Original Article

Characteristics of gastroesophageal reflux in adults with cystic fibrosis[☆,☆☆]

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Abstract

Background: Gastroesophageal reflux (GER) in adults with cystic fibrosis (CF) is poorly characterized. This study examines the frequency and predictors of GER symptoms and their relationship to lung function in adults with CF.
Methods: Cross-sectional study of adults at the University of Minnesota CF Clinic using two validated self report surveys: The Mayo GER questionnaire and the GERD Symptom Assessment Scale (GSAS).
Results: Of 274 invited patients, 201 (73%) completed the surveys and 173 performed spirometry at the same visit. Frequent symptoms (at least weekly) were reported by 24% of the patients and an additional 39% experienced occasional symptoms. Heartburn, acid regurgitation and dysphagia were the most common symptoms and 18% reported that GER symptoms worsened their respiratory condition. Females and patients reporting weight loss had more symptoms (mean GSAS symptom score 4.9 vs. 4.0, p=0.025 and 5.3 vs. 4.2, p=0.04) and more severe symptoms (mean GSAS distress score 5.6 vs. 3.8, p=0.005 and 6.8 vs. 4.0, p=0.01) compared to males and those who did not report weight loss. Patients on acid suppression (n=122, 61%) continued to report heartburn (n=80, 66%) and acid regurgitation (n=47, 23%). GER symptoms and severity of symptoms were not predictive of FEV_1 or FVC.
Conclusions: GER symptoms were present in a majority of patients. Females and patients with weight loss require special attention to their GER symptoms. Many patients on acid suppression continued to be report symptoms.
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Keywords: Cystic fibrosis; Gastroesophageal reflux; Spirometry; Proton pump inhibitor; Histamine-2 receptor antagonist; Self report survey

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1. Introduction

Gastroesophageal reflux disease (GERD) has long been suspected of exacerbating a variety of respiratory diseases. Asthmatics, lung transplant recipients, and patients with chronic obstructive pulmonary disease (COPD) have a higher prevalence of GERD than the general population [1,2]. Moreover, a number of studies suggest that treatment of GERD can improve the course of asthma [3] and reduce the risk of chronic rejection following lung transplantation [4]. Over the last 30 years, advances in care have resulted in a growing population of adults with cystic fibrosis (CF) [5], but the impact of GERD on this population remains poorly understood. GERD is more common in infants and children with CF than in the general population [6–9], but there are few comparable studies in adults [10,11]. Furthermore, evidence that GERD adversely impacts lung function in CF is limited [12]. However, GERD can complicate malnutrition in CF [13,14], and the possibility that acid blockade improves the clinical course of CF has prompted many physicians to aggressively treat GER symptoms.

Validated questionnaires are used to assess GER symptoms in the general population. The purpose of this study is to determine the frequency and predictors of GER symptoms in adults with CF using validated questionnaires, and to examine the relationship between reflux symptoms and lung function.

2. Methods

2.1. Study population

This is a prospective, cross-sectional study of CF patients attending the adult program of the Minnesota CF Center. The study was conducted between May, 2004 and May, 2005. Inclusion criteria were age >18 years, a diagnosis of CF by sweat chloride testing or genotyping, and ability to read English above a 6th grade level. Questionnaires were administered in conjunction with CF clinic visits. Many but not all patients performed routine spirometry in association with their clinic visit. In general those patients with recent sinus surgery or who were being seen for non-pulmonary issues did not perform spirometry in association with their clinic visit. Hospitalized patients and those with known esophageal pathology were excluded.

2.2. Survey instruments

Patients completed the modified Mayo GER questionnaire (GERQ) and the Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS). The Mayo GERQ is a validated self-administered questionnaire [15] that has been used in a large population based survey of GER symptoms [16] as well as to study GER in patients with COPD [2]. The questionnaire asks about 7 symptoms experienced during the preceding 12 months: heartburn, acid regurgitation, trouble swallowing, chronic cough, lump in throat, belching, and hiccups. The instrument characterizes each symptom by its timing, severity and relationship to respiratory symptoms.

The GSAS is a validated self-administered questionnaire that asks patients to report the presence, frequency, and distress associated with 15 symptoms during the preceding week [17]. The instrument yields a symptom score (range 0–15) and a distress score (range 0–45). The symptom score is based on the presence or absence of 15 symptoms: heartburn, chest pressure or discomfort, food coming back into the mouth, an acidic or sour taste in the mouth, frequent stomach gurgling, pressure or a lump in the throat, nausea, burning throat pain, bloating, belching, flatulence, early satiety, halitosis, cough, and hoarseness. The distress score is based upon the degree of distress caused by each of the aforementioned symptoms on a scale from 0 to 3 (not at all, somewhat, quite a bit, and very much).

