Original Article

Relationship Between Gastroesophageal Reflux Disease And Type 2 Diabetes Mellitus

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Abstract

Gastroesophageal reflux disease (GERD) has increased in prevalence over the past 20 years worldwide. Also, diabetes mellitus (DM) is becoming increasingly common in the general population. DM and GERD have a two-way association effect on health. Both conditions have had a significant negative impact on the cost of healthcare and have even impeded societal and economic growth. A Literature review in the field provides conflicting information regarding the prevalence of GERD in diabetes individuals. Studies have been performed recently to assess the relationship between GERD and type 2 diabetes. Some studies revealed a positive association between type 2 diabetes and GERD, while others found no association between these conditions.

Keywords: Gastroesophageal Reflux Disease, Type 2 Diabetes Mellitus

INTRODUCTION

Gastroesophageal reflux disease (GERD) is the most common disease in gastroenterology and surgery outpatient clinics. It is a chronic disease with a higher prevalence than incidence. It has been shown to harm the quality of life ***(1).***

The global definition of GERD is a disorder that occurs when the stomach contents reflux into the esophagus and causes symptoms and/or complications that make it troublesome for the patient ***(2).***

The disease prevalence increased between 1990 and 2019 by 77.53 percent, from 441.57 million to 783.95 million, respectively. The prevalence rate is high in North Africa and the Middle East, Latin America, the Caribbean, and South Asia (> 12,000 cases per 100,000 population) ***(3).***

Females had higher than males, and all sexes aging peaked in the 30–34 year age group ***(3).***

Obese people were more likely to have GERD than non-obese people, with a prevalence rate of 22% ***(4).*** The risk increases in both normal and overweight people as BMI rises from normal to obese **(5).**

Type 2 Diabetes Mellitus **(T2DM)** patients typically have gastrointestinal symptoms. The relationship between T2DM and GERD was compared to non-diabetic controls; the odd ratio (OR)of GERD was 1.61 in diabetic patients ***(6).***

The pathogenesis of GERD includes 1) anti-reflux barrier (lower esophageal sphincter (LES) and crural diaphragm), 2) dysfunctional esophagogastric junction, 3) reduced esophageal clearance, and 4) changes in esophageal mucosal integrity. Refluxing stomach juice into the esophagus causes the release of cytokines and chemokines, which attract inflammatory cells and may also contribute to symptoms ***(7).***

Reduced salivary production, delayed stomach emptying, and esophageal hypersensitivity may further contribute to GERD symptoms. As a result, Treating GERD as a single disease with various phenotypic manifestations and diagnostic issues is no longer possible ***(7).***

Gastroesophageal reflux symptoms have become troublesome when hurting a person's well-being and causing a significant decrease in quality of life. However, if there are no troublesome reflux symptoms, it should not be classified as GERD ***(2).***

Patients classify as troublesome when having mild symptoms that occur two or more days per week or moderate/severe symptoms that occur over one day per week ***(2).***

GERD manifestations are classified into esophageal and extra-esophageal syndromes. The esophageal syndromes are divided into ***symptomatic and esophageal injury syndromes*** **(*2*).**

Symptomatic syndromes may be typical reflux syndrome or reflux chest pain syndrome. However, extra-esophageal syndromes are divided into established and proposed associations ***(2).***

Typical reflux syndrome is characterized by troublesome heartburn or regurgitation. Other symptoms, such as epigastric pain

or sleep disturbance, may occur **(*2*).**
Heartburn is a burning sensation in the retrosternal region **(*2*).**
Regurgitation is the sensation of the flow of gastric content into the mouth or throat **(*2*).**
Heartburn and regurgitation are characteristic of GERD. GERD is the most common cause of heartburn, but many other causes exist. The diagnosis of typical reflux syndrome is based on the characteristic symptoms, and there is no need for diagnostic testing **(*2*).**
Non-erosive reflux disease (NERD) presents troublesome characteristic reflux symptoms and no esophageal injury at endoscopy **(*2*).**
Epigastric pain is one of the major symptoms of GERD. In addition, sleep disturbance frequently occurs with GERD **(*2*).**
Exercise-induced gastroesophageal reflux can cause troublesome GERD symptoms in persons with no or minimal symptoms at other times **(*2*).**
Reflux chest pain syndrome is chest pain that looks like ischemic cardiac pain but with no evidence of ischemia. GERD may cause chest pain without heartburn or regurgitation. Esophageal motor disorders can cause similar pain but are not as severe as GERD **(*2*).**

