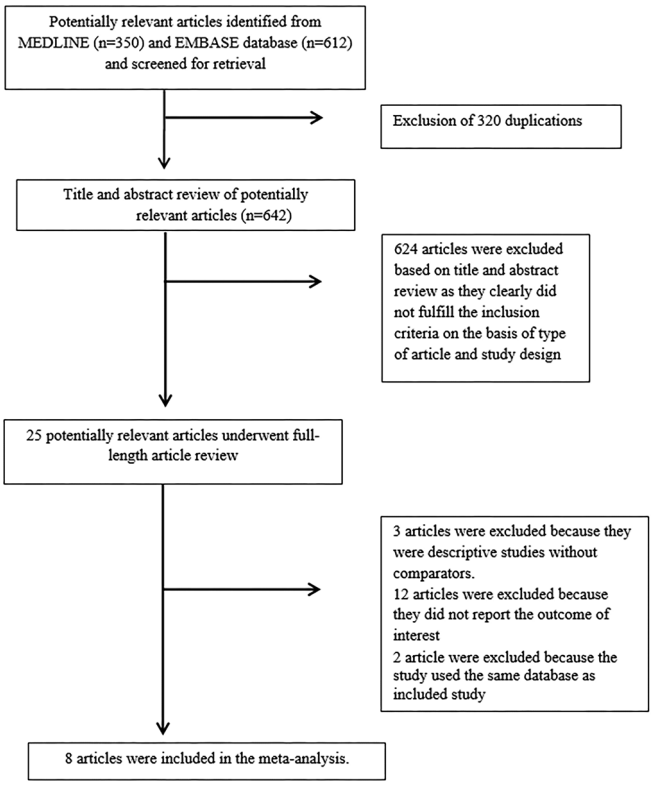

Figure 1: Literature review process

Because the statistical heterogeneity remained high in cross-sectional study subgroup, we have conducted a jack-knife sensitivity analysis by excluding one study at a time from the full analysis. Interestingly, we found that exclusion of the study by Chung *et al*.[26] dramatically reduced I^2 to 1% and did not significantly alter the pooled effect estimate of this subgroup (pooled OR 1.24; 95% CI, 1.14–1.35).

Evaluation for publication bias

Funnel plot was used to assess publication bias [Figure 3]. The graph is asymmetric and, thus, suggests that publication bias in favor of positive studies might have been present.

DISCUSSION

This study is the first systematic review and meta-analysis that summarizes all available data on the association between GERD and NAFLD. We found an approximately two-fold increased risk of NAFLD among patients with GERD compared with subjects without GERD.

Why patients with NAFLD have a higher risk of NAFLD is not well-understood. There are several possible explanations.

First, the apparent association may not be causal but is a result of shared underlying risk factors. Central obesity is the key feature of metabolic syndrome and is linked to both NAFLD and GERD. It is well known that visceral fat plays an important role in insulin resistance, the prime factor in the pathogenesis of NAFLD.[2,27] It has been demonstrated that increased abdominal pressure from the accumulation of visceral fat is a contributing factor to esophageal regurgitation and development of GERD.[28] Moreover, visceral adipose tissue in human is known to produce several proinflammatory cytokines and increased level of these cytokines is associated with a lower esophageal sphincter tone, which could predispose to GERD.[29-31] Increased oxidative stress associated with inflammation is also deleterious to the esophageal muscular layer.[32,33] Unhealthy eating habit such as heavy meals before bedtime could lead to both GERD and obesity (and, thus NAFLD). Hypertriglyceridemia is another component of metabolic syndrome and, thus, is common among patients with NAFLD.[34,35] Interestingly, studies have suggested that triglyceride could affect the lower esophageal sphincter's tone and could possibly be the shared underlying factor between NAFLD and GERD.[36,37]