2.3. Study protocol

The study and all survey materials were approved by the Institutional Review Board of the University of Minnesota. Subjects were recruited and completed the questionnaires in conjunction with their routine CF clinic visit. Incomplete surveys, defined as lacking responses to 3 or more items on the GSAS or missing two or more responses to symptom questions or two or more demographic items on the Mayo GERQ, were excluded. Patient height, weight, pulmonary function tests at the time of the clinic visit, diagnosis of CF related diabetes (CFRD) by a diabetologist, pancreatic enzyme use, and CF genotype data were obtained from the Minnesota CF Database and chart review.

2.4. Statistical analysis

Comparisons of continuous variables between two groups were assessed using t-tests (Minitab software, Minitab Inc. State College, PA). Associations between continuous variables were compared using Pearson's correlation coefficient. Because cough is present nearly universally in CF patients, we calculated correlations between GSAS scores and Mayo responses with, and without, cough included in calculations of GSAS scores. Chi-square tests were used to analyze categorical variables. Linear regression analysis was performed to investigate for possible associations between GER symptoms, GSAS symptom and distress scores and patient characteristics such as age, sex, BMI, presence of ΔF508 genotype, NSAID use, pancreatic enzyme use, diagnosis of CFRD and FEV_1 and FVC. Subgroups for severity of pulmonary disease were based on percent predicted FEV_1 as previously reported by the Cystic Fibrosis Foundation Patient Registry [5]. Statistical significance was defined as p value <0.05.

3. Results

3.1. Participants

Of the 431 CF patients registered at the University of Minnesota CF center, 274 (64%) were invited to participate in the study. We were unable to reach the remainder of the patients in

conjunction with a clinic visit to invite them to the study. Of those invited 204 (74%) completed the surveys, 41 (15%) did not return the surveys, and 29 (11%) declined participation. Three incomplete surveys were excluded from analysis. No patients were excluded due to the presence of co-existing esophageal pathology. Of the 201 patients who constitute our study group 109 (54%) were male, mean age (range), 31.4 (18–64) and BMI (range), 22.8 (15.8–30.8). Of these patients, 179 (89.5%) were taking pancreatic enzymes and 22 (11%) had CF related diabetes. Spirometry was performed in 174 (86%) in conjunction with completing the surveys with a mean FEV_1 of 68.9%. Based on the CF foundation criteria 47(27%) had a normal FEV_1 (> 90%), 34 (20%) had a mildly abnormal FEV_1 (70–89%), 57 (33%) had a moderate reduction in the FEV_1 (40–69%) and 35(20%) had a severe reduction in the FEV_1 (<40%). Genotype data was available in 158(79%); 95(60%) homozygous for $\Delta F508$ and 51 (32%) heterozygous for $\Delta F508$.

3.2. Prevalence and severity of symptoms

From the Mayo GERQ, 126 patients (63%) reported at least one GER symptom.

The most commonly reported symptoms were heartburn (53%, n=106), acid regurgitation (33%, n=68) and dysphagia (18%, n=36). Frequent symptoms, defined as experienced at least weekly [16] were reported by 24% of all patients (n=48). More specifically this was reported by 39% (n=41) of those with heartburn, 25% (n=17) of those with acid regurgitation and 36% (n=13) of those with dysphagia. When patients with GER symptoms (n=126) were asked about the impact on their respiratory condition, 29% (n=36) reported that their GER symptoms exacerbated their shortness of breath, increased their cough, wheezing or inhaler use. Of these patients 53% (n=19) also reported frequent GER symptoms.

3.3. Predictors of GER symptoms

A significantly greater number of symptoms and distress on the GSAS scale (Table 1) was found in females and in patients who regularly used NSAIDs (defined as greater than twice a

Table 1
Predictors of GER symptoms.

	Females vs. males	NSAID users vs. non-users	Weight loss vs. no weight loss
Mean GSAS [a] Symptom score	4.93 vs. 4.05 (p=0.025)	5.40 vs. 4.0 (p=0.003)	5.29 vs. 4.24 (p=0.04)
Mean GSAS distress score	5.63 vs. 3.75 (p=0.005)	6.0 vs. 3.9 (p=0.008)	6.75 vs. 3.99 (p=0.012)
Presence of acid reflux	N.S. [b]	41% vs. 29% (p=0.045)	N.S.
Percent predicted FEV_1	N.S.	N.S.	62% vs. 71% (p=0.045)
Percent predicted FVC	N.S.	N.S.	82% vs. 91% (p=0.019)

[a] Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS).
[b] Not statistically significant (N.S.).

week for at least one month, n=76, 38%). NSAID users also reported more acid regurgitation than non-users. Among patients with weight loss (self reported, n=51) there was also significantly greater symptoms and distress on the GSAS scale. Spirometry in this group showed the patients with weight loss also had significantly worse pulmonary disease than those without weigh loss (Table 1).

