Sex and Gender Differences in Gastroesophageal Reflux Disease

Young Sun Kim,1 Nayoung Kim,2,3* and Gwang Ha Kim4

1Department of Internal Medicine, Healthcare Research Institute, Seoul National University Hospital Healthcare System Gangnam Center, Seoul, Korea; 2Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do, Korea; 3Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea; and 4Department of Internal Medicine, Pusan National University School of Medicine, Busan, Korea

It is important to understand sex and gender-related differences in gastroesophageal reflux disease (GERD) because gender-related biologic factors might lead to better prevention and therapy. Non-erosive reflux disease (NERD) affects more women than men. GERD symptoms are more frequent in patients with NERD than in those with reflux esophagitis. However, men suffer pathologic diseases such as reflux esophagitis, Barrett’s esophagus (BE), and esophageal adenocarcinoma (EAC) more frequently than women. The prevalence of reflux esophagitis is significantly increased with age in women, especially after their 50s. The mean age of EAC incidence in women is higher than in men, suggesting a role of estrogen in delaying the onset of BE and EAC. In a chronic rat reflux esophagitis model, nitric oxide was found to be an aggravating factor of esophageal injury in a male-predominant way. In addition, the expression of esophageal occludin, a tight junction protein that plays an important role in the esophageal defense mechanism, was up-regulated in women. This explains the male predominance of reflux esophagitis and delayed incidence of BE or EAC in women. Moreover, the symptoms such as heartburn, regurgitation, and extra-esophageal symptoms have been more frequently reported by women than by men, suggesting that sex and gender play a role in symptom perception. Differential sensitivity with augmented symptoms in women might have diagnostic and therapeutic influence. Furthermore, recent studies have suggested that hormone replacement therapy has a protective effect against esophageal cancer. However, an anti-inflammatory role of estrogen remains compelling, which means further study is necessary in this area. (J Neurogastroenterol Motil 2016;22:575-588)

Key Words
Adenocarcinoma; Barrett esophagus; Esophagitis; Estrogen; Gender

Introduction

Gastroesophageal reflux disease (GERD) includes an entire spectrum of reflux diseases of the gastroesophageal junction. GERD complications include reflux esophagitis and Barrett’s esophagus (BE).1 GERD is categorized according to endoscopy as reflux esophagitis and non-erosive reflux disease (NERD).2 Functional heartburn is defined as retrosternal burning discomfort or pain refractory to optimal anti-secretory therapy in the absence of gastroesophageal reflux, histopathologic mucosal abnormalities, major motor disorders, or structural abnormalities.1 Both functional
heartburn and NERD are more common in women than in men. Currently, NERD is differentiated from reflux esophagitis by upper endoscopy because NERD does not show visible esophageal mucosal injury. NERD is further differentiated from functional heartburn by using 24-hour esophageal pH monitoring (± impedance) with symptom-reflux correlation analysis. However, 24-hour esophageal pH monitoring has been criticized for having limited sensitivity in diagnosing GERD. In addition, it is an uncomfortable testing tool not commonly used in general practice. Accordingly, accurate discrimination of functional heartburn from NERD in the general population is limited. Most available data on NERD have been collected in epidemiological studies conducted on patients with heartburn using validated questionnaires and esophagogastroduodenoscopy without using pathophysiological evaluation such as 24-hour esophageal pH monitoring.

It is commonly known that esophageal adenocarcinoma (EAC) arises from a sequential spectrum of GERD from reflux esophagitis, leading to BE, and finally resulting in EAC. Interestingly, there is a male-predominant sex difference through the spectrum of reflux esophagitis, BE, and EAC. In addition, the male to female ratio becomes higher with more progression towards EAC. Meanwhile, reflux symptoms and NERD generally affect more women than men. Epidemiological data have suggested that the esophageal mucosal epithelium is more fragile to refluxed gastroduodenal contents in men compared to that of women, although women are more susceptible to GERD symptoms than men.