Table 1: Characteristics of the studies

	Lee *et al.*[19]	Fujikawa *et al.*[14]	Kang *et al.*[16]	Miele *et al.*[18]
Country	Korea	Japan	Korea	Italy
Study design	Cross-sectional study	Case–control study	Cross-sectional study	Case–control study
Year	2011	2012	2012	2012
Number of participants	2,340	NAFLD: 96 Control: 139	14,723	NAFLD: 185 Control: 112
Participants	Participants were employee of three Korean universities who received anthropometric measurement and endoscopy from the study center between January 2007 and December 2009	NAFLD: Cases were recruited from hepatology clinic of the study center between July 2010 and January 2011 Control: Controls without NAFLD were recruited from the health check-up clinic of the same study center during the same period of time	Participants were adults who underwent EGD as a part of health check-up examination at the study center (Myongji Hospital, Goyang, Korea) between 2004 and 2011	NAFLD: Cases were consecutively recruited from hepatology clinic of the study center over a period of 2 years Control: Controls were healthy volunteers without NAFLD who were recruited from the same underlying population
Mean age of participants in years	NA	NAFLD: 54.6 Control: 50.1	NA	NAFLD: 46.4 Control: 46.6
Percentage of female	NA	NAFLD: 47.9 Control: 64.0	NA	NAFLD: 69.7 Control: 59.8
Diagnosis of GERD	Endoscopic assessment compatible with reflux esophagitis	Frequency scale for the symptoms of GERD >8	Endoscopic assessment compatible with reflux esophagitis	Questionnaire was used to assess GERS, having symptoms at least 3 months prior to enrollment
Diagnosis of NAFLD	Ultrasonographic evidence of hepatic steatosis with no other causes of secondary hepatic fat accumulation	Ultrasonographic evidence of hepatic steatosis with no other causes of secondary hepatic fat accumulation	Ultrasonographic evidence of hepatic steatosis with no other causes of secondary hepatic fat accumulation	Histological diagnosis of NAFLD was made based on the Brunt criteria
Confounder adjustment	Age, sex, overweight, HTN, DM	None	Age, sex, obesity, high BP, high FBG	BMI, MetS, increased WC, PPIs, and antacid use
Quality assessment (Newcastle-Ottawa scale)	Selection: 3 Comparability: 1 Outcome: 3	Selection: 3 Comparability: 1 Outcome: 3	Selection: 3 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3
	S. Yamamoto *et al.*[20]	**Hung *et al.*[15]**	**Chung *et al.*[26]**	**Catanzaro *et al.*[12]**
Country	Japan	Taiwan	Korea	Italy
Study design	Case–control study	Cross-sectional study	Cross-sectional study	Case–control study
Year	2014	2014	2014	2014
Number of participants	NAFLD: 36 Control: 73	12,090	1,139	NAFLD: 206 Control: 183
Participants	NAFLD: Cases were NAFLD patients who also underwent EGD at the study center between March 1998 and July 2012 Control: Controls without NAFLD were adults who underwent EGD as a part of health check-up examination at the study center during the same period of time	Participants were subjects who underwent a health checkup with EGD and liver ultrasound at the study center between January 1, 2000 and August 31, 2009	Participants were recruited from health promotion center at Yonsei University Health System, Seoul, Korea, who underwent EGD and liver transient elastography	Participants were outpatients who came to the Gastroenterology Outpatient Clinic at Policlinico “G. Rodolico” in Catania–Italy between January 2012 and December 2013
Mean age of participants in years	NAFLD: 65.0 Control: 64.0	48.9	NA	Median age NAFLD: 56 Control: 51
Percentage of female	NAFLD: 38.9 Control: 52.1	40.6	NA	59.9

Contd...

Table 1: Contd...

