What is the difference between Metabolic Dysfunction-Associated Steatotic Liver Disease, Eosinophilic Esophagitis and Gastroesophageal Reflux Disease?

Thai Hau Koo, MD[1], Rishi Chowdhary, MD[3], Yi Lin Lee, MD[2], Xue Bin Leong, MD[2], Andee Dzulkarnaen Zakaria, MMed (Surgery)[2]

[1]Gastrointestinal Function and Motility Unit, Hospital Pakar Universiti Sains Malaysia, School of Medical Sciences, Kubang Kerian, Kelantan, Malaysia, [2]Division of Colorectal Surgery, Department of Surgery, Hospital Pakar Universiti Sains Malaysia, School of Medical Sciences, Kubang Kerian, Kelantan, Malaysia, [3]Department of Medicine-Pediatrics, MetroHealth Medical Center, Cleveland, Ohio, USA

ABSTRACT

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is emerging as a key hepatic manifestation of metabolic syndrome that affects nearly 40% of the global population. While links between MASLD and conditions such as type 2 diabetes and cardiovascular disease are well recognized, recent evidence suggests a potential connection with eosinophilic esophagitis (EoE) and gastroesophageal reflux disease (GERD). This editorial explores overlapping pathophysiology and inflammatory mechanisms shared by MASLD, EoE, and GERD, drawing from the current global literature and a multicenter U.S. cohort study. This editorial highlights how systemic inflammation, oxidative stress, and gut microbiota imbalance may drive these associations. Notably, MASLD was associated with a 2.38-fold increased risk of EoE and a modest but significant association with GERD independent of obesity. These findings underscore the importance of considering MASLD beyond liver-specific pathology and call for further research on shared immunometabolic pathways. An improved awareness of these relationships may guide diagnostic and therapeutic strategies in clinical practice.

INTRODUCTION

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), an updated nomenclature for Non-Alcoholic Fatty Liver Disease (NAFLD), is gaining recognition as a hepatic manifestation of metabolic syndrome (MetS), encompassing a wide range of hepatic pathologies, ranging from hepatic steatosis to cirrhosis.[1] The term 'metabolic-associated fatty liver disease (MAFLD)" is a refined alternative and more accurate descriptor than NAFLD, intended to be a more accurate underlying metabolic dysfunction commonly present in affected individuals.[2] Concurrently, eosinophilic esophagitis (EoE) and gastroesophageal reflux disorder (GERD) have emerged with substantial symptom overlap and complex inflammatory underpinnings, where EoE may lead to GERD by reducing the ability of the esophagus to clear normal reflux, while GERD might contribute to EoE by damaging the epithelial barrier and allowing allergens to trigger inflammation.[3] This editorial explores the potential associations between MASLD, EoE, and GERD, drawing upon findings from a recent multicenter retrospective cohort study conducted in the United States, along with insights from global research.

Understanding MASLD and Its Systemic Reach

The MASLD reflects the liver-specific manifestation of MetS, which is marked by hepatic steatosis and is strongly associated with insulin resistance. To meet these criteria, an individual must have either one or more of the following conditions: excess weight including overweight or obesity, type 2 diabetes, or other features of metabolic dysfunction, as described by Sangro et al., with the presence of hepatic steatosis.[1] Meta-analyses conducted by Chan et al. revealed that MASLD affects over a third of the global population, with a notable proportion of cases occurring in individuals with a body mass index (BMI) within the normal range, among whom metabolic conditions, such as hypertension and type 2 diabetes, are commonly and significantly associated. The worldwide prevalence of MASLD has been reported at 38.77%, with rates of approximately 55.33% in certain regions such as Europe.[2] Its pathophysiology involves chronic low-grade inflammation, oxidative stress, and altered lipid metabolism.[4] As MetS continues to increase, its systemic effects, such as diabetes and cardiovascular disease, are increasingly mirrored in the liver through conditions such as MASLD, which is now recognized as a hepatic manifestation of these metabolic disturbances.[2] These effects extend beyond the liver and implicate other organs, suggesting MASLD's relevance as a driver of systemic disease.[5]