Sex means a human’s biological status based on their reproductive systems and functions assigned by chromosomal type. Gender means manners, feelings, and behaviors in a given culture associated with a person’s sex stereotypes. Sex-specific medicine is a medical practice in which sex differences between female and male are recognized and actively utilized in medical study, diagnosis, treatment, and education. Sex-specific medicine assumes that sex is a crucial factor in the pathogenesis, risk factor, disease progression, and prognosis of many diseases. According to sex-specific medicine, treatment of certain diseases should be specified based on a patient’s sex because female and male have different drug responses, prognoses, and risk factors. Thus, understanding sex and gender-associated differences in GERD is important for interpreting biological factors. They might provide better prevention and treatment protocols for both women and men.

However, there have been limited studies that investigate sex-gender differences between women and men in the area of GERD in published articles. Recently, Asanuma et al. have nicely reviewed the sex difference of GERD incidence and the important role of female estrogen. However, they did not include sex and gender differences in the aspect of clinical manifestations, pathophysiology such as the brain-gut axis, or treatment. Therefore, the aim of this review was to focus on sex and gender differences with regard to prevalence, pathophysiology, clinical presentations, and treatment of GERD using available literatures.

### Methodology

First, we searched the PubMed using MeSH terms combined with free text terms to have a broad coverage of articles on GERD using the following terms: sex, gender, epidemiology, pathophysiology, estrogen, symptoms, healthcare seeking, and treatment. Searches were then limited to full articles in English language. All searches were completed by February 20, 2016. All retrieved abstracts were independently reviewed. Inclusion criteria were: (1) results that included gender differences and (2) original data were presented. Abstracts that met the inclusion criteria were reviewed to evaluate study design, clinically evaluated parameters, and study population. We then retrieved and reviewed full-text articles meeting the inclusion criteria according to the contents in the abstract. Next, we searched potentially concerned articles and reviewed their reference lists. Finally, we found a total of 198 eligible papers (Fig. 1). Of them, 102 papers were excluded because of irrelevance to the specific questions being asked or being not written in English. In addition, case reports and letters to the editor were excluded. After the exclusion, a total of 96 original papers were included in our review (Fig. 1).

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**Figure 1.** Flow chart documenting the results of search strategy.
Prevalence of Gastroesophageal Reflux Disease

Global burden of GERD is increasing. However, the prevalence of GERD is different by country or research method. Furthermore, there are significant diversities in the distribution of GERD-related disorders (symptoms, reflux esophagitis, BE, and EAC) related to sex (Fig. 2). In this review we categorized these publications of GERD prevalence based on population or endoscopy-based study, and the prevalence of BE was separately introduced.

Population-based Study

Population-based research is regarded as suitable for GERD study because it is a common disease in the community. In addition, the diagnosis of GERD could be made based on symptoms. As GERD is not a serious disease, people do not always have to visit a hospital. According to a systematic review using the PubMed database between 1997 and 2011, the prevalence of GERD symptoms, majorly defined by weekly or frequent heartburn, did not differ between women and men (19.4 ± 2.3% vs 18.9 ± 2.4%, P = 0.87) or between regions (US or Europe vs Asian countries, P = 0.22). In a population-based study in Argentina (a representative geographical region of Latin America), there was no statistically significant difference in the prevalence of GERD according to sex. The prevalence of GERD was 9.5% (95% CI, 7.5-11.5%) in men and 14.1% (95% CI, 9.6-16.4%) in women, respectively (P = 0.21).

Endoscopy-based Study

In contrast, many epidemiologic studies of GERD have shown that reflux esophagitis is more common in men than in women. A meta-analysis has described that the men/women ratio in the prevalence of reflux esophagitis was 1.57 (95% CI, 1.40-1.76) and the mean age of men with reflux esophagitis was lower than that of women. In a systematic review based on data of 67,056 patients using the PubMed database between 1997 and 2011 (including 12 unbiased population-based studies, 8 studies from Asian countries, 2 studies from Europe, and 1 study from the US), the prevalence of reflux esophagitis was lower in women compared to that men (women: 6.1 ± 1.6%, range: 2.1-16.8%; men: 15.9 ± 2.5%, range: 7.0-28.1%; P < 0.01).