Gastroesophageal reflux disease (GERD) has increased in prevalence over the past 20 years worldwide **(*3*).** Also, diabetes mellitus (DM) is becoming increasingly common in the general population **(*8*).**
DM and GERD have a two-way association effect on health. Both conditions have had a significant negative impact on the cost of healthcare and have even impeded societal and economic growth **(*9*).**
A Literature review in the field provides conflicting information regarding the prevalence of GERD in diabetes individuals. Studies have been performed recently to assess the relationship between GERD and type 2 diabetes. Some studies revealed a positive association between type 2 diabetes and GERD**,** while others found no association between these conditions**(*6*).**
A recent meta-analysis of nine studies (one conducted in the United States, one in Europe, and seven in Asia) involving 9067 cases and 81,968 controls found a strong link between diabetes and GERD. The most considerable evidence for this association was found in Asian studies**,** as indicated in individual studies from China **(*6*).**
On the other hand, the prevalence of GERD was not noticeably higher in diabetic individuals. According to two sizable population-based investigations that used the Norwegian health survey **(*10*)** and the United Kingdom General Practice Research Database **(*11*),** respectively.
Ha, et al. (*12*) found that patients with type 2 diabetes had a similar prevalence of GERD to non-diabetics. Additionally, they discovered that GERD in type 2 diabetes was unrelated to age, DM duration, or peripheral and cardiovascular autonomic neuropathy **(*12*).**
Karpenko et al. (*13*). observed that GERD symptoms are more common in people with type 2 diabetes than in the general population **(*13*).** Therefore, 40.7 percent of patients in the research by **Wang et al. (*27*),** including 150 people with type 2 diabetes, showed symptoms of GERD. According to a Spanish study, 28 percent of DM patients had abnormal gastroesophageal (GE) reflux **(*14*).**
Hirata et al. (26), a group of Japanese researchers, found that patients with type 2 diabetes had a 23 percent prevalence of GERD symptoms. Korean researchers discovered an 18.4 percent prevalence of reflux esophagitis in type 2 diabetic patients**.** In a 2014s study by **Sun et al., (*6*).** on 775 patients with type 2 diabetes mellitus in Shanghai found that 16 percent had common GERD symptoms **(*6*).** Also, many studies have found a higher prevalence of GERD symptoms in type 2 diabetes **(*15*).**
In type 2 diabetes, gastroparesis is less common than esophageal problems. Esophageal abnormalities in diabetes have complex pathophysiology. The most significant risk factors are high blood sugar, autonomic neuropathy, presbyesophagus, biomechanical and sensory esophageal changes, and psychiatric comorbidity**.** Diabetes most likely causes esophageal morpho-dynamic and biomechanical remodeling, which causes sensorimotor dysfunction **(*16*).**
Heartburn is a symptom of GERD, most likely due to autonomic neuropathy, decreased lower esophageal sphincter (LES) pressure, increased transient LES relaxations; related to hyperglycemia, impaired tubular esophageal clearance function, delayed gastric emptying. Twenty-eight percent of diabetic patients who underwent 24-hour ambulatory pH meter testing had abnormal gastroesophageal reflux. In the same study, the prevalence was much higher than in the general population and was associated with autonomic neuropathy **(*14*).**
In another study, typical reflux symptoms occurred independently of peripheral neuropathy. However, esophagitis occurs more commonly with neuropathy than without neuropathy. That suggests autonomic neuropathy may be a separate risk factor for erosive esophagitis**.** Regurgitation may appear as a symptom of GERD, along with bronchospasm, laryngitis, and a chronic cough. Dysphagia is uncommon in diabetes **(*17*).**
Disturbance in hormonal balance might predispose to gastroesophageal reflux in patients with diabetes. These changes include insulin, leptin, ghrelin, and adiponectin serum levels **(*16*).**
Compared to healthy people, patients with type 2 diabetes experience less postprandial sensation of fullness, delayed gastric emptying and reduced antral contractions due to low serum glucagon-like peptide 1 (GLP-1) levels **(*18*).**

Chang et al. (*9*) explored the independent risk factors for diabetic patients with GERD. They reviewed the risk factors from previous studies and found that age, dietary habits, family history, gender, obesity, and smoking increased the risk of both GERD and DM. In their study, the statistically significant risk factors for diabetes were gender, age, body mass index, waist

circumference, betel quid chewing habit, lack of physical activity, and family history of DM. First, their study found that gender was a risk factor. Males had a higher risk of DM than females **(*9*),** consistent with previous studies showing that gender is an important modifier and a fundamental biological factor with a key role in regulating dynamic balance in health **(*19*).**
Age was inversely related to GERD's occurrence in 847 Japanese individuals with type 2 diabetes mellitus**.** Cross-sectional Chinese research of 775 patients with type 2 diabetes found that diabetic patients with GERD (62.7 years) were younger than those without GERD (65.3 years). However, the difference was insignificant (P = 0.051) **(*6*).** A Japanese study of 859 individuals with type 2 diabetes mellitus discovered that age was significantly inversely linked with GERD **(*20*).**