	S. Yamamoto *et al.*[20]	Hung *et al.*[15]	Chung *et al.*[26]	Catanzaro *et al.*[12]
Diagnosis of GERD	Endoscopic assessment compatible with reflux esophagitis	Endoscopic assessment compatible with reflux esophagitis	Endoscopic assessment compatible with reflux esophagitis	Compatible symptoms of reflux esophagitis and endoscopic assessment (resulted in LES incompetence, hiatal hernia, erosive esophagitis, gastritis and H. pylori infection)
Diagnosis of NAFLD	Review of medical record	Ultrasonographic evidence of hepatic steatosis with no other causes of secondary hepatic fat accumulation	CAP score was used to define severity of hepatic steatosis as S0<270 dB/m, S1 270-299 dB/m, S2 300-319 dB/m, and S3≥300 dB/m	Ultrasonographic evidence of hepatic steatosis with no other causes of secondary hepatic fat accumulation
Confounder adjustment	None	Age, sex, general obesity, central obesity, HTN, DM, hiatal hernia, high AST, Cr, hypertriglyceridemia, low HDL-C, alcohol consumption, tea drinking, smoking, habitual exercise	Sex, central obesity, hiatus hernia	Age, BMI, MetS
Quality assessment (Newcastle-Ottawa scale)	Selection: 3 Comparability: 1 Outcome: 3	Selection: 3 Comparability: 2 Outcome: 3	Selection: 3 Comparability: 1 Outcome: 3	Selection: 3 Comparability: 1 Outcome: 3

NAFLD: Nonalcoholic fatty liver disease, GERD: Gastroesophageal reflux disease, EGD: Esophagogastroduodenoscopy, BP: Blood pressure, FBG: Fasting blood glucose, HTN: Hypertension, DM: Diabetes mellitus, LES: Lower esophageal sphincter, H. pylori: Helicobacter pylori, BMI: Body mass index, MetS: Metabolic syndrome, CAP: Controlled attenuation parameter, EE: Erosive esophagitis, AST: Aspartate aminotransferase, Cr: Creatinine, HDL-C: High-density lipoprotein cholesterol, GERS: Gastroesophageal reflux symptom, NASH: Non-alcoholic steatohepatitis, WC: Waist circumference, PPIs: Proton pump inhibitors