In contrast, NERD is more common in women. A quantitative analysis of esophageal symptoms has showed that the symptom frequency and severity were significantly higher in women than in men. On the other hand, the grade of esophagitis by esophagogastroduodenoscopy and the time period at pH below 4 during ambulatory 24-hour esophageal pH monitoring did not show any significant differences between men and women. In a multicenter study performed in Korea in 2006 with 25,536 subjects who received esophagogastroduodenoscopic examination for medical check-up, the prevalence of reflux esophagitis was significantly higher in men (11.2%) than in women (3.1%) (P < 0.0001).
which was similar to the results in a 2011 nationwide multicenter study.\textsuperscript{30} Moreover, the degree of esophagitis was more severe in males than in females.\textsuperscript{34} However, the percentage of women having NERD (5\%) was higher than that of men having NERD (3\%).\textsuperscript{2}

With regard to risk factors for NERD or reflux esophagitis, a large scaled multicenter study using 25 536 Korean subjects showed that sex was a risk factor for reflux esophagitis and NERD, oppositely.\textsuperscript{2} That is, considering risk factors for reflux esophagitis and NERD compared to normal population, men, alcohol, hiatal hernia, a history of Helicobacter pylori eradication, and body mass index (BMI) $\geq 25$ kg/m$^2$ were risk factors for reflux esophagitis.\textsuperscript{2}

In contrast, females, smoking, age $< 40$ and $\geq 60$ years vs. 40-59 years, glucose $\geq 126$ mg/dL, BMI $< 23$ kg/m$^2$, usage of antibiotics, a stooping posture at work, and a monthly income $< \$1000$ were risk factors for NERD.\textsuperscript{2} Similarly, a study with 10 837 healthy Japanese adults (6332 men and 4505 women, aged 20-87 years) who received gastroesophagogastroduodenoscopy has revealed that men, older age, alcohol, smoking, no $H. \textit{pylori}$ infection, higher pepsinogen I/II ratio in serum, and higher BMI were positively associated with reflux esophagitis.\textsuperscript{36} In contrast, women, younger age, smoking, alcohol, $H. \textit{pylori}$ infection, higher pepsinogen I/II ratio in serum, and higher BMI were positively associated with NERD.\textsuperscript{36}

### Prevalence of Barrett’s Esophagus

BE is defined as a change in the distal esophageal epithelium of any length characterized by metaplastic columnar epithelium.\textsuperscript{40} However, its histological criteria vary by country. The prevalence of BE is substantially diverse across studies as various results could be obtained due to difference in study design, population, and endoscopic biopsy protocols.\textsuperscript{32} The prevalence of BE, was lower in women than in men (Table).\textsuperscript{7,19,40-51} A systematic review after analyzing the PubMed database between 1997 and 2011 has shown that the prevalence of BE was lower in women than in men (28 out of 10 337, range 0.03-4.6\% vs 70 out of 12 463, range 0.08-8.2\%).\textsuperscript{21} In addition, a meta-analysis has demonstrated that the men/women ratio of BE was 1.71 (95\% CI, 1.42-2.04), without considering the presence of intestinal metaplasia.\textsuperscript{7} With regard to BE with intestinal metaplasia, the men/women ratio was 2.13 (95\% CI, 1.87-2.46).\textsuperscript{7} Studies from Asian countries have shown that the prevalence of BE was more common in men with a men/women ratio of ap-

