Original Article

Correlation of Severity of Functional Gastrointestinal Disease Symptoms with that of Asthma and Chronic Obstructive Pulmonary Disease: A Multicenter Study

Abstract

Introduction: There is a growing clinical awareness about the influence of gut–lung axis on lung injury and coexisting manifestations of disease processes in both the intestine and lungs. Patients of chronic lung diseases such as chronic obstructive pulmonary disease (COPD) and asthma very often present with coexistent gut symptoms. In the present study, we have tried to establish the correlation of severity of pulmonary pathology of COPD and asthma patients with functional gastrointestinal (GI) symptoms of the patients. **Materials and Methods:** This is a prospective, questionnaire-based study comprising patients with asthma and COPD. After following strict inclusion and exclusion criteria, a total of 200 patients (100 patients of bronchial asthma and 100 patients of COPD) were included in the study. Functional GI symptom questionnaire [Annexure 1-Bowel Disease Questionnaire] is based on ROME III diagnostic criteria. On the basis of GOLD (Global Initiative for Obstructive Lung Disease) guidelines, COPD patients were divided into 4 categories (mild - GOLD 1, moderate – GOLD2, severe – GOLD3 and very severe – GOLD4). Asthma patients were divided into three categories (well controlled, partly controlled, uncontrolled) on the basis of GINA (Global Initiative for Asthma) guidelines. **Results:** Highest percentage of patients with maximum GI symptoms was found in "GOLD-4" group among COPD patients and "uncontrolled" group among asthma patients. Highest percentage of patients with least GI symptoms was found in "GOLD-1" group among COPD patients and "well controlled" group among asthma patients. **Conclusion:** We can conclude from our study that the phenomenon of gut–lung axis not only exists but also the severity of symptoms of one system (gut) carries a high degree of concordance with severity of other (lung).

Keywords: *Asthma, chronic obstructive pulmonary disease, functional gastrointestinal disease, gut microbiota, gut–lung axis*

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Introduction

There is a growing clinical awareness about the influence of gut–lung axis on lung injury and coexisting manifestations of disease processes in both the intestine and lungs.[1-4] Intestinal manifestations are commonly known to occur in viral respiratory infections.[4-6] Patients with chronic lung diseases such as chronic obstructive pulmonary disease (COPD) and bronchial asthma very often present with coexistent gut symptoms.[1-4] However, the underlying mechanism of this gut–lung vital cross talk is not well defined yet.[7] Several studies have already linked asthma with functional gastrointestinal (GI) diseases.[8,9] Functional GI diseases have been explained as "gut functioning abnormalities" defined on the basis of symptoms of patients without any demonstrable anatomical or biochemical disorders.[10,11]

In the present study, we have tried to assess these intestinal symptoms of asthma and COPD patients on the basis of a preset questionnaire. We have also tried to further establish the correlation of severity of pulmonary pathology with GI symptoms score of the patients.

Material and Methods

This is a questionnaire-based study comprising of patients with asthma and COPD. All patients were taken from the outpatient department of pulmonary medicine at two tertiary care institutes from October 2016 to June 2017. Patients with other respiratory diseases (except bronchial asthma and COPD), active or old history of tuberculosis, diabetes mellitus, pregnant females and HIV, and other immunocompromised states have been excluded from the study.

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A screening ultrasound (USG) abdomen was performed for all patients and patients with only normal screening USG were included in the study. On the basis of ROME III diagnostic criteria for common "Functional GI Disorders," a questionnaire was formulated [Annexure 1-Bowel Disease Questionnaire].

For tests of association using "Bivariate correlations," a "Moderate correlation" between "Severity of Asthma and COPD" and "GI symptom scores" (based on ROME III diagnostic criteria) was considered meaningful. To detect a moderate correlation (r = 0.25), a sample of 98 analyzable participants in each group of asthma and COPD provided 80% power, one sided to discover that the correlation was significantly different from there then being no correlation (i.e., that the correlation would be zero) at the 0.05 level. We have taken 100 analyzable participants in each group of asthma and COPD in our study.