Analysis of GER symptoms by age categorizing either by dichotomizing the patients based on median age (median=29.6 years) or arbitrary subgroups (18–24, 25–29, 30–39, 40–49 and 50+) did not yield any significant differences in GSAS scores or report of GER symptoms. Similar analysis of BMI did not yield any significant differences in GSAS scores or report of GER symptoms. In addition patient characteristics such as presence of $\Delta F508$ genotype, pancreatic enzyme use and diagnosis of CFRD did not produce any differences in GSAS scores or report of GER symptoms.

Multiple regression analysis identified NSAID use, female sex, pancreatic enzyme use, and absence of $\Delta F508$ alleles as significant predictors of GSAS symptom scores, while NSAID use, female sex, pancreatic enzyme use, weight loss and age predicted GSAS distress scores, and reporting of regurgitation and dysphagia (Table 2). None of the covariates were predictive of reporting of heartburn.

3.4. Treatment of GER symptoms

Gastric acid suppression was common, with 122 patients (61%) taking proton pump inhibitors (PPI) or histamine-2 receptor antagonists (H2RA) (Table 3). The patients on acid suppression reported more symptoms and more severe symptoms on the GSAS as well as more heartburn than patients

Table 2
Predictors of GER symptoms.

Dependant variable	Coeff±SD	P-value
Covariate [a]		
GSAS [b] symptom score		
NSAID use [c]	1.6±0.47	p<0.001
Female sex	1.1±0.56	p=0.05
Pancreatic enzyme use	1.8±0.77	p=0.021
Presence of $\Delta F508$	−0.85±0.39	p=0.029
GSAS distress score [b]		
NSAID use	2.2±0.78	p=0.005
Female sex	2.2±0.94	p=0.021
Heartburn		
No significant predictors	N/A	N/A
Acid regurgitation		
Age	0.009±0.004	p=0.05
NSAID use	0.16±0.08	p=0.04
Dysphagia		
Pancreatic enzyme use	0.22±0.10	p=0.04
Weight loss [d]	0.15±0.8	p=0.03

[a] Linear regression performed with age, sex, BMI, presence of $\Delta F508$ genotype, NSAID use, pancreatic enzyme use, diagnosis of CFRD, FEV_1 and FVC as covariates.
[b] Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS).
[c] Non Steroidal Anti-inflammatory Drug (NSAID) more than twice weekly.
[d] Self-reported weight loss.

Table 3
Symptom and spirometry for patients using acid suppressing medications.

	No acid suppression	H2RA [b]	PPI [c]	Both
N (% of CF patients)	79 (39%)	29 (14%)	62 (31%)	31 (15%)
Mean GSAS [a] symptom score	2.9	5.3	4.9	6.8
Mean GSAS distress score	2.9	5	4.9	8.7
N reporting heartburn (%)	26 (33%)	19 (65%)	36 (58%)	25 (81%)
N reporting acid regurgitation (%)	20 (25%)	10 (35%)	24 (39%)	13 (42%)
Mean FVC	90.5 %	96.4 %	81.5 %	91.2 %
Mean FEV$_1$	70.5 %	76.6 %	62.5 %	70.4 %

[a] Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS).
[b] Patients on Histamine-2 receptor antagonists (H2RAs) in the preceding year had a worse symptom score (p=0.035) and distress score (p=0.001) than patients not on acid suppression.
[c] Patients on proton pump inhibitors (PPI) had a worse symptom score (p<0.0001) and distress score (p=0.0024) than patients not on acid suppression. More patients on PPI (p=0.003) and H2RA (p=0.03) reported heartburn than patients not on acid suppression. Patients on H2RA had a higher mean FVC (p=0.0033) and mean FEV$_1$ (p=0.023) compared to those on PPI.

Table 4
Comparison of symptoms based on use of acid suppressing medications.