### Table. Effect of Sex and Gender on Gastroesophageal Reflux Disease

| Effect of sex and gender | References |
|--------------------------|------------|
| **Prevalence**           |            |
| Symptom-based population study | Women $>$ men | 96 |
|                          | Women $=$ men | 21-25 |
| Endoscopy-based study    |            |
| Reflux esophagitis       | Men $>$ women | 9,26-38 |
| NERD                     | Women $>$ men | 2,7,15,16,34,39 |
| Barrett’s esophagus      | Men $>$ women | 7,21,40-51 |
| **Effect of aging**      |            |
| Reflux esophagitis       | Increase with aging in both men and women: | 29,30,37,52 |
|                          | Age of women $>$ men | 29,30,37 |
|                          | Increase after menopause (after 50s) in women: | 29,30, |
| Barrett’s esophagus      | Age of women $>$ men | 47-49 |
|                          | Increase after menopause (after 60s) in women: | 7,54 |
| EAC                      | Age of women $>$ men | 57,59 |
| **Symptoms**             |            |
| Heartburn or regurgitation | More frequent in women $>$ men | 28,97 |
| Extra-esophageal symptoms | Women $>$ men | 9,28,79 |
| Comorbid anxiety or depression | Women $>$ men | 79 |
| **Treatment**            |            |
| Response to PPIs         | Men $>$ women | 110-114,116 |
| Dose escalation of PPIs  | Women $>$ men | 115 |
| Postmenopausal HRT in women | Increase the risk of gastroesophageal reflux symptoms | 123,125 |
|                          | Reduced esophageal cancer risk | 120,121 |

NERD, non-erosive reflux disease; EAC, esophageal adenocarcinoma; PPIs, proton pump inhibitors; HRT, hormone replacement therapy.

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Effect of Aging on the Prevalence of Gastroesophageal Reflux Disease or Barrett’s Esophagus in Women

A close relation between women’s reproductive hormones and the severity and prevalence of GERD has been reported. During the postmenopausal period, the prevalence of the GERD spectrum rises rapidly. However, it is lower than that in men during the reproductive age. In a large endoscopy-based study performed in the UK, the mean ages of men and women with reflux esophagitis were 59.7 ± 16.1 and 64.4 ± 15.1 years, respectively. Several studies have also suggested that the incidence of reflux esophagitis increased with aging, with women having the trend to be older than men. Moreover, older women showed more severe reflux esophagitis than older men and the incidence of severe reflux esophagitis tends to be increased higher in postmenopausal women than in men. 

Another endoscopy-based study has reported that the incidence of reflux esophagitis was increased in women after the age of 50 years. The incidence of reflux esophagitis in women was similar to that in men by the age of 80 years. A recent Japanese study using 7670 study subjects (5166 men and 2504 women) who visited a medical center for health check-up adults has shown that the prevalence of BE was 0.84% in 25 536 health check-up adults. The risk factors for BE were men (OR, 1.82; 95% CI, 1.32-2.50), hiatal hernia (OR, 5.66; 95% CI, 3.70-8.66), age > 60 compared to age < 40 (OR, 1.81; 95% CI, 1.07-3.09), and nonsteroidal anti-inflammatory drug use (OR, 2.02; 95% CI, 1.28-3.20) based on multivariate analysis. 

With regard to EAC, 17 years of delay in age-specific incidence has been reported in women compared to that in men in a recent study. These results might be due to the disappearance of the protective effect of female sex hormones in postmenopausal women.

Pathophysiology

Role of Estrogen

GERD is influenced by multiple factors, including gastric acid secretion, hiatal hernia, lower esophageal sphincter function, esophageal motility, esophageal nociception, and others. A male-predominant gender bias including reflux esophagitis, BE, and EAC allude to sex and gender differences in the vulnerability or resistance of the esophageal epithelium to caustic compounds of gastro-duodenal contents. Decreased estrogen after menopause might be related with the rise in the incidence and severity of reflux esophagitis (Fig. 3). However, the detailed mechanism of estrogen in controlling the pathogenesis of GERD spectrum remains unclear.

