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Pulmonary function in ulcerative colitis

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Abstract

Background: Pulmonary involvement in ulcerative colitis (UC) is thought to be rare. There is not a definite document about the question that "Is the lung a target organ in inflammatory bowel disease?" The aim of the present study is to compare lung function between cases with UC and healthy controls. This study will also be of interest about searching the outbreak of pulmonary function abnormalities in a sample of Iranian patients with UC and factors associated with severity of UC.

Methods: In an analytic cross sectional study between July 2006 and September 2007, we evaluated 70 patients with histologically confirmed UC and 70 matched healthy people. Our checklist addressed demographic variables, symptoms, smoking behavior, drugs, laboratory findings and pulmonary function tests.

Results: None of the lung volumes and capacities were significantly different in cases as compared to controls. Severity of UC was mild in 65.7%. It was correlated with smoking (P=0.019) and allergy (P=0.017). Patients with moderate UC had lower hemoglobin (P<.001), MCH (P=0.002), MCV (P=0.047), MCHC (P=0.028) and higher REFF (P=0.032) and BF (P=0.01).

Conclusion: The controversies about the relation between UC and lung disease can be due to different sample sizes, activity of UC at the time of measurement of lung volumes, methods of measuring lung capacities at the time of PFT and different nationalities.

Keywords: ulcerative colitis, inflammatory bowel diseases, respiratory function tests

Introduction

Ulcerative colitis (UC) is a systemic illness with a number of extraintestinal manifestations affecting various organs. The most frequent lesions are cutaneous, ocular, hepatic and articular. In contrast, pulmonary involvement in UC is thought to be rare [1].

However, pulmonary lesions have been reported in inflammatory bowel disease (IBD), including chronic bronchial suppuration in patients with UC [2], localized obstruction of the upper airways [3], bronchiolitis obliterans, organizing pneumonia [4], diffuse obstructive disease [5], bronchiectasis [6], granulomatous lung disease [6], pulmonary vasculitis [6], and diffuse or localized interstitial lung fibrosis [6].

Some authors described alterations of pulmonary function in asymptomatic patients, most commonly reduced lung diffusion capacity and small airways function and bronchial hyperreactivity [7-9].

A recent review article showed that respiratory symptoms and diagnosed respiratory system

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disorders are more common among patients with IBD than generally appreciated [10]. It has been shown that the incidence of respiratory changes is higher in patients with ulcerative colitis as opposed to those with Crohn's disease (CD) [5,6].

It is important to recognize the association between IBD and pulmonary disease so that proper management can be better defined [11].

Is the lung a target organ in inflammatory bowel disease? Despite that it is not a new question; there are no definite documents yet.

The aim of the present study is to investigate lung function in patients with UC and to compare their pulmonary function test results with healthy controls.

Methods

Study population and assessments

In an analytic cross sectional study between July 2006 and September 2007, we evaluated 70 patients with histologically confirmed UC and 70 age-gender matched healthy people (frequency matched) as controls.

We completed a checklist for each case and control according to medical history, physical examination and laboratory findings. It addressed demographic variables (age, gender, job, income, area of their home), height, weight, duration of the disease, symptoms, smoking behavior, history of pulmonary diseases, allergy, hypertension, drugs, complete blood count (CBC), platelet, and ESR.

Medical history and pulmonary function tests (PFT) determined the condition of the lung. One expert technician performed all the spirometries by a Fukuda spirometer showing FEV1 (forced expiratory volume in one second), FVC (forced vital capacity), PEFR (peak expiratory flow rate), VC (vital capacity), FEV1/VC (proportion of FEV1 to VC), MMEF (maximum mid-expiratory flow), MEF25%, MEF50% and MEF75% values. According to predicted values for their age, gender, height and weight, the percentage of obtained values were recorded and expressed as percent of parameter. Normal range of indices are considered as VC>80%, FEV1>75%, and FEV1/FVC >75% for both men and women [12].

A blood sample determined the value of CBC parameters, platelet, and ESR.