EoE and GERD: Distinctions and Diagnostic Convergence

EoE is a long-standing condition marked by eosinophilic infiltration of the esophageal mucosa, which is driven by a Th2-driven immune reaction triggered by food or environmental allergens, cytokine activity (interleukin (IL)-4, IL-5, and IL-13), and epithelial barrier dysfunction.[3,6] According to studies by Dellon et al., the clinical features of EoE in adults include dysphagia (about 60% to 100%), heartburn (about 30% to 60%), and non-cardiac chest pain (approximately 8% to 44%). These individuals also frequently have coexisting allergic conditions (food allergies, allergic rhinitis, sinusitis, asthma, and atopic dermatitis).[3] In contrast, GERD occurs when backward movement of gastric

Corresponding Author: Andee Dzulkarnaen Zakaria
Email: andee@usm.my

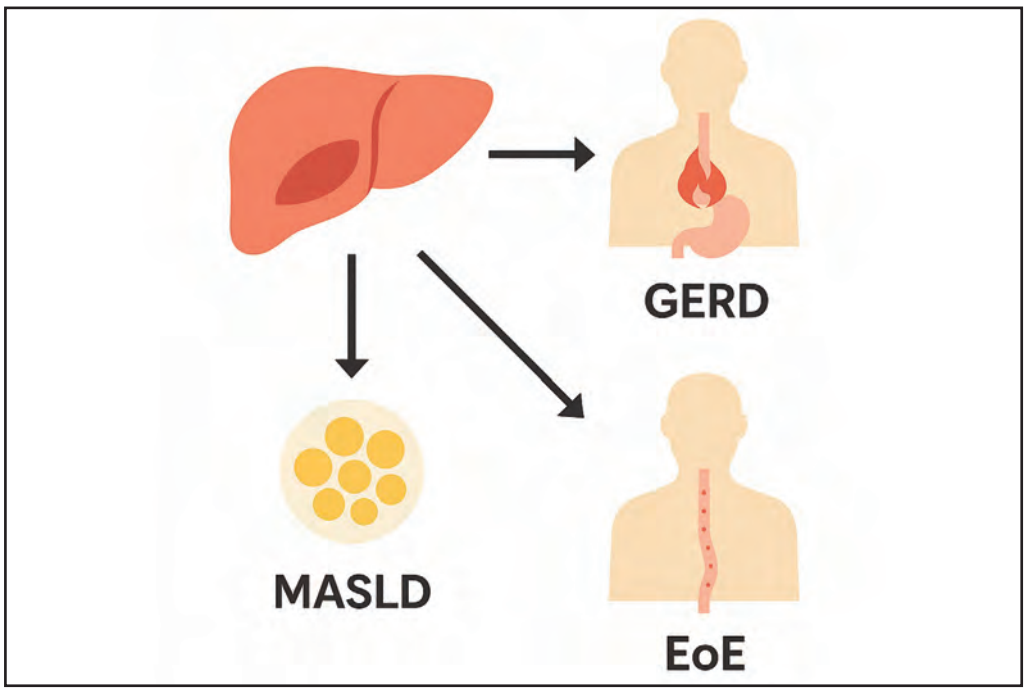

Fig. 1: This figure visually represents the proposed associations between MASLD and two esophageal conditions: GERD and EoE