Fujiwara et al., (*21*) found that endoscopic GERD is more common in men than women; it affects young patients and has a short duration of DM. Also, they found that GERD was more common in diabetic patients of "big built" (i.e., taller and heavier) than in those with a relatively high BMI. Endoscopy may be effective in diabetic patients with such a clinical background to confirm the presence of GERD **(*21*).**
Karpenko et al. (*13*). discovered that patients with GERD and type 2 diabetes revealed a significant incidence of extra-esophageal manifestations; specifically, 2/3 of cases had atypical GERD manifestations, with the majority being cardiac complaints and ENT diseases **(*13*).**
Modern literature does not have enough data to show a link between GERD manifestations and the severity of GERD in type 2 diabetes. Sakitani and colleagues **(*22*)** found that the frequency of symptoms of acid regurgitation was lower in diabetic patients than in non-diabetics, even those with severe endoscopic GERD. **Sakitani et al. (*22*)** said that endoscopic GERD severity and subjective symptoms are inversely or slightly associated **(*22*).**
Karpenko and colleagues(*13*). discovered that typical GERD symptoms (heartburn, regurgitation, acid burping) were only seen in 30% of erosive esophagitis patients with GERD and type 2 diabetic patients **(*13*).**
Zhelezniakova et al. (*23*) did a cross-sectional study on 107 patients diagnosed by upper GIT endoscopy with GERD and 67 with type 2 diabetes. They found 62 (92.5 percent) with erosive esophagitis, while the comparison group was only 25 (62.5 percent). Also, they had seen significant redistribution toward the aggravation of the severity of erosive esophagitis in type 2 diabetic patients **(*23*).**
HbA1c had high levels in type 2 diabetes with GERD related to an increased risk of acid-related upper GI endoscopic abnormalities**.** Tseng and colleagues discovered that type 2 diabetes and better glucose control are related to a reduced prevalence of GI symptoms but a higher prevalence of endoscopic abnormalities. Such various GI manifestations underline the reality of diabetic subjects' frequent under-recognition of GI complications. Efforts toward better glycemic control and early diagnosis of associated GI complications are necessary to prevent late complications in diabetic patients **(*21*).**

There was no significant association between endoscopic GERD and other existing diabetic complications. In addition, there was no association with glycemic control or arteriosclerosis markers; therefore, GERD is not a pathology involving the so-called angiopathy **(*21*).**
Nishida et al., (*15*) discovered that oral hypoglycemic medications (OHA) were associated with an increased risk of symptomatic GERD in type 2 diabetic patients **(*15*).** Because many patients were on numerous OHAs, the investigators could not identify any specific drugs that caused GERD. However, compared to type 2 diabetic patients treated with diet, those on OHAs had a 2.2-fold higher risk of developing symptomatic GERD **(*15*).**
Noguchi et al. (24) used the Japanese adverse drug event report database to look at the symptoms of GERD in people who took incretin-based drugs (GLP-1-receptor agonists and dipeptidyl peptidase 4 (DPP-4) inhibitor). Two GLP-1-RAs (exenatide and liraglutide) showed GERD-like symptoms among the incretin-based medications. In contrast, all DPP-4-Is detected no symptoms **(*24*).**

DPP-4-Is had no GERD signal, but an opposite association with the GERD signal was detected. Instead, this finding shows that DPP-4-Is may help to prevent GERD because it elevates GLP-1 and gastric inhibitory peptide (GIP) levels, leading to slightly reduced gastric peristalsis compared to GLP-1 R agonist, which has a stronger gastric peristalsis-suppressing action **(*24*).**

Metformin, an oral biguanide, is a common drug used in type 2 diabetes. It is known to cause gastrointestinal side effects such as diarrhea and vomiting. Concomitant therapy between metformin and PPI medications leads to drug interactions. **Punjabi et al. (*25*)** showed that PPI might interfere with Metformin to get into target tissues like the liver, muscle, and fat. This is because PPI drugs stop organic cation transporters (OCTs) from helping Metformin get into cells **(*25*).**

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