Impact of Overlapping Functional Gastrointestinal Disorders on the Quality of Life in Patients With Gastroesophageal Reflux Disease

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Gastroesophageal reflux disease (GERD) and functional gastrointestinal disorders (FGIDs), including irritable bowel syndrome and functional dyspepsia, are common afflictions within the general population. Both conditions have a considerable impact on the daily health related quality of life (HRQoL) of affected individuals. Risk factors surrounding any impaired HRQoL in patients with GERD involve those of younger age, obesity, an increase in reflux symptom frequency, and overlapping FGIDs. The risk factors for subjects experiencing an overlap in FGIDs and GERD involve those who are female, younger age, cigarette smoking, non-erosive reflux disease, more GERD symptoms, and psychological performances including anxiety, somatization, and more frequent healthcare-seeking behavior. The overlap of GERD and FGIDs is associated with a worsening of both physical and mental health, an increase in bothersome symptoms, impaired functional capacity, and a higher likelihood of consulting a physician. Acid secretion suppressors could offer therapeutic efficacy to some patients experiencing overlapping GERD and FGIDs.

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Key Words
Dyspepsia; Female; Gastroesophageal reflux; Quality of life

Introduction

Gastroesophageal reflux disease (GERD) and functional gastrointestinal disorders (FGIDs) are very common within the general population, and both conditions have a considerable impact on the daily lives of affected individuals.1-4 According to previous studies, the risk factors in patients with GERD include older age,5,6 obesity,7,8 hiatus hernia,9 and an unhealthy lifestyle, involving alcohol intake and cigarette smoking.10

The symptoms of GERD affect many aspects of a patient’s life, including sleep disruption, lower attention concentration levels, and limitations in physical activity; as well as impairing the psychosocial aspects of a patient’s well-being, including the enjoying of social gatherings, intimacy, and sex. Health related quality of life (HRQoL) is lower in individuals with GERD than in the general population, and is comparable to that in individuals with other chronic diseases, such as diabetes, arthritis, and chronic heart failure.1

FGIDs, such as irritable bowel syndrome (IBS), functional
dyspepsia (FD), and chronic constipation, all pose an extensive healthcare burden and negatively affect quality of life (QoL). Patients with GERD also suffer more commonly from FGIDs.

The aim of this review is to investigate the impact of HRQoL of the subjects experiencing an overlap of GERD and FGIDs.

**Definition of Gastroesophageal Reflux Disease and Functional Gastrointestinal Disorders**

According to the Montreal definition, GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications. In addition, based on the Genval guidelines, a negative impact on the QoL is a criterion for reflux disease in patients with frequent heartburn.

Clinically, individuals with GERD may experience its classic syndromes, including heartburn and regurgitation; along with non-classic syndromes, including chest pain, globus sensation, chronic cough, and hoarseness. Heartburn is usually characterized by the involvement of a burning substernal or epigastric discomfort which radiates towards the mouth. Here, regurgitation refers to the reflux of food or bitter-tasting gastric contents emanating from the stomach into the mouth.

GERD is further classified based on the appearance of the esophageal mucosa seen from an upper endoscopy into erosive esophagitis and non-erosive reflux disease (NERD).

Over the years, FGIDs have been diagnosed and classified according to the Rome criteria. Within the Rome II criteria, FD is defined as pain or discomfort centered in the upper abdomen, with no emphasis given to meal-related symptoms. As defined by the Rome III criteria, FD is a disorder including 1 or more of the following: bothersome postprandial fullness, early satiation, epigastric pain, epigastric burning, and no evidence of any structural disease. The criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis. FD can be further divided into postprandial distress syndrome, characterized by meal-induced dyspeptic symptoms, and epigastric pain syndrome, which refers to epigastric pain or epigastric burning that does not occur exclusively postprandially, according to symptom presentation. IBS manifests itself as recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months, with at least 2 of the following characteristics: (1) relief through defecation, (2) onset associated with a change in the frequency of stool, and (3) onset associated with a change in the form of stool. The type of IBS is further divided into diarrhea, constipation, and a combination of the two.