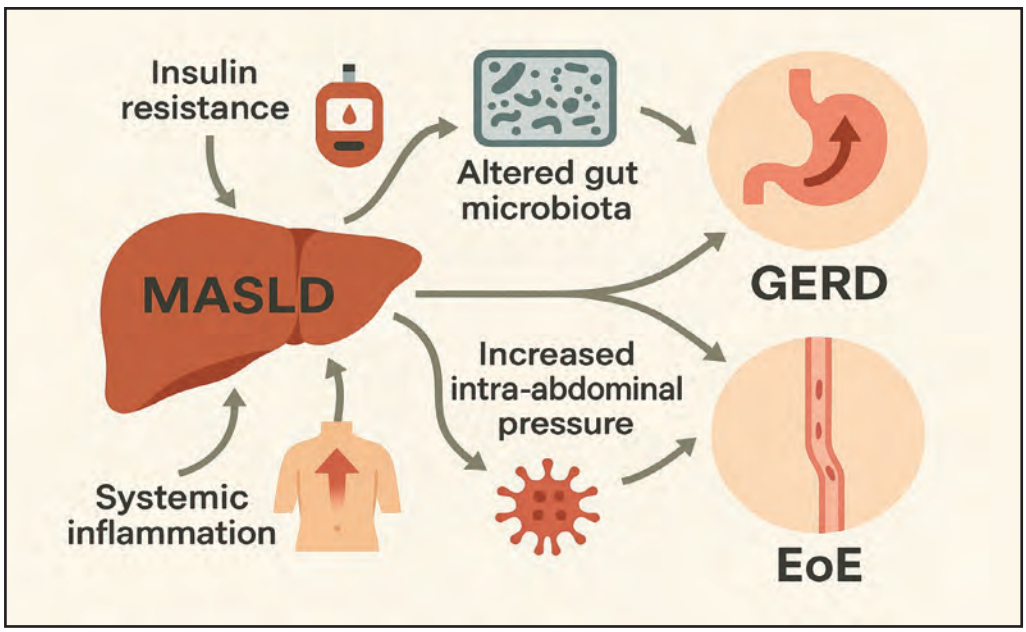

Fig. 2: This figure illustrates the proposed pathophysiological links between MASLD and esophageal disorders such as GERD and EoE

and duodenal contents into the lower esophagus leads to the development of a chronic condition.[4] Despite differing pathogenesis, GERD and EoE often present overlapping symptoms.[3,7] PPI-responsive esophageal eosinophilia (PPI-REE) and EoE share overlapping clinical, endoscopic, and histological features, which makes differentiation challenging. Standard diagnostic tools, such as pH monitoring and endoscopy, are often inadequate, as both conditions exhibit similar inflammatory mediators and molecular markers.[3] A trial on PPI therapy is required before confirming the diagnosis of EoE. According to the current definitions, patients whose esophageal eosinophilia resolves with this treatment are excluded from EoE diagnosis.[3] However, studies have shown that up to 74% of patients with esophageal eosinophilia respond to PPIs.[3]

Interlinking MASLD with GERD: Epidemiologic and Mechanistic Evidence

Research spanning multiple continents, including longitudinal cohorts and meta-analyses, has demonstrated a consistent association between NAFLD/MASLD and GERD.[5] In a Korean cohort of over 34,000 individuals, NAFLD was

initially linked to an increased risk of reflux esophagitis; however, the association weakened after adjusting for BMI, further highlighting the mediating role of obesity.[8] Conversely, meta-analyses by Xue et al. support that MASLD remains significantly associated with GERD even after adjusting for metabolic risk factors, indicating that the association persists regardless of age, sex, or obesity.[5] Xue et al. also reported an odds ratio estimated at 1.28, yielding a 95% CI between 1.12 and 1.44, and the association persisted in both adjusted and unadjusted models.[5]

Mechanistically, visceral obesity may increase intragastric and transesophageal pressures, leading to structural changes at the gastroesophageal junction, such as hiatal hernia formation and shortening of the lower esophageal sphincter (LES). Additionally, systemic inflammation is driven by adipose tissue and resident immune cells through the secretion of proinflammatory cytokines, which may result in esophageal mucosal injury. Both mechanisms promote reflux[4] Moreover, increased oxidative stress, as evidenced by elevated biomarkers, has been associated with overweight and MetS. In GERD, reactive oxygen species (ROS) combined with acid exposure may aggravate the damage to the esophageal lining[4]

