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RESEARCH ARTICLE

The relationship of gastroesophageal reflux disease and asthma control

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ABSTRACT

Purpose: To study whether ACT responses are confounded by gastro-esophageal status (GERD), and if this is in concordance with the variation in Forced Expiratory Volume in 1 second (FEV1%) and Fractional Excretion of Nitric Oxide (FeNO).

Materials and Methods: This is a prospective cohort study ($n = 307$). Patients were surveyed for demographics data, and underwent ACT scoring, FEV1% and FeNO testing.

Results: Patients with GERD had mean ACT scores that were 4.1 ($p < .001$) lower than without-GERD group. Not-well-controlled asthmatics (FEV1% <80, high FeNO) with-GERD had mean ACT scores that were 2.9 ($p < .001$) for FEV1% <80 and 3.8 ($p = .008$) for high FeNO lower than without-GERD group respectively. Well-controlled asthmatics (FEV1% ≥80, low FeNO) with-GERD had mean ACT scores that were 5.2 ($p < .001$) for FEV1% ≥80 and 5.1 ($p < .001$) for low FeNO lower than without-GERD group respectively.

Conclusion: Our study demonstrates that symptoms of GERD can lead to an inaccurate perception of asthma control and ACT as compared to objective measures, such as FEV1% and FeNO. Hence, this can lead to mismanagement of asthma, especially when objective measures are not conducted along with ACT.

Introduction

Asthma is a chronic inflammatory lung disease characterized by reversible airway obstruction and bronchospasms in response to various triggers, including exercise, allergens, and other environmental factors. Management is guided by quantifying patients' asthma control which is monitored using several parameters (e.g. symptoms, nighttime awakenings, interference with normal activity, short acting beta agonist use for symptom control, lung function [FEV1%, FEV1%/FVC], and validated questionnaires [ATAQ, ACQ, ACT]) [1].

The asthma control test (ACT) is a patient-based tool that aids healthcare practitioners (HCP) in identifying those with uncontrolled asthma and monitoring their response to treatment over time, without the use of spirometry or other tools [2]. Patient's responses are quantified into three categories – well controlled (a score of 20 to 25), not well controlled (a score of 16 to 19), and very poorly controlled (a score of less than or equal to 15) [1,3]. There is a pediatric equivalent of this test, the ACT-C. The results are categorized similarly as the adult ACT [4]. The smallest change in score that is clinically significant, also known as the minimally important difference (MID), for the ACT is 3 [5,6]. The ACT has been found to correlate well with specialist assessments [3]. For this reason, and because the ACT does not require spirometry, it has become a useful tool for HCPs in making clinical decisions regarding a patient's treatment plan [4,7].

The forced expiratory volume in 1 second (FEV1%) is utilized to estimate asthma control per the NIH guidelines [1]. Well controlled is defined as a value greater than 80%, not well controlled is designated a value of 60 to 80%, and very poorly controlled is a value less than 60%. The American Thoracic Society (ATS) guidelines strongly recommends fractional excretion of nitric oxide (FeNO) in addition to spirometry in monitoring airway inflammation in patients with asthma [8]. Higher FeNO levels are also a predictive factor for asthma exacerbations, and declining lung function. FeNO is cost-effective and has been shown to improve patient management when combined with standard assessment methods [9].

The variable time of onset and chronic clinical course of asthma allows for comorbid conditions and other risk factors to obscure ongoing assessment of

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asthma control, as these assessments usually rely heavily on patients' perception of their symptomatology.

Symptoms such as cough, dyspnea, and chest tightness are commonly shared between asthma and chronic conditions like GERD, which has a higher prevalence, anywhere from 30% to 80% in asthmatics [10]. A high proportion of this population, 40% to 60%, manifest non-classical symptoms of GERD [11]. Patients diagnosed with both conditions may find it hard to distinguish whether their symptoms are caused by asthma or GERD or a combination of both.

In our study, we hypothesize that the presence of GERD in asthmatics leads to inaccurate ACT as compared to objective measures such as spirometry and FeNO and hence, could lead to improper treatment of asthma.