Immune Response

In experimental animal models, females have been less injured than males by gastric inflammation in response to chemical substances or bacterial infection. Sometimes, these chemical insults and bacterial infections resulted in a difference in male predominant carcinogenesis. Estrogen has been revealed to have anti-inflammatory activity which contributes to tissue resistance in females in animal models. Recently, Masaka et al explored the role of estrogen (E2) in protecting esophageal damage in a chronic rat reflux esophagitis model. In addition, a significant male-predominance in esophageal tissue damage by exogenous nitric oxide (NO) has been found. In male rats, severe esophageal ulcers and inflammation with polymorphonuclear cell and lymphocyte infiltrates have been induced by exogenous NO. However, only mild tissue dam-

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age has been observed in female rats. Furthermore, exogenous 17β-estradiol binding and signaling through E2 receptors attenuated esophageal tissue damage in males and ovariectomized rats through reducing mast cell-mediated cytotoxicity and the production of cytokines, specifically TNF-α that drives inflammation. In contrast, treatment with 17α-estradiol that binds E2 receptors but does not induce downstream signaling has no effect on tissue damage. While esophageal damage was more severe in ovariectomized rats compared to sham ovariectomized rats, the aggravated esophageal damage could be weakened by 17β-estradiol. Furthermore, aggravated esophageal damage in male rats could be reduced by 17β-estradiol. Interestingly, estrogen can significantly suppress the levels of the esophageal macrophage inhibitory factor. Because estrogen can target the tissue macrophage inhibitory factor to promote wound healing by inactivating macrophages, it is suggested that this anti-inflammatory role associated with estrogen has contributed to sex and gender differences in GERD.

**Esophageal Nociception**

The understanding about how heartburn is experienced has been greatly improved with the detection of transient receptor potential vanilloid subfamily member-1 receptors (TRPV1) in esophageal mucosa. TRPV1 may lead to visceral hypersensitivity as one of the important factors in the pathogenesis of NERD. It has been hypothesized that TRPV1 activation could trigger inflammation by releasing substance P and calcitonin-gene-related peptide in primary afferent neurons. Therefore, up-regulation of TRPV1 expression in the esophageal mucosa might be the underlying mechanism of the visceral hypersensitivity in NERD. Several studies have shown that the expression levels of esophageal mucosal TRPV1 are more increased in patients with GERD than those in patients without GERD, and that the expression of esophageal TRPV1 in NERD was higher than that in reflux esophagitis.

In contrast, a study on Koreans has shown that not only the levels of TRPV1, but also the levels of glial cell line-derived neurotrophic factor, nerve growth factor, protease-activated receptor 2 (PAR2), and IL-8 at mRNA level were the highest in the reflux esophagitis group, followed by those in NERD and control groups. The differences in these expression levels between the

![Figure 3. Schematic of the proposed effects of aging and hormonal changes. Proposed mechanism of the loss of mucosal epithelial integrity and microbial translocation and the effects of hormonal changes associated with aging. Reduced levels of E2 due to aging, especially, after women’s menopause, can potentially increase epithelial permeability and microbial translocation (adapted from Grishina et al).](image-url)
control and reflux esophagitis groups were statistically significant. Interestingly, up-regulation of the TRPV1 and PAR2 pathways played a role in the development of distal esophageal inflammation and reflux symptoms, but not in the extra-esophageal reflux symptoms.

In addition, TRPV1 has been proposed as a possible mechanism involved in the manifestation of gastrointestinal symptoms. TRPV1 activation in primary afferent neurons evoked the burning sensation, as well as inducing inflammatory and neuro-inflammatory effects, hence causing GERD. Further studies are needed to evaluate the mechanistic importance in the relationship between estrogen and esophageal TRPV1 expression.

Gender Difference in Esophageal Acid Exposure

Ambulatory 24-hour esophageal pH monitoring is the gold standard method to evaluate esophageal acid exposure. There are gender-related differences in esophageal acid exposure among men and women. Women have significantly fewer reflux events at both esophageal measuring spots, and significantly less total reflux time and percentage of time with pH < 4 in a study for subjects without reflux symptoms or GERD. These results have implications with regard to men's higher prevalence of BE than women while women have lower esophageal acid exposure in comparison to men.