Emerging Link Between MASLD and EoE: A Novel Frontier
Using the U.S. National Inpatient Sample, Kohli et al. conducted a multicenter cohort analysis and found that patients presenting with MASLD had more than double the odds of acquiring EoE, which is independent of obesity and other metabolic factors, with an adjusted odds ratio of 2.38 was reported with a 95% CI ranging from 1.82 to 3.11, and a p-value of less than 0.001. The study reported a 6.1% incidence of MASLD in patients with EoE compared to 2.9% in those without EoE.[7] Lamb et al. additionally reported a higher prevalence of radiographic hepatic steatosis in approximately 26% of patients with EoE compared to 21% in controls.[9] In patients with EoE, reduced HIF-1α signaling may impair oxygen-sensing pathways and compromise epithelial barrier integrity by affecting the expression of tight junction proteins, such as claudin-1.[6] Additionally, individuals with EoE and GERD have shown changes in their microbiomes, which include a general reduction in microbial diversity in EoE patients. In models of high-fat intake, saturated fats reaching the distal intestine are associated with gut microbial shifts, particularly an elevated Firmicutes-to-Bacteroidetes ratio. These microbiota disturbances may contribute to increased cytokine expression, potentially driving the shared inflammatory responses observed in both EoE and MASLD.[7]

Shared Mechanisms and Immunometabolic Crosstalk
All three disorders, MASLD, EoE, and GERD, have convergence in inflammatory signaling, oxidative stress, and free radicals at the cellular level.[7] For example, changes in the microbiome, esophagus, or gut occur with EoE, and MASLD can lead to downstream overexpression of cytokines, resulting in similar pro-inflammatory changes in EoE and MASLD.[7]

In addition, ROS are believed to contribute to the pathophysiological mechanisms underlying gastrointestinal diseases including GERD.[4] Patients with GERD were observed to exhibit elevated sensitivity to H2O2 and lipid peroxidation when compared to controls, implying a multifactorial mechanism involving acid exposure and the resulting generation of ROS as a contributing factor to mucosal damage and might be involved in hepatocellular damage and inflammation.[4] Cytokines such as IL-8 and platelet-activating factor (PAF) are upregulated in the esophageal mucosa of individuals with GERD.[4] In addition, elevated serum levels of IL-6 and IL-8 have been observed in both experimental animal models and individuals with NAFLD.[4]

The patatin-like phospholipase domain contains (PNPLA3) protein gene, a powerful modulator of lipid droplet deposition observed in both hepatocytes and hepatic stellate cells, which has demonstrated a strong connection to the disease mechanism of NAFLD due to overexpression of downstream inflammatory pathways.[7] Interestingly, PNPLA3 was found to be a genetic locus associated with EoE (odds ratio, 1.343).[7] Apart from genetics, MASLD, EoE, and GERD involve a complex interplay of pathways that include the overexpression of cytokines.[7]

Clinical and Translational Implications
Higher rates of MASLD were found in the EoE group than in those without EoE, with rates of 6.1% and 2.9%, respectively ($p < 0.001$). When uncontrolled factors were controlled for, MASLD was associated with a 2.38-fold increased likelihood of developing EoE, with a 95% confidence interval of 1.82 to 3.11 and a p-value of less than 0.001.[7] Patients must be initiated on PPI therapy prior to excluding the diagnosis of EoE; responders with esophageal eosinophilia do not have EoE as presently defined.[3] Heartburn occurs in 30%-60% of patients with EoE.[3] In adults with reflux symptoms that are resistant to PPI, the etiology is EoE in 1–8% of cases.[3] Other factors that have been linked to a higher risk of EoE include younger age, Caucasian ethnicity, irritable bowel syndrome (IBS), GERD, inflammatory bowel disease (IBD), and celiac disease (CD).[7] A meta-analysis of observational studies provides evidence of a strong positive correlation between NAFLD and GERD risk that remained even after controlling for age, sex, BMI, diabetes, triglycerides, and other metabolic risk factors.[5]