Materials and methods

Ethics

The study was approved by the institutional review board (protocol number 2014–139) at MedStar Health Research, Baltimore, Maryland. Oral informed consent was required for all adults, and for subjects below the age of 18, both consent on a guardian and assent of the minor was required.

Study population and setting

Subject recruitment and data collection occurred over a 2-year period at the outpatient offices of Asthma, Allergy and Sinus Center (Rockville, Union Memorial Hospital, Waldorf, and White Marsh). 307 patients were selected based on previous diagnosis of asthma, ranging from ages 4 to 80. Of the 307 patients, 286 were included in the study and 21 were excluded due to having either incomplete questionnaires or incomplete physiologic testing data (FeNO, FEV1%). Of the 286 patients, FeNO data was available for $n = 229$ patients.

Study design

This study is a prospective cohort review and survey. Previously diagnosed asthmatics were given the option to participate in the study through an informed consent process. Self-administered ACT's and spirometry testing that included pre-bronchodilator FEV1%, and FeNO were completed. The pediatric ACT forms were filled by the pediatric patients between the ages of 4 to 11, with the aid of their parents. The adult ACT form was administered to patients over the age of 11. Adult patients and parents of the pediatric patients were given a demographics questionnaire (Table 1). All patients enrolled in the study were asked on the

Table 1. Demographics and Baseline Characterestics of Study Population.

	Number of Patients	Percentage of Total Study Population
Age in Years		
4–17	117	41%
18–64	139	49%
65+	30	10%
Gender		
Female	109	38%
Male	177	62%
Ethnicity		
African American	133	47%
Hispanics	8	3%
Caucasian	104	36%
Other	41	14%
GERD Status		
Positive	127	44%
Negative	159	56%
Spirometry		
FEV1% ≥ 80%	156	55%
FEV1% < 80%	130	45%
Fractional Exhaled Nitric Oxide ($n = 229$)		
Low FeNO	157	69%
High FeNO	72	31%

FEV1% = Forced Expiratory Volume in the first second of expiration.
FeNO = Fractional Exhaled Nitric Oxide.
Demographics and baseline characteristics of the $n = 286$ study participants with the exception of FeNO ($n = 229$). Low FeNO encompasses adults with FeNO ≤ 25 ppb and children younger than 12-years-old with FeNO ≤ 20, and High FeNO encompasses adults with FeNO > 25, children younger than 12-years-old with FeNO > 20.

questionnaire whether they had a history of GERD. The GERD symptoms they were asked about were the following: dry cough, tickle in the throat, phlegm in the throat, a feeling of chest tightness and heart burn.

FEV1% ($n = 307$) and FeNO ($n = 229$) were used as objective measures. Statistical analysis was conducted for GERD status within the well-controlled and poorly controlled categories. Similarly, adults with FeNO ≤ 25 ppb and children less than 12-years-old with FeNO ≤ 20 were placed into a well-controlled asthma group. Adults with FeNO > 25 ppb and children less than 12-years-old with FeNO > 25 ppb were placed into a poorly controlled asthma group. Similar statistical analysis was repeated for these groups.

Statistical analysis

A multiple linear regression model was created with ACT score as a dependent variable, and GERD as the independent variable (defined in Table 2). The effect of GERD on ACT scores, FEV1%, and FeNO were compared. Bivariate analysis was conducted by using two sample T-test and analysis of variance (ANOVA). Post hoc comparisons between groups were conducted if ANOVA results were significant. p value in post hoc

comparison was adjusted for multiple comparisons using Bonferroni method. Stratified bivariate analysis was also conducted. Stratification was done by FEV1% < 80% and FEV 1 ≥ 80%, and by low FeNO and high FeNO. Statistical significance was achieved at p < 0.05. Software used for statistical analysis was RStudio, version 1.0.143 (RStudio Inc, Massachusetts).

Results

The baseline characteristics for all study participants are given in Table 1. A total of 307 patients were enrolled. The prevalence of GERD in the analyzed sample was high, with 127 patients (44%) reporting GERD symptoms in the administered questionnaire. Of these 307 patients, 286 had complete demographics data and FEV1% values. However, only 229 patients were able to complete the FeNO test. 156 (55%) patients had an FEV1% value ≥ 80% and 157 (69%) had a low FeNO score, hence were classified as having well-controlled asthma by these metrics.