IBS has traditionally been subcategorized into 4 subtypes based on predominant stool pattern: constipation, diarrhea, mixed, or unsubtyped.

The updated Rome IV diagnostic criteria categorize the FGIDs of gut-brain interaction, and define the symptom based diagnostic criteria for each category. The classifications of FGIDs according to the Rome IV criteria include esophageal disorders (globus, functional chest pain, functional heartburn, functional dysphagia, and reflux hypersensitivity), gastroduodenal disorders (FD, belching disorders, nausea/vomiting disorders, and rumination syndrome), along with bowel disorders (including IBS, functional abdominal bloating/distension, functional constipation, and functional diarrhea).

According to the current consensus, FGIDs are considered to be a group of disorders classified by gastrointestinal (GI) symptoms relate to any combination of the following: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system processing.

**Risk Factors of Impaired Health Related Quality of Life in the Individuals With Gastroesophageal Reflux Disease**

GERD is a chronic disease reportedly to be more severe and possessing a higher incidence of severe complications in older versus younger patients. On the contrary, elderly patients present themselves less frequently with the typical symptoms of heartburn, acid regurgitation, and pain. Therefore, the younger GERD patients are found to have a significant degree of QoL impairment than the elderly.

As for the impact gender has on HRQoL in GERD, a previous study found that women had poorer general scores than men. However, this trend may be due to a heightened sensitivity and symptom perception of female patients diagnosed with NERD.

One cross-sectional study in the United States enrolled 1524 subjects who were reported to be obese (defined as a body mass index over 30 kg/m²), and were associated with experiencing frequent reflux symptoms (OR, 2.8; CI, 1.7 to 4.5). Additionally, the condition of being overweight or obese has been associated with a deterioration in HRQoL, and the risk of suffering from any longstanding illness is associated with an increased body mass index. For these obese patients, women perceived themselves having markedly more psychosocial problems due to their obesity than did men.

NERD accounts for 60% of all chronic heartburn cases in a community due to the heterogeneous form of its pathophysiological

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mechanisms. A meta-analysis of 5 trials incorporating a total of 11,945 GERD subjects found no correlation between the severity of esophagitis and its symptoms. In addition, patients with erosive esophagitis and those with NERD had similar general HRQoL scores according to previous investigations.

One study was conducted within Sweden’s general population which assessed the impact of the severity and frequency of GERD symptoms. Those results showed that even symptoms rated as mild are associated with a clinically meaningful reduction in wellbeing. Other studies have documented an increasing symptom frequency of heartburn which has led to significant decreases in wellbeing.

One past study enrolling 136 Swedish subjects showed that patients with GERD symptoms reported a 23% reduced productivity rate while at work, and a 30% reduced productivity rate while doing regular daily activities. In addition, time absent from work for health reasons and reduction in productivity at work both became significantly more pronounced with increasing severity of GERD symptoms.

Another study containing 3000 Swedish adults reported that weekly reflux symptoms were associated with meaningfully impaired HRQoL in the physical dimensions of short-form (SF)-36, while daily symptoms had meaningfully impaired HRQoL in both physical and psychosocial dimensions.

A systematic review of 19 studies, including a total of 55,834 participants with reflux symptoms, disclosed that both the mean physical health and mental health scores were 1.1-fold lower in the groups with “disruptive,” which mean severe and frequent GERD, than in those with “non-disruptive” GERD. Additionally, the groups with more severe reflux symptoms had lower physical health scores than those with less severe symptoms.

One large European multicenter observational study noted that more than half of GERD patients experienced sleep disturbance, and that persistent regurgitation was associated with more hours of missed work. Sleep disturbance and associated daytime sleepiness, a decrease in mealtime enjoyment, and increased medication costs that may also contribute to the burden of disease.