We assessed the severity of ulcerative colitis in all patients according to Truelove Index for UC [13]. This index implements clinical symptoms (abdominal tenderness and distention), vital signs (temperature and pulse rate), number of defecations per day, blood in stool, laboratory findings (Hemoglobin and ESR) and radiographic findings (distention, air in colon, edematous intestinal wall, and thumb print sign).

Data processing, analysis and ethical considerations

Mean±SE (standard error), t-test, chi-square and Pearson's correlation coefficient were used in description and analysis of data. All tests with $P<0.05$ were considered statistically significant. SPSS 13 software (SPSS Inc. Chicago, Illinois, USA) was used in analysis.

The Gastrointestinal and Liver Disease Research Center Ethical Committee of Iran University reviewed and approved the study protocol. All patients signed an informed consent.

Results

There was no significant difference between cases and controls in demographic variables (age, sex, job, income, area of their home), weight, height, BMI, BSA, smoking behavior, CBC (except WBC and platelet), ESR, history of lung diseases, allergy, and hypertension (Table 1). So, the two groups were matched and compared.

VC less than 80% was found in 4 (5.8%) cases and 5 (7%) controls without a statistically significant difference between the two groups.

Severity of UC was mild in 46 cases (65.7%), moderate in 13 cases (18.6%), severe in 1 case (1.4%) and undetermined in 10 cases (14.3%). Severity of disease was correlated with smok-

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Variables	*Cases [mean±SE] or [No. (%)]*	*Controls [mean±SE] or [No. (%)]*	*Sig.*
Age (yr)	34.9±1.6	37.3±1.6	NS
Male gender	35 (50%)	25 (35.2%)	NS
Income (Toman)	99515±26839	520003±231803	NS
Area of home (sqm)	115.7±15.74	149.9±24.92	NS
Weight (kg)	68.5±1.41	67.7±1.37	NS
Height (cm)	166.4±1.25	164.4±1.07	NS
BSA	1.76±.02	1.74±.02	NS
Smoking behavior			
Year	13.8±6	6.2±2.8	NS
Number per day	9±4.1	8.8±4.2	NS
WBC (cells/microl)	7444±307	6351±219	.004
RBC (million)	4.575±.073	4.732±.068	NS
Hgb (g/dl)	13±.24	13.3±.16	NS
MCV(fl)	85.4±1.1	84.7±.7	NS
MCH (Pg)	28.2±.4	28.5±.3	NS
MCHC (g/dl)	32±.25	32±.2	NS
Platelet ($\times 10^3$/microl)	256.7±11.8	229.9±5.9	.045
ESR (ml/hr)	18.3±2.7	14.9±1.7	NS
History of lung diseases	2 (2.9%)	1 (1.4%)	NS
Allergy	10 (14.3%)	8 (11.3%)	NS
Hypertension	6 (8.6%)	3 (4.2%)	NS

NS= Not significant

Table 1. Comparison of cases and controls.

ing (P=0.019) and allergy (P=0.017). Patients with moderate UC had lower hemoglobin (P<.001), MCH (P=0.002), MCV (P=0.047), MCHC (P=0.028) and higher REFF (P=0.032) and BF (P=0.01).

Patients with UC had dyspnea [16 cases (22.9%)], chest pain [10 cases (14.3%)], cough [8 cases (11.4%)], fever [2 cases (2.9%)], defined history of lung disease [2 cases (2.9%)], allergy [10 cases (14.3%)], and hypertension [6 cases (8.6%)]. Abnormal FEV_1 was found in only 3 cases (4.3%).

Comparison of cases and controls showed higher WBC (7444 ± 307 vs. 6351 ± 219, P= 0.004) and platelet counts (256734 ± 11826 vs. 229851 ± 5917, P= 0.045) in cases, however both were in normal ranges and were not clinically significant.

