Turk J Gastroenterol *2017; 28(Suppl 1): S44-S47*

Which diseases are risk factors for developing gastroesophageal reflux disease?

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Cite this article as: Akyüz F, Mutluay Soyer Ö. Which diseases are risk factors for developing gastroesophageal reflux disease? Turk J Gastroenterol 2017;28(Suppl 1); S44-S47

ABSTRACT

Although the pathophysiology of gastroesophageal reflux disease (GERD) remains unclear, it is accepted as a multifactorial disease. It is thought that some of the interventions that might cause alterations in the normal gastrointestinal tract anatomy and diseases that affect the lower esophageal sphincter, esophageal clearance, and stomach motility (gastric emptying) might lay a foundation for GERD development. Moreover, it is common knowledge that GERD might cause various extraesophageal symptoms and complications. A possible connection between GERD and sarcoidosis, amyloidosis, hypothyroidism, rheumatoid arthritis, mixed connective tissue disorders, Sjögren's syndrome, systemic sclerosis, diabetes mellitus, cholecystectomy, sleeve gastrectomy, sleep apnea syndrome, chronic obstructive pulmonary disease, and asthma were summarized in this literature review.

Keywords: Gastroesophageal reflux disease, pathogenesis of GERD, sarcoidosis, amyloidosis, hypothyroidism, rheumatoid arthritis, mixed connective tissue disease, Sjögren's syndrome, systemic sclerosis, diabetes mellitus, cholecystectomy, sleeve gastrectomy, sleep apnea syndrome, chronic obstructive lung disease, asthma

Gastroesophageal reflux disease (GERD) is known to present with various extraesophageal symptoms and complications. In contrast, several diseases affecting the motility of the esophagus and some approaches that alter the upper gastrointestinal tract anatomy may result in GERD. Certain diseases and conditions often mentioned with GERD will be briefly discussed in this section.

Systemic Sclerosis

Esophageal motility is impaired in 70-90% of patients with systemic sclerosis (1-3). On histological examination, smooth muscle atrophy and fibrosis causing motor activity abnormalities in two-thirds of the distal esophagus are often determined (4). Motility studies have shown that the amplitude of peristaltic contractions decreases or that there is no peristaltic contraction in this region (5-7). Abnormal peristalsis and decreased lower esophageal sphincter (LES) pressure reduce acid clearance and prolong the contact of acid with the mucosa (8). As a result, GERD develops in patients with scleroderma. In many cross-sectional studies using different methodologies, the prevalence of GERD has been reported to be at rates of up to 70% (9-15).

Diabetes Mellitus

Furthermore, various factors showing tendency to GERD were identified in diabetes mellitus. Among these,

- Reduced salivary secretion associated with diabetic neuropathy,
- Delayed gastric emptying,
- Decreased acid clearance due to reduced motor activity of the esophagus/stomach related motor/autonomic neuropathy,
- Increased sensory thresholds associated with sensory nerve damage of the esophagus,
- Acid regurgitation caused by the increased frequency of transient LES relaxations related to neuropathy,

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 • Available online at www.turkjgastroenterol.org • DOI: 10.5152/tjg.2017.12

- Reduced LES pressure, and peristaltic wave transmission speed caused by hyperglycemia can be deemed (16). In a cross-sectional study by Nishida et al. (17), GERD prevalence in patients with diabetes was 25.3%, while it was 9.5% in the control group (p=0.02). In a study without a control group by Wang et al. (18), GERD prevalence was found to be 40.7%. Increased BMI in most patients with diabetes may also contribute to the reflux. In a study conducted using the impedance technique by Gokturk et al. (19), acid reflux was higher in diabetics than in controls. While there was no significant difference between controls and non-obese patients with diabetes in sub-group analysis (p>0.05), a difference between control and obese diabetic patient group was observed (p<0.05). The authors emphasized the contribution of obesity to reflux in patients with diabetes. Furthermore, the presence of neuropathy may contribute to GERD development in patients with long-standing diabetes.

Cholecystectomy

The reservoir function of the gallbladder disappears after cholecystectomy, and bile flow becomes continuous (20,21). Qualitative changes may appear at the levels of gastrointestinal hormones (22,23). Consequently, alterations in the qualitative bile content and more frequent transient LES relaxation may occur (24). Moreover, it was thought that reflux symptoms in these patients worsen with increased biliary symptoms after cholecystectomy due to a high-fat diet intake and weight gain. Alterations in the motility of the upper gastrointestinal tract and delayed stomach emptying caused by duodenal adhesions may also contribute to GERD (25). There was no significant increase in reflux after cholecystectomy in the limited number of studies based on these data. Uyanıkoğlu et al. (26) used the impedance method and reported increased reflux after surgery and that the pH was <4% higher than that before surgery; however, it was similar to the control group. In another study, Lin et al. (27) compared patients with hernia surgery and cholecystectomy. Reduction in the reflux symptom score was 35% in patients, while it was 39% in controls (p=0.11).