Overlapping FGIDs have a significant impact on the HRQoL of subjects with GERD, and the details regarding that will be discussed later.

The Prevalence and Risk Factors for Individuals With Overlapping Functional Gastrointestinal Disorders and Gastroesophageal Reflux Disease

GERD and FGIDs are very common within the general population. Since GERD and FGIDs are both prevalent, coexistence may often be observed.

Past epidemiological studies which investigated the prevalence of dyspeptic and esophageal symptoms have reported a higher prevalence of dyspeptic symptoms in patients with GERD, suggesting that the degree of overlap is greater than could be predicted through chance alone. The reason for this may be due to the 2 diseases sharing pathophysiological mechanisms, including visceral hypersensitivity and altered GI motility.

A nationwide study of 100,000 individuals within the Danish population implemented a web-based questionnaire survey. Respondents with GERD-FD, GERD-IBS, or GERD-FD-IBS complexes numbered 881 (1.9%), 790 (1.7%), and 770 (1.6%), respectively. One study in France reported FGIDs overlap to be as high as 72.0% in all 3,318 GERD patients using the Rome II diagnostic criteria, with more GERD symptoms found to be associated with an increased prevalence of FGIDs. Another study involving 1001 Swedish subjects from the Kalixanda study found FD in 157 (16.0%) patients when applying the Rome III criteria. Among these cases, the overlap of GERD-FD and GERD-FD-IBS was 39 (3.9%) and 58 (5.8%) respectively.

One cross-sectional study which enrolled 63 GERD and 48 overlapping GERD-FD Chinese patients in Taiwan found a significantly younger age (40.54 ± 15.75 years vs 51.43 ± 16.64 years, P = 0.001), and significantly higher number of the female gender (70.8% vs 34.9%, P = 0.001) in the GERD-FD group compared to those in the GERD only group.

In a recent review, the overlap of GERD with IBS spanned in values ranging from 3.0-79.0%, which may be due to different diagnostic criteria of IBS, such as the Manning, Rome I, Rome II, or Rome III criteria. Another meta-analysis study involving 13 reports found the proportion of IBS with GERD-type symptoms in IBS individuals was as high as 42.0%. The overall OR of GERD-type symptoms in individuals with IBS was 4-fold to that of individuals without IBS. The strength of positive association between GERD and IBS varied from 3.53 (CI, 2.05 to 6.10) when the Rome I criteria for IBS were used, to 9.59 (CI, 7.14 to 12.87) with the Rome III criteria.
Table 1. Prevalence and Risk Factors of Overlapping Functional Gastrointestinal Disorders and Gastroesophageal Reflux Disease