The multiple linear regression model (Table 2) isolates the effect that GERD has on the ACT score. When patients with GERD were compared to those without the disease, a statistically significant decrease of 3.6 (p < .001) in ACT score was noted.

A T-Test performed on the with and without GERD groups found a statistically significant decrease of 4.1 (p < .001) in the ACT means, thereby crossing the threshold ACT score of 20 that separates classification of well-controlled and not well controlled asthma (Figure 1). When utilizing the FEV1% objective metric, for the poorly controlled group, T-Testing indicated a statistically significant decrease of 2.9 (p < .001) in the mean ACT score when comparing the with-GERD group to the without-GERD group, and similarly, the well-controlled group showed a statistically significant decrease of 5.2 (p < .001) (Figure 2). When utilizing the FeNO objective metric, the poorly controlled group showed a decrease of 3.8 (p = .008) in the mean ACT scores when comparing the with-GERD group to the without-GERD group, similarly, the well-
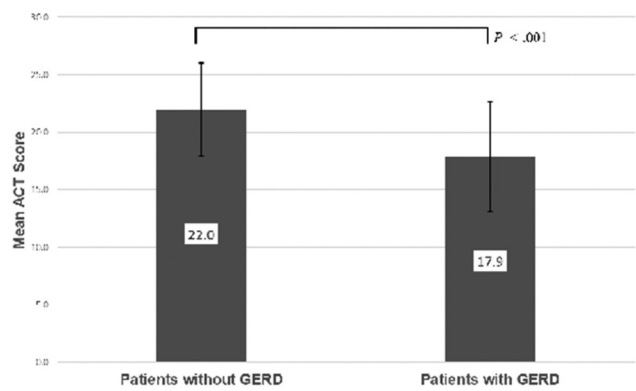
Figure 1. Mean ACT scores (± SD) of asthmatics patients with GERD and without GERD diagnosis. Line over bar indicates comparison groups and statistical significance stated as P-values.

controlled group showed a statistically significant decrease of 5.1 (p < .001) (Figure 3).

Discussion

In this study of asthmatic patients at our outpatient asthma and allergy clinic, we evaluated GERD as it correlates with the ACT score, FEV1%, and FeNO. A previous study has already demonstrated that the socioeconomic status and education level has an impact on the ACT scores and hence, the management of asthma [11]. However, the impact of GERD on ACT scores has not been shown in any previous studies.

GERD is a pathologic reflux of stomach contents, that is diagnosed clinically, and can cause (a) classical symptoms (i.e. heartburn, and/or regurgitation), or (b) non-classical symptoms (i.e. chest pain, cough, wheezing, nausea, and hoarseness) [12]. The Reflux theory

Table 2. Adjusted Effect of GERD Status on ACT Score using Linear regression Model.

Variable	Estimate	95% CI	P value
Intercept	18.6	(17.2, 20.0)	<.001
GERD Status			
No GERD		Reference	
GERD	−3.6	(−4.6, −2.6)	<.001