Psychological Factors

Previous epidemiological surveys have shown that psychological factors play an important part in the pathogenesis of GERD. Psychological stress increased the perception of heartburn and aggravated GERD symptoms. Fass et al. have shown that acute stress can enhance the sensitivity to intraesophageal acid perception in both reflux esophagitis or NERD patients. They also demonstrated that the increased perceptual responses to acid was related to greater emotional response to the stress factor.

Previous reports have revealed that low quality of life (QOL) was severe in patients with extra-esophageal symptoms. The QOL of patients with GERD was associated with psychological factors, including symptoms and mental factors. A recent study with 217 Korean subjects has shown that sleep dysfunction and anxiety were higher and QOL was low in patients with GERD, especially in patients with NERD. In addition, the GERD impact scale score was higher in the NERD group (9.2 ± 0.4) than that in the reflux esophagitis group (6.5 ± 0.3) (P < 0.001). Furthermore, interruption in daily life was more severe in the NERD group than that in the reflux esophagitis group. Anxiety subscales of hospital anxiety and depression scale scores were higher in NERD and reflux esophagitis groups compared to those in the control group.

In NERD, visceral hypersensitivity is an important pathophysiological mechanism. Three possible mechanisms are associated with visceral hypersensitivity: peripheral sensitization, central sensitization, and psychoneuroimmune interactions. Pass and Tougas have suggested that pathologic or physiologic intraesophageal stimuli may result in symptoms of NERD. Their study has highlighted the role of central (through brain-gut interactions) and peripheral (not esophageal) mechanisms in regulating perception of intraesophageal stimuli.

Depression and anxiety are more common in women than in men in the general population. The prevalence of NERD is also more common in women. Accordingly, comorbid depression and anxiety may play a role to the increased symptom burden in women. Women might have different symptoms and physical signs of diseases due to differences in afferent signals, hormone levels, and GERD severity. However, limited studies are available regarding sex and gender differences in psychological factors associated with GERD.

Symptoms

Symptoms of GERD can be subdivided into esophageal symptoms (such as heartburn and regurgitation) and extra-esophageal symptoms (such as chronic cough, chest pain, hoarseness, and globus sensation in the throat).

Whether extra-esophageal reflux symptoms are truly related to esophageal reflux remains controversial. A recent study has shown that the presence of reflux symptoms is related to significantly higher levels of TRPV1, PAR2, and IL-8. Notably, not extra-esophageal reflux symptoms, but esophageal reflux symptoms, are significantly associated with them. These results suggest that the pathophysiology of extra-esophageal reflux symptoms might be different from that of esophageal reflux symptoms. That is, extra-esophageal reflux symptoms might not be due to direct sensitization at the distal esophagus, but due to indirect mechanisms involving vagally-mediated reflex from acid exposure on the distal esophagus. In addition, up-regulation of inflammation-related genes might be located in other areas such as the proximal esophagus or pharynx. Many studies have shown significant difference in symptom expression between women and men with GERD.
Esophageal Symptoms and Sex/Gender

In a population-based study performed in Iran using the most commonly accepted GERD definition (either heartburn or acid regurgitation), female gender (OR, 1.55), NSAID use (OR, 4.23), smoking (OR, 1.83), BMI > 30 kg/m² (OR, 1.79), less education (OR, 1.52), and GERD in spouse (OR, 1.82) were associated with frequent GERD based on multivariable analysis.96 A recent population-based telephone survey performed in Brazil has shown that women have reported significantly higher frequencies (> 1.5-fold) of symptoms corresponding with GERD (occurring at least twice per week), including heartburn (P = 0.047), a burning sensation in the stomach (P = 0.012), acid regurgitation (P < 0.001), swallowing difficulty (P = 0.012), or pain on swallowing (P = 0.009) compared to men (Table).97 Another study showed that quantitative esophageal symptom scores for heartburn, regurgitation, belching, and nocturnal symptoms which had been analyzed by endoscopy, ambulatory pH, and esophageal manometry, were significantly higher in women than in men.9 Women have also reported higher symptom scores of lower abdominal symptoms such as diarrhea, abdominal pain, and constipation (P < 0.01).9 These results imply that gender difference might exist in symptom perception and reporting of symptoms.9

Extra-esophageal Symptoms and Sex/Gender

The ProGerd study performed in patients with GERD has shown that there are gender differences in extra-esophageal symptoms between women and men (Table). Extra-esophageal symptoms were found to be significantly more common in women than in men (OR, 1.15; 95% CI, 1.03-1.30; P < 0.0178).96 These results imply that gender difference might exist in symptom perception and reporting of symptoms.