| Author (yr)       | Area   | GERD definition | FGIDs definition | Total numbers of subjects | Prevalence of overlapping GERD-FGID | Risk factors of overlap |
|-------------------|--------|-----------------|------------------|---------------------------|-------------------------------------|-------------------------|
| Jarbøl, DE. (2017)<sup>13</sup> | Denmark | Montreal definition | Rome III | 100 000 subjects in a general population | 1.9% with GERD-FD, 1.7% with GERD-IBS-C, 1.6% with GERD-FD-IBS-C | More GERD symptoms |
| Guillemot et al,<sup>36</sup> 2005 | France  | Questionnaire   | Rome II | 3318 subjects with GERD | 72.0% with any FGIDs (27.0% IBS, 16.0% FD, 57.0% both) | More GERD symptoms |
| Aro et al,<sup>37</sup> 2011 | Swedish | Montreal definition | Rome III | 1001 subjects in a general population | 3.9% with GERD-FD, 5.8% with GERD-FD-IBS | More GERD symptoms |
| Lee et al,<sup>38</sup> 2014 | Taiwan | Montreal definition | Rome III | 48 subjects with GERD-FD, 63 subjects with GERD only | 11.2% with GERD, 7.7% with FD, 10.5% with IBS, 6.5% with overlap | Younger age, female |
| Rasmussen et al,<sup>41</sup> 2015 | Denmark | Montreal definition | Rome III | 49 706 subjects in a general population | 79 subjects with GERD-IBS | More severe GERD, more health-care-seeking behavior, depression |
| Hsu et al,<sup>42</sup> 2015 | Taiwan  | Questionnaire   | Rome III | 2604 subjects in a health check-out cohort | 107 subjects with GERD-FD | IBS |
| Hsu et al,<sup>43</sup> 2017 | Taiwan  | Questionnaire   | Rome III | 868 subjects with GERD | 6.0% with overlaps | Cigarette smoking |
| Fujiwara et al,<sup>46</sup> 2011 | Japan   | Questionnaire   | Rome III | 2680 subjects in a health check-out cohort | 6.0% with overlaps | Cigarette smoking |
| Noh et al,<sup>47</sup> 2010 | Korea   | Endoscopy        | Rome III | 360 subjects with GERD | 8.1% with FD, 10.1% with IBS | NERD |
| Nam et al,<sup>48</sup> 2013 | Korea   | Questionnaire and endoscopy | Rome III | 2769 subjects in a health check-out cohort | 9.3% with IBS, 7.9% with NERD, 10.1% with EE | NERD |
| Jung et al,<sup>49</sup> 2007 | United States | Questionnaire | Rome III | 2298 subjects in a general population | 3.0% men with GERD-IBS, 4.0% women with GERD-IBS | Insomnia, abdominal pain, somatization |
| Lee et al,<sup>50</sup> 2009 | Korea   | Questionnaire   | Rome II | 1443 subjects in a general population | 2.3% with GERD-FD, 2.0% with GERD-IBS, 1.3% with FD-IBS | Anxiety |

GERD, gastroesophageal reflux disease; FGIDs, functional gastrointestinal disorders; FD, functional dyspepsia; EE, erosive esophagus; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; NERD, non-erosive reflux disease.
One nationwide study in Denmark enrolling 49,706 randomly selected individuals who underwent a web-based questionnaire survey, showed the prevalence of GERD, FD, and IBS (Rome III criteria) to be 11.2%, 7.7%, and 10.5%, respectively. Notably, the overlap between these conditions was 6.5%.\textsuperscript{41}

In a case-control study including 2604 healthy check-up subjects from Taiwan, the prevalence of IBS (Rome III criteria) was at least 10.0% in patients with GERD and 5.5% in those without. Those experiencing an overlap of the 2 conditions had more severe GERD, more frequent healthcare-seeking behavior, and higher depression scores.\textsuperscript{42} In a further subgroup analysis of 868 GERD cohort involving 107 cases with overlap GERD and dyspepsia, overlapping subjects were more often associated with IBS, as compared to subjects with GERD alone (OR, 3.54; CI, 1.92 to 6.52).\textsuperscript{43}

The majority of FGIDs are more prevalent in women than in men,\textsuperscript{47} and the pathogenesis may be associated with delayed gastric emptying in the female sex.\textsuperscript{47} Another study reported that cigarette smoking was significantly associated with overlaps among GERD, FD, and IBS in Japanese adults.\textsuperscript{46} Furthermore, NERD has been reported to be more frequently overlapped with both FD and IBS.\textsuperscript{47,48}

Emotional factors, such as anxiety and higher somatization, are common in the overlaps between GERD and FGIDs.\textsuperscript{49,50}

Table 1 summarizes the studies demonstrating the prevalence and risk factors of overlapping GERD and FGIDs.