	On acid suppression and reported GERD [b]	On acid suppression and did not report GERD [c]	Not on acid suppression
N (% of CF patients)	44 (22%)	78 (39%)	79 (39%)
Mean GSAS [a] symptom score	7.2	4.5	2.9
Mean GSAS distress score	7.7	4.9	2.9
Heartburn (%)	32 (73%)	48 (62%)	26 (33%)
Acid regurgitation (%)	23 (52%)	24 (31%)	20 (25%)
Dysphagia (%)	17 (40%)	9 (12%)	10 (13%)

[a] Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS).
[b] Patients who reported a diagnosis of GERD had worse GSAS symptom scores (p<0.001) and distress scores (p=0.015) and reported more acid regurgitation (p=0.026) than patients on acid suppression who did not report a diagnosis of GERD.
[c] Those on acid suppression who did not report a diagnosis of GERD had worse GSAS symptom (p=0.01) and distress scores (p=0.02) and reported more heartburn than those not on acid suppression.

not on acid suppression. Patients on PPI had significantly worse FVC and FEV$_1$. Of the patients on PPI or H2RA 36% (n=44) reported the indication for taking their medication as "Gastro-esophageal reflux disease, GERD, or reflux" (Table 4). Patients who reported a diagnosis of GERD had significantly more symptoms than other patients on acid suppression not reporting GERD as an indication.

Of the 79 patients who were not on gastric acid suppression, 35 (44%) reported GER symptoms with 26 (33%) reporting heartburn, 20 (25%) with acid regurgitation and 10 (13%) with dysphagia. Compared to patients on gastric acid suppression, these patients reported less heartburn (33% vs. 66%, p<0.001) but there were no significant differences in the report of acid regurgitation or dysphagia (25% vs. 49% and 13% vs. 21% respectively). Frequent symptoms (at least weekly) were reported by 5 (19%) with heartburn, 1(5%) with acid regurgitation and 3(30%) patients with dysphagia. Among patients not on gastric acid suppression, there were no significant differences in spirometry between patients with and without GER symptoms or with frequent GER symptoms.

3.5. Symptom severity and lung function

Spirometry did not differ significantly between patients reporting GER symptoms, frequent GER symptoms or no symptoms on the Mayo GERQ. There were no differences in spirometry between patients who reported their GER symptoms exacerbating their pulmonary function and those who did not. To further examine the relationship between GER symptoms and lung function, patients were categorized into four groups based on percent predicted FEV$_1$ (>90%, 70–89%, 40–69% and <40% as on previous report by Cystic Fibrosis Foundation [5]) (Table 5). There were no significant differences in GSAS symptom or distress scores, or prevalence of heartburn, acid regurgitation or dysphagia symptoms between the four groups. As expected patients with the most severe pulmonary disease

(FEV1<40%) were significantly older (vs. FEV1 >90%, 28.0 vs. 36.8, p=0.03), but BMI, ΔF508 genotype, CFRD status, and pancreatic enzyme use did not differ between groups.

4. Discussion

This study is a survey based cross-sectional study of GER symptoms in adults with CF at a single CF center. Most of our patients (63%) had GER symptoms and almost a quarter (24%) had frequent symptoms. Previous studies [6–9] of both adults and children with CF have reported a prevalence of GER symptoms of 25–81%, though they have employed differing criteria. Two small studies (n=50, n=10) comprised exclusively of adults with CF found a high prevalence (80%–88%) of GERD by pH probe in patients with GER symptoms and patients awaiting and having received a lung transplant respectively [10,11]. In a related study Ledson et al. demonstrated tracheal acidification in adult CF patients with GERD [18]. In our study there is a disparity between the

Table 5
Symptom scores by pulmonary severity–FEV$_1$ percent predicted [a].

	Normal ≥90%	Mild 70–89%	Moderate 40–69%	Severe <40% [c]
n (%)	47 (27%)	34 (20%)	57 (33%)	35 (20%)
Mean GSAS [b] symptom score	4.8	4.8	4.1	3.9
Mean GSAS distress score	4.6	5.3	4.3	4.3
Heartburn (%)	28 (60%)	14 (41%)	32 (56%)	16 (45%)
Acid regurgitation (%)	17 (36%)	10 (29%)	19 (33%)	15 (43%)
Dysphagia (%)	9 (19%)	5 (15%)	10 (18%)	5 (14%)

[a] Based on previous classification from Cystic Fibrosis Foundation. Patient Registry 2002 Annual report. Bethesda, MD: Cystic Fibrosis Foundation, 2003.
[b] Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS).
[c] There were no statistically significant differences in symptoms between any of these four severity groups.

numbers of patients experiencing frequent symptoms (24%) and the previously reported 80% of patients with positive pH probe who may be micro-aspirating. It is possible this is attributable to the prevalence of acid suppression in our study population. However, many of our patients on acid suppression continued to experience significant GER symptoms including heartburn and acid regurgitation (Table 3). Another important consideration is that GERD can be clinically silent, as a recent investigation found silent GERD in a third of studied CF patients [10].

