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EDITORIAL

Investigating causal links between gastroesophageal reflux disease and essential hypertension

Gowthami Sai Kogilathota Jagirdhar, Yatinder Bains, Salim Surani

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Abstract

Gastroesophageal reflux disease (GERD) is a prevalent global health concern with a rising incidence. Various risk factors, including obesity, hiatal hernia, and smoking, contribute to its development. Recent research suggests associations between GERD and metabolic syndrome, cardiac diseases, and hypertension (HTN). Mechanisms linking GERD to HTN involve autonomic dysfunction, inflammatory states, and endothelial dysfunction. Furthermore, GERD medications such as proton-pump inhibitors may impact blood pressure regulation. Conversely, antihypertensive medications like beta-blockers and calcium channel blockers can exacerbate GERD symptoms. While bidirectional causality exists between GERD and HTN, longitudinal studies are warranted to elucidate the precise relationship. Treatment of GERD, including anti-reflux surgery, may positively influence HTN control. However, the interplay of lifestyle factors, comorbidities, and medications necessitates further investigation to comprehensively understand this relationship. In this editorial, we comment on the article published by Wei *et al* in the recent issue of the *World Journal of Clinical Cases*. We evaluate their claims on the causal association between GERD and HTN.

Key Words: Gastroesophageal reflux disease; Hypertension; Metabolic syndrome; Gastroesophageal reflux disease; Hiatal hernia

Core Tip: The relationship between gastroesophageal reflux disease (GERD) and hypertension (HTN) is multifaceted, involving mechanisms such as autonomic dysfunction, nitric oxide levels, and medication effects. GERD treatment, including anti-reflux surgery, may improve HTN control, highlighting the clinical relevance of understanding this association. However, the complex interplay of comorbidities and medications warrants further investigation to elucidate causal pathways and optimize patient management strategies.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is becoming a prevalent disease globally. There were 783.95 million cases of GERD globally per the Global Burden of Diseases, Injuries, and Risk Factors Study of 2019. The prevalence is rapidly rising, with a 77.58% increase in prevalence from 1990 to 2019. Risk factors for GERD include obesity, hiatal hernia, smoking, pregnancy, and many others. In their bidirectional Mendelian randomization study, Wei *et al*[1] found that GERD was associated with hypertension (HTN), and it increased the risk of HTN. We expand on the potential mechanisms, pathophysiology, and relation between GERD and HTN.

POTENTIAL FACTORS ASSOCIATED WITH GERD

In recent studies, GERD has been found concurrently with metabolic syndrome and cardiac disease[2]. Metabolic syndrome patients have higher GERD symptoms. Metabolic syndrome is associated with autonomic dysfunction, and this can worsen gastroesophageal motility, causing GERD. Further metabolic syndrome is proposed to be an inflammatory state that can cause increased levels of interleukin-1β and interleukin-6, interleukin-8, tumor necrosis factor-alpha, Nuclear factor kappa-β, which can cause chronic stimulation of the lower esophageal sphincter (LES), worsen LES contractility, causing GERD[3,4]. Patients often have concomitant diabetes, which is associated with autonomic nerve damage that affects the Vagus nerve, leading to LES dysfunction and GERD[4,5]. Weight and obesity can predispose to GERD through an increase in intraabdominal fat pressure that causes relaxation of the LES and increased episodes of reflux. Dietary habits associated with obesity, such as increased fat intake, also promote reflux[5,6]. GERD is related to cardiovascular and ischemic heart disease by increasing proinflammatory cytokines, causing endothelial dysfunction and sympathetic tone, and causing autonomic imbalance. This results in decreased nitric oxide (NO) metabolites decreased esophageal tissue resistance, and dysfunction leading to GERD[3,7]. Studies in the literature describe the relationship between GERD and stroke[8]. Some of these studies lack specificity on the definition of GERD and heartburn and the absence of endoscopic diagnosis to confirm it misclassified patients[9]. Often patients have additional comorbidities and are on medications that influence GERD in these studies. If these factors are unadjusted in the analysis, it can lead to false results.

RELATIONSHIP BETWEEN GERD AND HTN

HTN in prior studies was associated with an odds ratio of 1.5 for the risk of GERD[10]. The mechanism of proposed low blood pressure (BP) in GERD patients is based on decreased sympathetic function in patients with GERD, causing blunting of BP responses to stressors. Recent studies examined the role of NO and low BP, stating that NO causes LES relaxation. Patients with GERD have higher NO levels in their blood, causing low esophageal sphincter resting tone, thus increasing GERD and decreasing BP.