**Overlap Functional Gastrointestinal Disorders on the Quality of Life in Individuals With Gastroesophageal Reflux Disease**

A study which enrolled 1001 adult Swedish subjects revealed that the overlap of GERD with FD had a statistically significant impact on SF-36 scores for bodily pain compared with FD only (mean scores 63.1 vs 72.4, \(P = 0.020\)).\textsuperscript{47}

A previous study involving 111 ethnic Chinese individuals in Taiwan found that patients in the GERD-FD group exhibited the lowest QoL scores, with respect to both physical (58.13 ± 15.31 vs 71.27 ± 15.98, \(P = 0.001\)) and mental health (50.46 ± 15.51 vs 68.33 ± 15.87, \(P = 0.001\)), when compared to the GERD group without FD.\textsuperscript{35}

In another case-control study from Taiwan, the patients with overlap GERD and IBS reported poorer sleep quality (OR, 1.11; CI, 1.01 to 1.21), and greater levels of depression (OR, 1.06; CI, 1.02 to 1.10), than those with GERD alone.\textsuperscript{42,50}

One cross-sectional study of 2680 Japanese workers noted that overlaps of GERD, FD, and IBS significantly worsened HRQoL in most domains, and the overlap of GERD was associated with a significantly worsening physical health score than FD alone and IBS alone.\textsuperscript{51}

One study which enrolled 263 patients in the Netherlands found overlapping GERD + FD, GERD + IBS, and GERD + FD + IBS having significantly lower scores on 6, 8, and 7 scales of the SF-36 questionnaire, when compared to those without (\(P < 0.0005, P < 0.001, P < 0.0005\), respectively). When compared to subjects diagnosed with GERD only, those with overlapping GERD + FD, GERD + IBS, and GERD + FD + IBS had lower scores on 5, 8, and 6 subscales of the SF-36 questionnaire, when compared with those diagnosed with GERD only (\(P < 0.001, P < 0.0005, P < 0.001\), respectively).\textsuperscript{52}

A nationwide study of 100,000 individuals within the Danish population used a web-based questionnaire survey. Respondents with GERD-FD or GERD-IBS complexes had significantly higher odds of reporting poor self-rated health (OR, 6.07 vs 3.33) and impaired functional capacity (OR, 6.05 vs 2.88), compared to respondents with GERD alone. The individuals with 3 symptom complexes (GERD, FD, and IBS) were at the highest risk for reporting poor self-rated health (OR, 13.57) and impaired functional capacity (OR, 10.22).\textsuperscript{53}

One cross-sectional survey study which enrolled 2641 subjects in the United States found that higher GI symptoms to be more bothersome in the cases with overlapping IBS with constipation (IBS-C)-GERD (65.7%) or IBS-C-GERD-FD (73.5%) than those with GERD only (28.3%). The percentage of respondents who sought physician care for GI symptoms in the past 12 months of the study was also highest in the group with overlapping IBSGERD-FD (67.3%), following by the groups of overlapping GERD-FD (58.9%) and GERD only (56.6%).\textsuperscript{54}

Table 2 summarizes studies demonstrating the impact of HRQoL of subjects with overlapping GERD and FGIDs.

**Treatments for Overlapping Gastroesophageal Reflux Disease and Functional Gastrointestinal Disorders**

The management of GERD and FGIDs include the avoidance of risk factors through both lifestyle and dietary modifications. To the individuals with GERD, acid secretion suppressors are considered the most effective means towards determining adequate symptom relief, while proton pump inhibitors (PPIs) are the most potent agents.\textsuperscript{54}
Table 2. The Impact of Overlapping Functional Gastrointestinal Disorders on the Health Related Quality of Life in the Individuals With Gastroesophageal Reflux Disease