Neither frequency nor severity of GER symptoms were a primary predictor of severity of lung disease in our study population. Subjectively, some patients (18%) found their GER symptoms to exacerbate their respiratory symptoms. The European Epidemiologic Registry of Cystic Fibrosis found a "history of GER" was associated with a 5 to 10% lower percent predicted FEV_1 [19]. Although the registry does not supply a definition for "a history of GER", the chronic nature of their findings suggests that the impact of GER on lung function and spirometry may occur over time and may not be reflected in evaluation of spirometry from a single time point.

There is no clear mechanism why females with CF have more frequent and severe GER symptoms. Investigating GER symptoms in healthy young adults (mean age 18 years) diagnosed with GER in childhood El-Serag et al. found oral contraception to be the major risk factor for those on maintained on antireflux therapy [20]. Oral contraception is reported to be used as commonly in the CF as the general population [21]. Contraception was not investigated as a specific risk factor in our study however in the year prior to the study a survey of our post-menarchal female CF patients (n = 113) over the age of 14, mean age 27.6 (±9.1) years showed that 67 (59%) of the women were not using any form of birth control (personal communication, Dr. Joanne Billings). Females with CF do have decreased survival relative to males [22], and this warrants further investigation of GERD in females with CF to determine if there is any impact on survival. Patients with weight loss were found to have worse GER symptoms as well as lung function. This is another sub-group that should continue to receive attention as GER has been shown to complicate malnutrition in CF [13,14] and because of the strong links between nutrition and survival in CF [5].

Many of our patients were taking a PPI, H2RA or both at the time of survey completion. The patients not reporting GERD as an indication for acid suppression reflect the common practice in our center to use acid blockade to enhance pancreatic enzyme efficiency. A third of patients who reported taking acid suppression for treatment of GERD had persistent symptoms, in fact significantly more than patients on acid suppression for other indications. Also of concern was the number of patients on acid suppression who continued to experience acid regurgitation and heartburn. This calls to question the response of adults with CF to PPIs and H2RAs at the current recommended doses. It may be that gastric acid suppression is inadequate to relieve GER symptoms and that fundoplication may be of more therapeutic value because of bilious or non-acid reflux [23]. Blondeau et al. have investigated the relationship between airway and esophageal symptoms, the role of acid versus non-acid reflux and aspiration in both children and adults [24,25].

While acid and alkaline reflux can occur and bile acids have been demonstrated in saliva of individuals with CF a causal relationship or particular treatment methodologies have yet to be determined.

Regression analysis identified several other predictors of GER symptoms that did not show statistically significant differences in univariate analysis including NSAID and pancreatic enzyme use as well as absence of the ΔF508 genotype. Other factors such as age, BMI, CFRD were not found to be predictive of GER symptoms. It is possible that the ΔF508 genotype lacks GER as a frequent manifestation and other alleles may predispose to GER. Our sample size limited the study of specific alleles other than ΔF508. Blondeau et al. however reported bile acids in the saliva and bronchial lavage of patients homozygous for ΔF508 exclusively [25].

Our study is limited in that it is a cross-sectional study and many of our patients were on acid suppression at the time of survey. However, our sample is representative of what providers see in their day-to-day care for adults with CF. Comparison to a control population of age and gender matched normal adults or patients with other pulmonary disorders would be ideal but difficult to achieve as other respiratory disorders do not share the same natural history as CF. Despite these short falls our goal was to characterize GER symptoms rather than compare prevalence between CF patients and this was achieved. We were unable to recruit all of the patients registered in our center to participate in our study. It is possible that there is a selection bias and those patients with more severe diseases were more likely captured during recruitment from clinic. However, spirometry results do indicate an equitable distribution of disease severity. As with any self report instrument, recall bias may affect responses, although both instruments have been validated by specialists. The two sub groups, females and patients with weight loss, both with associations with decreased survival, have a higher symptom burden clearly indicating future studies should focus on females and patients with weight loss. Persistence of symptoms on acid suppression, previously reported rates of silent reflux and our finding of the disparity between prevalence of GER symptoms and the prevalence of GERD by pH probe all suggests that the mechanism and treatment of GER symptoms in patients with CF requires further investigation. Our results indicate that GER symptoms should not be implied as a primary predictor for the severity of lung disease but the literature does suggest an impact on lung function over time.

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