In a prospective study by Li *et al*[2], patients were classified as GERD based on esophageal impedance and pH monitoring. Seventy-five percent have at least one episode of high BP associated with acid reflux symptoms. After treatment with antacid therapy for 14 d, these populations had a statistically significant decrease in BP parameters. However, chronic proton-pump inhibitor (PPI) use may cause elevation in BP by disrupting pathways that cause NO production and bioavailability. They reduce NO synthase activity in the endothelium and endothelium-dependent vasodilation. They decrease the availability of protons in the gastric juice, thereby decreasing NO formation from nitrates. Thus, it decreases the reduction in BP from ingested nitrates by disrupting the nitrate-nitrite-NO pathway[11]. Symptoms of GERD often result in chest pain and discomfort. This can induce neural reflux, causing increased sympathetic activity, which can induce HTN.

In the study by Wei *et al*[1], the authors describe pleiotropy in the initial analysis suggesting the association with the exposure is weak between GERD and essential HTN (odds ratio 1.46) that required changing the data of HTN. The final odds ratio after changing the data is 1.002 between GERD and essential HTN. The authors also state they detected hetero-

geneity and horizonal pleiotropy between GERD and diastolic BP suggesting absence of a strong causal relationship between GERD and diastolic BP. GERD is also thought to provoke arrhythmia and bradycardic episodes predisposing to hypertensive heart disease in literature[7,12]. Wei *et al*[1] also describes the association between GERD and hypertensive heart disease. Similar to prior studies Wei *et al*[1] also describes an association between GERD and renal disease[8].

Patients with HTN are frequently on beta blockers and calcium channel blockers. Yoshida *et al*[13] found that atenolol increased esophageal body contraction, and nifedipine decreased it in the short term. Calcium channel blockers can reduce the tone of the LES and decrease esophageal clearance, thereby increasing GERD. Thus, patients can have higher GERD symptoms while on these medications. Treatment for GERD has improved HTN control in patients in some studies. In a retrospective study by Hu *et al*[14], 40% of patients with GERD who underwent Nissen or Toupet fundoplication either decreased or stopped using anti-hypertensives post-procedure. Further, there was also a decrease in the mean BP that was statistically significant. Often, studies done to evaluate the relationship between GERD and HTN do not consider the antihypertensive drugs or PPI patients are on. Often, the results of these studies are not adjusted for various confounding factors, thus producing variable results. Patients with HTN often have additional comorbidities, including obesity and increased abdominal girth, which can worsen GERD symptoms. Wei *et al*[1] describe a decreased risk of Barrett's esophagus with HTN. Few studies in the literature describe increased risk of Barrett's esophagus in patients with metabolic syndrome in the absence of GERD[15-17]. However, the definition of GERD, reflux esophagitis, and underlying confounding factors, including sex, appear to give conflicting results in these studies compared to controls. Often, the risk of Barrett's metabolic syndrome may be marginally increased and often not clinically significant, necessitating further research on the association[18,19]. GERD is a disease that can be influenced by several factors. Certain lifestyle factors, dietary habits, medications, or comorbidities that were not adequately accounted for in the analysis could influence the observed associations. The Mendelian randomization study conducted by Wei *et al*[1] is unable to measure multiple confounding factors that influence the association between GERD and HTN and therefore the results drawn may be distorted.

The study conducted by Wei *et al*[1] may not be generalizable to the global population since it was conducted in Europe, and genetic factors and disease prevalence may vary in different populations. While the study primarily investigates the causal effect of GERD/BE on HTN, reverse causation cannot be entirely ruled out. HTN may also influence the development or exacerbation of GERD/BE, leading to bidirectional causality. Further, longitudinal studies or alternative causal inference methods may help elucidate the directionality of the observed associations. The efficacy of gastroesophageal reflux treatment (*e.g.*, proton pump inhibitors, anti-reflux surgery) in preventing or managing HTN requires further investigation through randomized controlled trials or observational studies.

CONCLUSION

The is a causal and bidirectional relationship between GERD and HTN. This correlation is influenced by patients underlying comorbidities, medications, dosage, and duration of usage.

FOOTNOTES

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