Gender and Healthcare Seeking

Even though similar results were found in the number of men or women getting medical advice for GERD, women seem more likely to visit physicians more often.98,99-101 This might be caused by the higher possibility of diagnostic testing to evaluate symptoms of GERD that are not fully explained by mucosal changes such as less prevalent esophagitis or BE in women. A population-based study on GERD in south China has shown similar results.102 That is, women were an independent factor related to health care-seeking behavior (P < 0.001), frequency of heartburn (P = 0.032), degree of depression (P = 0.004), and social morbidity (P < 0.001).102

Treatment

Understanding sex and gender-related differences in GERD is important for gender-related biological factors which might provide better treatment strategy for both men and women.

Sex/Gender and Treatment Response

Treatment of GERD includes lifestyle modification and medications.104,105 PPIs are the most effective medicines for treating GERD.106 Therefore, patients with GERD are frequently treated with PPIs.107-108 However, 17-32% of patients with GERD experienced persistent and troublesome heartburn or regurgitation despite standard-dose PPI treatment. In addition, the majority experienced refractory symptoms at higher doses.109-113 Several studies have shown that there are gender differences in the prevalence of partial response to PPIs (Table).79,110-113 In a study conducted in patients newly diagnosed with GERD in primary care clinics, partial symptomatic response to PPI therapy was found to be related to women (OR, 1.20; 95% CI, 1.05-1.37).112 In a systemic review, persistent GERD symptoms despite PPI treatment were more likely to be revealed in women than in men (risk ratio [RR]: 3.66; P < 0.001).110
In another study performed in patients with reflux esophagitis and frequent heartburn, men were found to be more likely to have improvement in heartburn than women (OR, 1.35; 95% CI, 1.14-1.59; \( P < 0.001 \)).\(^{114} \) A recent Korean GERD study regarding predictive factors of response to PPI has shown that BMI < 23 kg/m\(^2\) (OR, 2.20; 95% CI, 1.12-4.34), history of psychotherapy or neuropsychiatric medication (OR, 2.44; 95% CI, 1.23-4.85), higher total Pittsburgh sleep quality index score (OR, 1.20; 95% CI, 1.05-1.35), and NERD (OR, 3.30; 95% CI, 1.54-7.11) was related to poor response to PPIs.\(^{107} \) However, gender did not have a statistically significant association with PPI therapy response.\(^{108} \)

However, female gender is associated with requiring dose escalation of PPIs for treatment.\(^{113} \) In a post hoc analysis using 5-year data from patients in the LOTUS trial who were randomized to take esomeprazole at 20 mg once daily, female sex, smoking, absence of \( H. \text{pylori} \) infection, a long duration of GERD history, and high supine baseline acid reflux into the esophagus was related to increased possibility of requiring dose escalation to esomeprazole at 40 mg daily (all \( P < 0.05 \)).\(^{115} \)

Forecasting the success of PPI therapy for symptomatic GERD patients would contribute to preventing empiric PPI drug attempts or repeating additional tests, thus reducing health care costs.\(^{116} \) Several recent studies have suggested that women, lower BMI, and psychologic disorders such as anxiety and depression was related to poor response to PPI therapy in patients with GERD.\(^{112,117} \) While men, obesity, typical reflux symptoms such as heartburn and regurgitation, and alcohol consumption was related to positive therapeutic responses to PPIs in a retrospective study of 683 subjects suspected of GERD who underwent pH-metry/impedance measurement (pH/MII).\(^{116} \) It has been suggested that pH/MII (including evaluation of the symptom index) instead of empiric PPI therapy should be considered in non-obese women with atypical reflux symptoms.\(^{116} \) However, response rates and associated factors for PPI treatment could be different according to study population and study design.\(^{107} \)