After taking informed consent from every patient, the questionnaire [Annexure 1-Bowel Disease Questionnaire-based on various abdominal symptoms] was filled up by the investigators. Different questions in questionnaire have grades ranging from 0 to 1 (Grade "0" for answer 1 and Grade "1" for answer 2). GI symptom scores of patients have been divided into three categories (severe >10, moderate 5–10, and mild <5) reflecting severity of functional GI disorders. After following strict inclusion and exclusion criteria, a total of 200 patients (100 patients of bronchial asthma and 100 patients of COPD) were included in the study. A total of 56 males and 44 females were included in bronchial asthma group. A total of 65 males and 35 females were included in COPD group. Patients of <15 years and >80 years were excluded from the study. All patients were subjected to spirometry. COPD patients were divided into 4 categories (mild – GOLD1, moderate – GOLD2, severe – GOLD3, and very severe – GOLD4) as per the GOLD guidelines, depending on their airflow limitation severity (defined on the basis of postbronchodilator FEV1 on spirometry). Asthma patients were divided into three categories (well controlled, partly controlled, and uncontrolled) on the basis of their "level of asthma symptom control" as defined on the basis of GINA assessment of asthma control in adults, adolescents, and children. GI symptom score of every asthma and COPD patient was measured on the basis of questionnaire.

Statistical analysis was performed using the SPSS statistical package (version 17.0; SPSS Inc., Chicago, IL, USA). Categorical variables are expressed as frequencies and percentages. Pearson's Chi-square test was used to determine the relationship between disease (COPD or asthma) stage and GI symptom score.

Results

All COPD patients were categorized into GOLD 4 (30 patients), GOLD 3 (32 patients), GOLD 2 (26 patients), and GOLD 1 (12 patients) groups. Table 1 shows the distribution of numbers of COPD patients of varying severity (depending on COPD stage), according to their GI symptom scores. Numbers of patients with GI symptom scores >10 were 21 (42%), 20 (40%), 7 (14%), and 2 (4%) in GOLD 4, 3, 2, and 1 groups, respectively [Table 1]. Highest percentage of patients with least GI symptoms was found in "GOLD-1" COPD group.

Asthma patients were categorized into uncontrolled (31 patients), partly controlled (25 patients), and well controlled (44 patients) groups. Table 2 shows distribution of numbers of asthma patients of varying severity (depending on their asthma control level), according to their GI symptom scores. Number of patients with GI symptom score >10 were 21 (60%), 8 (22.9%), and 6 (17.1%) in uncontrolled, partly controlled, and well controlled groups, respectively [Table 2]. Highest percentage of patients with least GI symptoms was found in "well-controlled" asthma group.

The results of our study clearly showed that majority of COPD and asthma patients presenting with maximum

Table 1: Distribution of numbers of chronic obstructive pulmonary disease patients of varying severity as per their gastrointestinal symptom score

COPD stage	GI symptom score			Total patients	*P*
	>10 (%)	5-10 (%)	<5 (%)		
GOLD 4	21 patients (42)	6 patients (19.4)	3 patients (15.8)	30	χ^2=26.097 *P*<0.001
GOLD 3	20 patients (40)	9 patients (29)	3 patients (15.8)	32	
GOLD 2	7 patients (14)	13 patients (41.9)	6 patients (31.6)	26	
GOLD 1	2 patients (4.0)	3 patients (9.7)	7 patients (36.8)	12	
Total patients	50 (100)	31 (100)	19 (100)	100	

COPD: Chronic obstructive pulmonary disease; GI: Gastrointestinal; GOLD: Global Initiative for Obstructive Lung Disease

Table 2: Distribution of numbers of asthma patients of varying severity as per their gastrointestinal symptom score

Asthma control level	GI symptom score			Total patients	*P*
	>10 (%)	5-10 (%)	<5 (%)		
Uncontrolled	21 patients (60)	7 patients (24.1)	3 patients (8.3)	31	χ^2=41.084 *P*<0.001
Partly controlled	8 patients (22.9)	13 patients (44.8)	4 patients (11.1)	25	
Well controlled	6 patients (17.1)	9 patients (31)	29 patients (80.6)	44	
Total patients	35 (100)	29 (100)	36 (100)	100	

GI: Gastrointestinal

severity (GOLD 4 and uncontrolled, respectively), also presented with worst GI symptom scores. On the contrary, majority of stable COPD and asthma patients (GOLD 1 and well controlled, respectively) presented with mild GI symptom scores.