| Author (yr) | Area | GERD definition | FGIDs definition | Total numbers of subjects | Assessment of HRQoL | Impact of HRQoL |
|-------------|------|----------------|------------------|--------------------------|---------------------|----------------|
| Aro et al,17 2011 | Swedish | Montreal definition | Rome III | 1001 subjects in a general population | SF-36 | Lower scores on bodily pain in the subjects with GERD-FD than those with FD only |
| Lee et al,38 2014 | Taiwan | Montreal definition | Rome III | 48 subjects with GERD-FD, 63 subjects with GERD only | SF-36 | Lower scores of PCS and MCS in the subjects with GERD-FD than those with GERD only |
| Hsu et al,42 2015 | Taiwan | Reflux Disease Questionnaire | Rome III | 2604 subjects in a healthy check-out cohort | SF-36 | Poorer sleep quality and greater depression in the subjects with GERD-FD than those with IBS only |
| Kaji et al,11 2010 | Japan | Having GERD symptoms at least once a week | Rome III | 2680 subjects in a healthy check-out cohort | SF-8 | Worsening PCS score in the subjects with GERD-FGIDs than those with FGID only |
| De Vries et al,52 2007 | Netherlands | 24-hour pH-metry | Rome III | 215 GERD subjects and 48 control subjects | SF-36 | Lower scores of dimensions in the subjects with GERD-FGIDs than those with GERD only |
| Jarbøl et al,53 2017 | Denmark | Montreal definition | Rome III | 100 000 subjects in a general population | Self-rated health and functional capacity questionnaire | More reporting poor health and impaired functional capacity in the subjects with GERD-FGIDs than those with GERD only |
| Vakil et al,35 2016 | United States | Montreal definition | Rome III | 2641 subjects with FGIDs or GERD | Five-point Likert scale questionnaire | More GI symptom bothersome in the subjects with GERD-FGIDs than those with GERD only |

GERD, gastroesophageal reflux disease; FGIDs, functional gastrointestinal disorders; HRQoL, health related quality of life; SF, short-form; FD, functional dyspepsia; PCS, physical component summary; MCS, mental component summary; IBS, irritable bowel syndrome; GI, gastrointestinal.
However, according to previous studies, the presence of FGIDs reduced the response to PPIs in GERD patients.\textsuperscript{15,16} Whereas on the contrary, some past reports found the symptoms of FGIDs resolution of patients after PPI therapy.\textsuperscript{17,18} The reason for this may be due to PPIs being associated with alterations in intestinal barrier function,\textsuperscript{19} and subsequently with secondary changes in intestinal microbiota composition,\textsuperscript{20} which could be a determining role in FGIDs pathogenesis.

Considering the sharing pathogenesis of GERD and FGIDs, the medications which are aimed at reducing visceral sensitivity, including tricyclic antidepressant agents, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors, may offer therapeutic benefits to individuals with any overlapping syndromes.\textsuperscript{21} Unfortunately, few studies have been performed in the past. Therefore, further investigation regarding effective therapies for both GERD and FGIDs needs to be performed.

Past studies that have discussed the therapeutic efficacy of prokinetics to patients with GERD and FGIDs were few. One small, randomized controlled trial with tegaserod (a 5-hydroxytryptamine 4 agonist), enrolling 25 cases with overlapping GERD and FD (Rome II), were randomized to receive tegaserod or a placebo. However, tegaserod did not achieve overall symptom improvement.\textsuperscript{62} The role of prokinetics to these subjects should need larger studies for confirmation.

### Conclusion

Risk factors involving impaired HRQoL in individuals with GERD include being a younger age, obesity, an increase in reflux symptom frequency, and overlapping FGIDs. The risk factors for subjects experiencing an overlap in FGIDs and GERD involve those who are female, younger age, cigarette smoking, NERD, more GERD symptoms, and psychological performances including anxiety, somatization and more frequent healthcare-seeking behavior. The overlap of GERD and FGIDs is associated with the worsening of both physical and mental health, an increase in bothersome syndromes, an impaired functional capacity, and a greater likelihood to consult physicians. Acid secretion suppressors may offer therapeutic efficacy to some patients with overlapping GERD and FGIDs. Clinical guidelines and regulatory guidance may need to be followed for those patients with overlapping disorders, due to a substantial proportion of patients seeking health care.

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