LIMITATIONS AND FUTURE DIRECTIONS

There is no therapy yet for MASLD to halt disease progression to liver fibrosis or to reduce established fibrosis because biological drug targets are difficult to find owing to the pathophysiology of MASLD complexity.[1] A meta-analysis of observational studies provides evidence for a strong correlation between NAFLD and the risk of GERD, but the temporal association between GERD and NAFLD has not been definitively established.[5] Another question concerns the phenotype of EoE. It is unclear whether EoE may progress from one phenotype to another or whether the phenotypes are stable.[3] The causal association between NAFLD and GERD remains uncertain and requires confirmation in future large-scale cohort studies.[5] At present, it is uncertain whether NAFLD is an independent pathogen in the pathogenesis of GERD, irrespective of obesity. Further prospective studies are required to confirm this correlation are required.[7]

CONCLUSION

Briefly, MASLD increases the risk of both GERD and EoE. There are numerous overlapping symptoms of GERD and EoE. GERD can also cause increased infiltration of the esophagus by eosinophils, making it extremely difficult to distinguish between GERD and EoE. EoE may induce GERD (because of impaired ileal clearance) and GERD can induce EoE (through augmented epithelial permeability and antigen presentation). Patients with MASLD had a 2.38-fold greater risk of indicating a strong association with EoE (95% confidence interval: 1.82 to 3.11; $p < 0.001$). MASLD and EoE share parallel pathologies that are possibly linked by metabolic or microbiome-mediated mechanisms. MASLD was linked to a heightened risk of GERD, with a pooled OR of 1.28 and a 95% confidence interval ranging from 1.12 to 1.44, suggesting a modest but significant risk elevation. GERD manifestations were significantly associated with elevated BMI and MetS. However, NAFLD was significantly associated with GERD independent of MetS.

ACKNOWLEDGEMENTS

Not applicable.

REFERENCES

1. Sangro P, de la Torre Aláez M, Sangro B, D'Avola D. Metabolic dysfunction-associated fatty liver disease (MAFLD): an update of the recent advances in pharmacological treatment. J Physiol Biochem 2023; 79(4): 869-79.
2. Chan KE, Koh TJL, Tang ASP, Quek J, Yong JN, Tay P, et al. Global Prevalence and Clinical characteristics of metabolic-associated fatty liver disease: aA meta-analysis and systematic review of 10,739,607 Individuals. J Clin Endocrinol Metab 2022; 107(9): 2691-700.
3. Dellon ES, Liacouras CA. Advances in clinical management of eosinophilic esophagitis. Gastroenterology 2014; 147(6): 1238-54.
4. Catanzaro R, Calabrese F, Occhipinti S, Anzalone MG, Italia A, Milazzo M, Marotta F. Nonalcoholic fatty liver disease increases risk for gastroesophageal reflux symptoms. Dig Dis Sci 2014; 59(8): 1939-45.
5. Xue J, Xin H, Ren N, Zhou C, Yang J, Song L, Qin S. Nonalcoholic fatty liver disease increases the risk of gastroesophageal reflux disease: A systematic review and meta-analysis. Eur J Clin Invest 2019; 49(9): e13158.
6. Ryan S, Crowe L, Almeida Cruz SN, Galbraith MD, O'Brien C, Hammer JA, et al. Metabolic dysfunction mediated by HIF-1α contributes to epithelial differentiation defects in eosinophilic esophagitis. J Allergy Clin Immunol 2024; 154(6): 1472-88.
7. Kohli I, Sohal A, Patel J, Roytman M. Analysis of the association between eosinophilic esophagitis and MASLD: retrospective, observational, cohort analysis of the national inpatient sample 2016-2020. J Gastrointestin Liver Dis 2024; 33(3): 309-15.
8. Min YW, Kim Y, Gwak GY, Gu S, Kang D, Cho SJ, Guallar E, Cho J, Sinn DH. Non-alcoholic fatty liver disease and the development of reflux esophagitis: A cohort study. J Gastroenterol Hepatol 2018; 33(5): 1053-8.
9. Lamb B, Jophlin L. S1207 Association of eosinophilic esophagitis (EoE) with non-alcoholic fatty liver disease (NAFLD). Off J Am Coll Gastroenterol 2021; 116(1): S558.