Discussion

In recent years, multiple theories and animal experimental models have been proposed to explain this phenomenon of gut–lung cross talk.

Effect of gut microbiota-Few studies have pointed toward qualitative or quantitative changes in gut microbiota, playing a possible role in variety of chronic lung diseases like asthma. Recent studies have described that both humans and animals are susceptible to develop allergic disorders later in life due to disturbances in microbiota in early life.[12] Russel *et al*. have proved in their experimental study on mice that there is a crucial window period during early developmental stage of life, during which suppression of microbial load and diversity by antibiotics administration will lead to airway inflammation on exposure to aeroallergens during later stages of life.[13] Similar findings were confirmed by Gollwitzer *et al*. in their study.[14] Another study by Abrahamsson *et al*. has revealed that infants with reduced diversity of gut microbiota during 1st month of their life, were more likely to be affected from asthma at 7 years of their age.[15] Babies born after cesarean section are said to have lower diversity of microbiota in their gut,[16] and these babies were found to have high likelihood of developing asthma in the future.[17] Bruzzese *et al*., in their study, have shown that restoration of gut microbiota (through administration of probiotics) is helpful in reducing both intestinal inflammation and pulmonary exacerbations in cystic fibrosis patients.[18]

Food habits-According to another theory, food habits can also significantly contribute to this gut–lung axis phenomenon by affecting microbiota of gut. Trompette *et al*. have revealed in their experimental study conducted on animal model that a high fermentable fiber diet could protect the mice from allergic inflammation of the lung.[19] Possible explanation to this is, a diet rich in fermentable fiber can result in the production of short-chain fatty acids which can, in turn, suppress allergic reactions through a gut–bone axis by enhancing hematopoiesis of macrophages and dendritic cell precursors.[20] This will bring about increased phagocytic activity in lungs with reduced ability to drive helper T-cell type 2 (Th2) cell effector functions.[19] This is a well-known fact that Th2 overactivation brings about type-1 IgE-mediated allergy and hypersensitivity reactions.[19] According to another hypothesis, regular diets enriched with high-fiber content are considered to be beneficial for lung function and helpful in reducing COPD risk.[21]

Secondary organ involvement in COPD patients-Secondary organ damage in COPD patients is another area of growing clinical interest nowadays. A study conducted by Ekbom *et al*. showed a significantly higher risk of both ulcerative colitis (hazards ratio: 1.83) and Crohn's disease (hazards: 2.72) among COPD patients.[20] It is commonly believed nowadays that both COPD and inflammatory bowel diseases may share common inflammatory pathways.[20,22] Another possible mechanism among COPD patients was proposed in the study of Rutten *et al*.[23] According to this study, a possible mechanism may be compromised intestinal perfusion leading to ischemia, owing to high metabolic demands among COPD patients.[23]

Smoking-Smoking is considered to be an independent risk factor for both COPD and a variety of GI pathologies like Crohn's disease.[24] Multiple studies have suggested till date that smoking may increase risk of developing Crohn's disease by as much as 3 folds.[24-28] Another school of thought says that smoke antigens are capable of initiating an immune response which in turn may cause secretion of elastases (MMP-9,12 and neutrophil elastase) from neutrophils and macrophages.[29] These elastases are capable of degrading elastin proteins.[30] Since elastin is an integral protein in intestinal mucosa as well, we can easily elucidate the mechanism involved in intestinal pathology in relation to smoking. In a recent study, smoking has been found to be associated with several functional GI diseases and functional symptoms such as functional bloating, functional abdominal pain, functional diarrhea, and functional constipation.[31]

Genetic predisposition-Till date, multiple different genetic mutations have been defined which predispose the development of COPD and inflammatory bowel diseases separately. Among various genetic mutations identified till date which may predispose to the development of Crohn's disease, NOD 2 genetic mutation (nucleotide-binding oligomerization domain containing 2) is of particular importance.[32-34] Recently, Kinose *et al*. have identified NOD-2 genetic mutation in COPD patients as well.[35] This may further support the theory of genetic influence on gut–lung axis. Hedgehog-interacting protein (HHIP) is another gene among various other described genes, which has been shown to be a potentially susceptible locus for predisposition of COPD.[36,37] Same HHIP gene locus was earlier found to be important in intestinal crypt axis development.[38]

Our study further endorses the phenomenon of gut–lung cross talk. Most of the participants in our study were found suffering from bowel symptoms. Their high GI symptom scores were significantly correlated with severity of their lung diseases (Low FEV1 in COPD patients and poor control in asthma patients).