**Hormone Replacement Therapy**

It has been shown that estrogen has an anti-inflammatory action that can modulate immune cell activity such as cell activation and proliferation, cytokine production, and wound healing.\(^{12,60} \) Systemic and topical estrogen treatment are related to promotion of cutaneous wound healing compared to age-matched controls in studies on postmenopausal women.\(^{118,119} \) These results raise the possibility that estrogen might be used as a medication for GERD treatment due to its protective function.\(^{120} \)

Estrogen replacement in postmenopausal women might potentially confer a protective effect against esophageal cancer by reducing the extent of esophageal injury caused by gastric acid, thus decreasing the risk of BE and EAC.\(^{120} \) A recent case control cohort study performed in UK has shown that reduced esophageal cancer risk is associated with prolonged hormone replacement therapy (HRT) for 5-10 years (hazard ratio [HR], 0.25; 95% CI, 0.07-0.95) and time-dependent covariate with increasing duration of HRT use (HR, 0.06; 95% CI, 0.01-0.43) (Table).\(^{110} \) In a meta-analysis, risks for HRT use vs. never use of HRT significantly decreased for esophageal cancers (RR, 0.68; 95% CI, 0.55-0.84; \( P < 0.001 \)) (Table).\(^{121} \) However, a population-based retrospective cohort study for men who were exposed to quite a lot of estrogen has shown that there is no reduction in the risk of EAC by estrogen treatment.\(^{116} \) The role of estrogen as an anti-inflammatory agent remains uncertain. Further studies are needed to determine the potential role of hormonal factors in the pathogenesis of EAC to understand the importance of gender difference.\(^{120} \)

On the other hand, it has been suggested that female sex hormones can increase the risk of gastroesophageal reflux symptoms by relaxing the lower esophageal sphincter via NO.\(^{122-124} \) A population-based study demonstrated a positive correlation between reflux symptoms and postmenopausal HRT use.\(^{122} \) The risk of reflux symptoms is significantly increased among severely obese (BMI > 35 kg/m\(^2\)) men (OR, 3.3; 95% CI, 2.4-4.7) and women (OR, 6.3; 95% CI, 4.9-8.0) compared to those with BMI < 25 kg/m\(^2\).\(^{123} \) The correlation between BMI and reflux symptoms was stronger (\( P < 0.001 \)) in premenopausal women compared to that in postmenopausal women. The use of postmenopausal hormone therapy increased the strength of the association (\( P < 0.001 \)).\(^{125} \) For women with normal body weight, a weak association between hormone therapy and reflux symptoms has been found.\(^{125} \) BMI reduction is positively associated with decreased risk of reflux symptoms.\(^{125} \) The association between hormone therapy and reflux symptoms is stronger with increasing BMI, implying that estrogen replacement is an effective modifier of the association between BMI and reflux symptoms.\(^{125} \) Further studies are warranted to determine whether HRT is associated with GERD symptoms or esophageal injury that leads to EAC.

**Conclusions**

Reflux symptoms and NERD affect women more than men. However, men suffer pathologic changes more frequently. Women have higher mean age (such as postmenopausal period) of cancer.
incidence than men, suggesting a role of estrogen in delaying the onset of BE and EAC. Anti-inflammatory action of estrogen and esophageal epithelial resistance against reflux are likely to be associated with the sex and gender differences in GERD spectrum between men and women. In terms of GERD symptoms, women are more likely to have heartburn, regurgitation, belching, and extra-esophageal symptoms than men. These results imply that sex and gender play a role in symptom nociception. Differential sensitivity and enhanced symptoms reported by women might have diagnostic and therapeutic implications. The role of estrogen as an anti-inflammatory agent remains intriguing. Further studies are warranted to determine the role of estrogen in the pathogenesis of EAC. Differential disease recognition and medical care for sex and gender should be taken into account in the GERD spectrum.

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