GERD = Gastro-esophageal reflux disease.
Multiple variable linear regression model looking at the adjusted effect of GERD status on ACT score compared to a base reference value. The effect of GERD on ACT scores, FEV1%, and FeNO were compared.
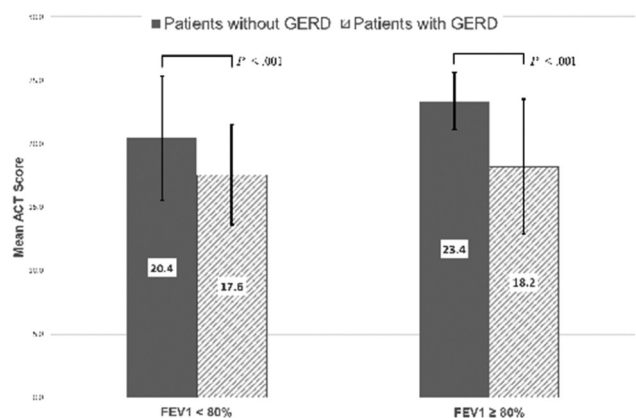
Figure 2. Mean ACT scores (± SD) for asthmatics with and without a GERD diagnosis as grouped by FEV1% < 80% and FEV1% ≥ 80%. Line over bar indicates comparison groups and statistical significance stated as P-values.
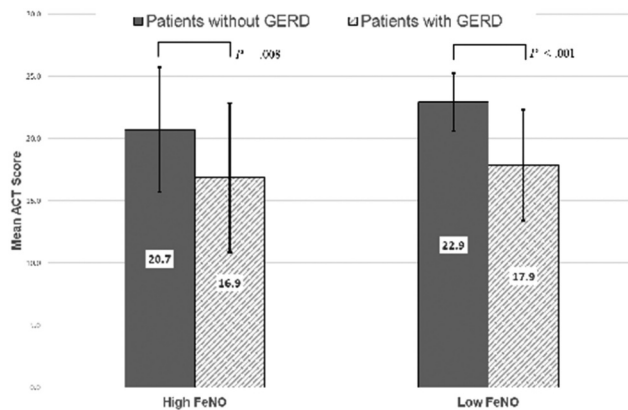
Figure 3. Mean ACT scores (± SD) for asthmatics with and without a GERD diagnosis as grouped by low FeNO and high FeNO. Line over bar indicates comparison groups and statistical significance stated as P-values.

proposes that GERD-mediated micro-aspirations of gastric contents are the cause of respiratory effects, while the Reflex theory maintains that the shared embryological origin of the bronchial tree and the esophagus leads to any acid exposure of the lower esophagus causing concurrent vagally mediated bronchoconstriction [12–14]. In a cyclical manner, cough associated with asthma can worsen reflux through negative intrathoracic pressure. Furthermore, drugs commonly prescribed for asthma can lower esophageal sphincter tone and worsen reflux [12,13].

When the patient sample was split based on FEV1% and FeNO, the difference in ACT score means between patients with GERD (lower scores) and those without GERD (higher scores) remained statistically significant, highlighting furthermore the effect GERD may have on the asthmatic population. Our study suggests that GERD should be considered an important confounder for patients with lower ACT scores, compared to FEV1% and FeNO results, thus prompting a formal assessment and treatment of GERD in those without classical symptoms of GERD. This has particular implications in management of patients with symptoms such as chest heaviness and cough that are occurring as a consequence of GERD, resulting in lower ACT scores and hence, the improper treatment of asthma. These patients are then at the risk of misguided escalation in medication therapy, including unnecessary use of oral cortical steroids, which may in fact worsen the GERD-associated symptoms. Although there is no current indisputable evidence on whether optimization of GERD treatment (medical or surgical) leads to better asthma outcomes, future prospective studies should be conducted to explore this concept. A previous study on 'The effect of esomeprazole (40 mg) Once or Twice Daily on Asthmatics' showed that esomeprazole demonstrated minor improvements in the asthma-related quality of life and pulmonary

function [15]. However, another study demonstrated treatment with proton-pump inhibitors did not improve asthma control, quality of life, and lung function in people with GERD [16].

Limitations

This study does not incorporate a specialist's assessment as the ultimate determinant of asthma control. We must acknowledge that factors such as improper administration, especially in the pediatric population, can influence these tests. We asked the pediatric patients to complete their own pediatric ACT forms as independently as possible, but with patients as young as 4 years old, it is expected that the scoring may not be entirely reflective of their actual status.

Conclusion

This study demonstrates that GERD is associated with differences in the way patients perceive their asthma control as indicated on the ACT. Though it is well known GERD affects the control of asthma, our study demonstrates that the presence of GERD affects ACT scores in patients. Hence, if ACT is the only tool used for measurement of asthma control, without objective measures such as spirometry and FeNO, it will lead to the improper management of their asthma.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability statement

All data relevant to the findings of the study are included within the article or its supplementary materials. The raw anonymized data extracted from individual patient records can be made available if requested.

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