It is worth noting that epithelia of both GI system and respiratory system develop from a common embryonic origin from primitive foregut.[39,40] This may possibly explain the remarkable structural similarities between

respiratory and GI tracts,[41-42] and we can conclude that structural and immunological similarities may be the reason behind common and overlapping pathological presentations of both systems.

Conclusion

We can conclude from our study that the phenomenon of gut–lung axis not only exists but also the severity of symptoms of one system (gut) carries a high degree of concordance with severity of other (lung). Our study clearly demonstrates that it is not mere a coincidence that patients of asthma and COPD, very frequently present with abdominal complaints. These findings are of vital importance, as a better understanding and further researches on this phenomenon can lead to opening of new dimensions for prevention, treatment, and rehabilitation of patients of chronic respiratory ailments as well as patients of multiple GI pathologies. One important limitation of our study is that we have taken into account only functional GI disorders; therefore, further studies are needed to study the correlation of demonstrable (anatomical and biochemical) GI diseases with obstructive airway diseases and other lung pathologies.

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Conflicts of interest

There are no conflicts of interest.

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Annexure 1: Bowel disease questionnaire

In every question, mentioned criteria must be fulfilled for last 3 months with symptom onset for last 6 months

1. Do you have recurrent abdominal pain or discomfort for at least 3 days/month?
   1. No
   2. Yes
2. If answer to question number 1 is yes, does this pain improve after defecation?
   1. No
   2. Yes
3. If answer to question number 1 is yes, does this pain associated with alteration in stool frequency?
   1. No
   2. Yes
4. If answer to question number 1 is yes, does this pain onset associated with change in appearance of stool?
   1. No
   2. Yes
5. Do you need to strain during 25% or more defecations?
   1. No
   2. Yes
6. Did you notice hard stools in at least 25% of defecations?
   1. No
   2. Yes
7. Did you have feeling of incomplete evacuation for at least 25% of defecations?
   1. No
   2. Yes
8. Did you have feeling of anorectal blockade for at least 25% of defecations?
   1. No
   2. Yes

Contd...

Annexure 1: Contd...

In every question, mentioned criteria must be fulfilled for last 3 months with symptom onset for last 6 months

9. Did you need manual maneuvers (like digital evacuation) to facilitate at least 25% of defecations?
   1. No
   2. Yes
10. Did you have fewer than 3 defecations per week?
   1. No
   2. Yes
11. (Answer the following question, if two or more answers are "yes" from question number 5 to 10) Did you rarely present with loose stools without laxative use?
   1. Yes
   2. No
12. Did you have troublesome feeling of fullness after meals and/or sense of early satiation?
   1. No
   2. Yes
13. Did you have recurrent episodes of epigastric pain and/or burning?
   1. No
   2. Yes
14. Did you have loose or watery stools without associated pain for at least 75% times?
   1. No
   2. Yes
15. Did you have troublesome feeling of fullness after ordinary sized meals for at least several times in a week?
   1. No
   2. Yes
16. Did you have early satiation that prevents finishing a regular meal for at least several times in a week?
   1. No
   2. Yes
17. Did you have intermittent burning pain localized to area of upper abdomen (epigastrium), of at least moderate severity for at least once per week and which is not relieved by defecation or passage of flatus?
   1. No
   2. Yes
18. Did you have troublesome nausea occurring for at least several times per week which is usually not associated with vomiting?
   1. No
   2. Yes
19. Did you have one or more episodes of vomiting per week?
   1. No
   2. Yes
20. Did you have nearly continuous abdominal pain (which is not related to eating, defecation, or menses) associated with some loss of daily functioning?
   1. No
   2. Yes