Sleeve Gastrectomy

Mechanisms that may induce increased GERD in patients with GERD with sleeve gastrectomy include hypotensive LES (28), blunting of the angle of His (29), decreased gastric compliance (30), delayed gastric emptying (29), reduced plasma ghrelin levels (31), gastric sleeve anatomy (32), and hiatal hernia (33). In the cohort study by Himpens et al. (34), GERD occurred at a rate of 23.6% at six years after surgery. The highest reflux rate following surgery in the literature is 31%, as reported by Tai et al. (35).

Obstructive Sleep Apnea Syndrome

Contradictory results are reported in the literature on reflux and respiratory system diseases. Recurrent airway occlusion during sleep may cause a negative intrathoracic pressure. It may predispose reflux in these patients due to the aspiration of stomach matter. In a survey by Shepherd et al. (36), reflux prevalence in sleep apnea syndrome was 33.8% in patients and 26.6% in controls (p<0.05). There are also some data suggesting that reflux triggers sleep apnea syndrome due to various mechanisms. Reflux may directly enhance airway reactivity or indirectly cause bronchoconstriction by vasovagal reflex. In a study by Emilsson et al. (37), where sleep apnea syndrome symptoms in GERD were investigated, the prevalence of apnea for more than one night in a week was 10.2% in GERD patients and 5.2% in controls (p=0.02). In other studies investigating the tendency of sleep apnea syndrome in GERD, alterations in sleep apnea syndrome were examined using a proton pump inhibitor. In a cross-sectional impedance study by Ermis et al. (38), the apnea-hypopnea index (AHI) before treatment was 32.2, while the AHI after treatment was 18.4 (p=0.01). In a double-blind, placebo controlled study by Borlotti et al. (39), the incidence of weekly apnea attacks significantly decreased compared to baseline values and placebo (73% decrease at six weeks).

Chronic Obstructive Pulmonary Disease

Functional diaphragmatic changes may lead to the development of reflux during hyperinflation in patients with chronic obstructive pulmonary disease (COPD). Age, obesity, smoking, use of respiratory drugs, and degree of airway obstruction are potential factors causing predisposition (40,41). The effect of bronchial obstruction on LES may be another risk factor for progress of reflux in COPD (42). In a prospective cohort study by Rodríguez et al. (43), there was a risk enhancement for GERD in COPD [RR: 1.46 (CI, 1.19-1.78)]; there was no risk for COPD in GERD [RR:1.17 (CI, 0.91-1.49)].

Asthma

Asthma is the most studied disease in terms of a relationship with GERD and for which relatively more accurate information is available. Two possible mechanisms may be responsible for the development of asthma as a result of acid reflux:

- Pulmonary tree damage (reflux theory) as a result of direct exposure to acid reflux content
- Bronchoconstriction (reflex theory) as a result of vagal stimulation (44).

In addition, cough and increased respiratory effort may exacerbate reflux in patients with asthma (45). In a meta-analysis, GERD symptom prevalence was 59.2% in patients with asthma and 38.1% in controls, while asthma prevalence was 4.6% in patients with GERD and 3.9% in controls. Odds ratio was 5.45 for GERD in asthma, while it was 2.26 for asthma in GERD (46).

In conclusion, GERD interacts with various diseases and conditions, and there is a reciprocal relationship in patients with respiratory system diseases in particular. Further well-designed prospective cohort studies are required to explain this complexity.

RECOMMENDATIONS

- There are insufficient data on sarcoidosis, amyloidosis, hypothyroidism, rheumatoid arthritis, mixed connective tissue disease, and Sjögren's syndrome.
- Systemic sclerosis is a risk factor for gastroesophageal reflux disease (GERD) (Level of evidence: 2b).
- Reflux incidence increases in patients with diabetes mellitus (Level of evidence: 3b). The presence of increased body mass index (BMI) and neuropathy in these patients can be considered as risk factors for GERD development (Level of evidence: 5).
- There are limited data in the literature, and there is no significant increase in GERD after cholecystectomy (Level of evidence: 3b).
- In the literature, data may be variable, and sleeve gastrectomy may exacerbate reflux symptoms, thereby leading to new reflux symptoms (Level of evidence: 2a).
- There is a bidirectional relationship between sleep apnea syndrome and the reflux disease (Level of evidence: 2b, 3b). In addition, increased BMI is a risk factor for reflux in patients with sleep apnea syndrome (Level of evidence: 5).
- GERD is common in chronic obstructive pulmonary disease (COPD) (Level of evidence: 1b). Obesity and smoking may also cause increased reflux in COPD (Level of evidence: 5). However, there is insufficient evidence showing that COPD is a primary risk factor for GERD (Level of evidence: 5). The presence of reflux may exacerbate COPD (Level of evidence: 5).
- There is a strong relationship between asthma and reflux (Level of evidence: 1a).

Conflict of Interest: No conflict of interest was declared by the authors.

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