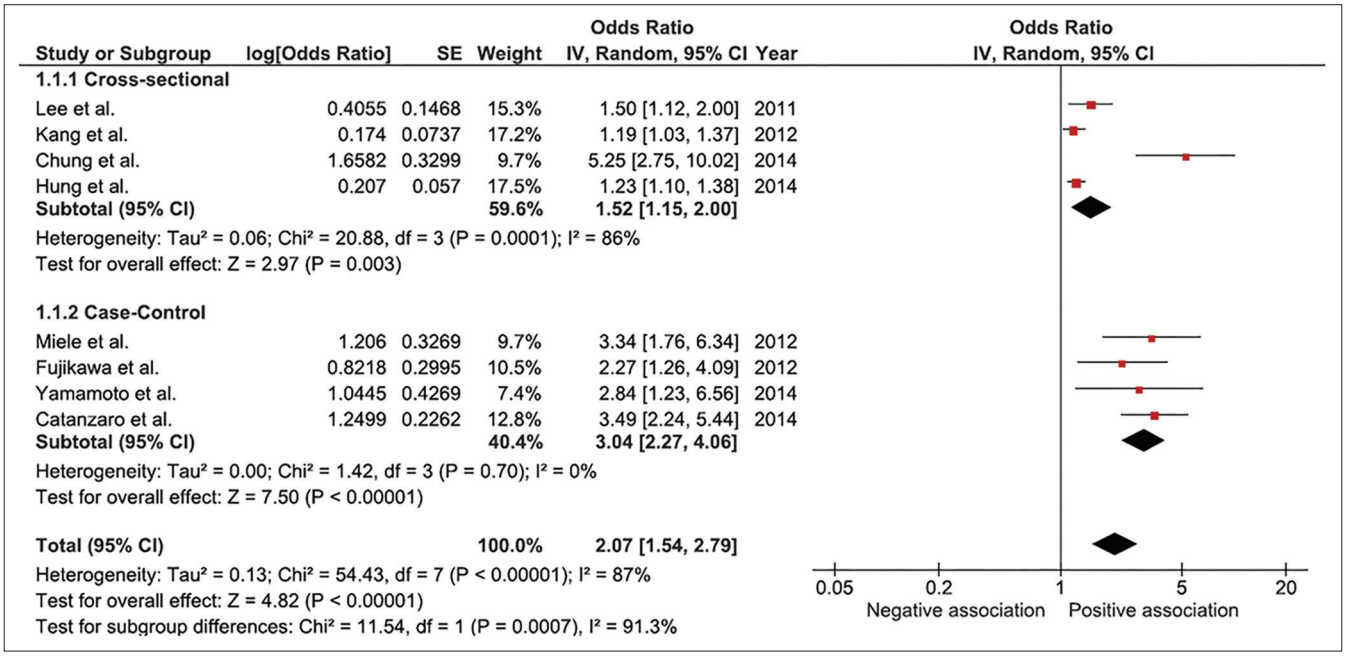

Figure 2: Forest plot

Second, NAFLD may be linked to GERD via autonomic nervous system dysfunction. Studies have demonstrated that patients with NAFLD had a higher prevalence of autonomic disturbance.[38-40] The cause of this increased autonomic abnormality is still not known. Studies have also shown that autonomic dysfunction could lead to abnormal gastric and esophageal motility and, thus, predispose to development of GERD.[41-43]

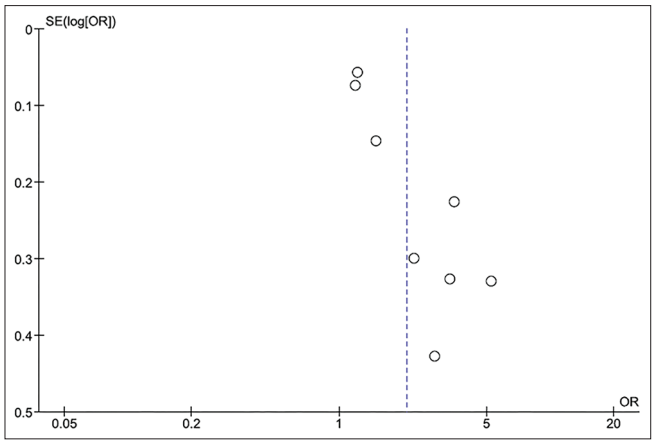

Figure 3: Funnel plot

Although the quality of included studies was high as reflected by the high Newcastle-Ottawa scores and the literature review process was comprehensive, we acknowledge that this study has some limitations and the results should be interpreted with caution.

First, statistical heterogeneity was high in the meta-analysis. We believe that the difference in study design was the main source of the between-study variation as subgroup analysis of only case–control studies showed an I^2 of 0%. Nonetheless, the statistical heterogeneity remained high in cross-sectional study subgroup. The I^2 decreased dramatically after the exclusion of the only study[26] that used transient elastography to diagnose NAFLD (other cross-sectional studies used ultrasonography), which may suggest that the difference in the methods used to diagnose NAFLD was also responsible for the high between-study variation. Second, all of the included studies were cross-sectional and case–control studies. There is no longitudinal study that investigates this association. Therefore, the temporal relationship between GERD and NAFLD could not be clearly established. Third, the funnel plot of this meta-analysis was asymmetric. Therefore, publication bias in favor of positive study may have been present. Fourth, almost all of the included studies were conducted in Asian countries, which have a lower prevalence for both GERD and NAFLD. Therefore, generalizability of the results to other populations could be limited.

CONCLUSION

In summary, this study demonstrated a significantly increased risk of NAFLD among patients with GERD. However, it is not known whether this association is causal or is a result of shared underlying risk factors. Further investigations are required to characterize the underlying pathogenesis.

Disclosure

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Authors' contributions

All authors had access to the data and a role in writing the manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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