Chest pain [10 subjects (14.3%) vs. 1 subject (1.4%), P=.004] and dyspnea [16 subjects (22.9%) vs. 6 subjects (8.5%), P=0.018] were more prevalent in cases significantly. However, there was no significant difference in fever and cough between the two groups. None of the quantitative volumes and lung capacities were significantly different in cases in comparison with controls. Findings of PFT are summarized in Table 2.

Interpretation of PFT showed no significant difference between cases and controls. Mild, moderate and severe expiratory limitation existed in 7 (10.1%), 5 (7.2%) and 1 (1.4%) patient in case and 7 (9.9%) and 1 (1.4%) patient in control groups, respectively. None of the controls demonstrated severe expiratory limitation.

Duration of UC was 5.1±.46 years in all cases. There was a significant correlation between duration of UC and RV (r=0.26, P=0.04), FEF75% (r=-0.25, P=0.046), history of pulmonary problems (15 ± 5 vs. 4.7 ± .4, P < 0.001), and allergy (7.8 ± 1.36 vs. 4.6 ± .47, P=0.02). Men had UC with more duration (6 ± .7 vs. 4 ± .6, P = 0.03).

Discussion

Little is known about lung function in patients with IBD. Camus et al [6] evaluated pul-

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monary function tests in 13 patients with IBD and detected a decline in the FEV1/FVC ratio in bronchiectatic patients. Latent pulmonary involvement has also been reported in adult IBD patients recently. Bronchial hyperreactivity (BHR) was seen in 48% of patients with ulcerative colitis and CD without any bronchopulmonary symptoms and with normal baseline lung function [14]. These findings may indicate that a latent inflammation exists in the airways of IBD patients which is not detectable by routine pulmonary function tests. In our study, we focused on UC patients because they are clinically and histologically different from CD. However, the pulmonary evaluation was assessed only by spirometry, a limitation of the present study. Therefore, we did not find significant difference between UC patients and controls.

Increased bronchial hyper-responsiveness in patients with IBD with no bronchopulmonary symptoms and with normal baseline lung function has recently been reported [14]. This latter observation may also indicate that an inflammation exists in the airways that are not detectable by routine pulmonary function tests.

Small peripheral airways (less than 2 mm in diameter) contribute less than 20% of the total airway resistance, and lesions in this region are difficult to detect. However, it is likely that

Variables	*Cases [mean ± SE]*	*Controls [mean ± SE]*	*Sig.*
SREFF	77.9530±4.75743	77.6586±4.76395	NS
REFF	93.2625±9.14648	109.7614±13.97984	NS
ITGV	109.1209±5.85942	100.2414±5.17866	NS
RV	128.5754±9.56347	119.6045±7.53450	NS
TLC	108.1970±2.89507	103.5718±2.75624	NS
VC	102.4029±1.86917	100.6732±1.74474	NS
RVTLC	114.7726±4.68092	108.7215±4.44195	NS
ITGVTLC	99.8738±2.89735	98.3500±2.96978	NS
VCEX	101.9116±1.94155	100.4859±1.79567	NS
VCIN	101.4203±1.81478	100.3972±1.75630	NS
BF	89.9323±3.47253	99.2588±3.61815	NS
MV	154.8956±6.98121	166.7014±9.17651	NS
VT	180.9015±8.59854	176.5812±9.28624	NS
IC	108.2986±3.17709	107.1915±2.55660	NS
ERV	93.8304±5.30314	87.7246±4.48066	NS
FEV_1	102.2101±1.76116	101.8718±1.92807	NS
FEV_1/FVC	101.8625±8.62799	117.6500±1.35000	NS
FEV_1/VCMX	100.7913±.96794	102.8944±1.12227	NS
FVC	102.9652±1.90956	100.3380±1.79024	NS
FEF25%	92.6739±2.53909	95.2479±2.31304	NS
FEF50%	87.2261±2.84735	93.1859±3.28784	NS
FEF75%	72.0014±3.53620	81.2577±4.75569	NS
PEF	88.6261±2.37411	91.5282±2.19747	NS
FEF50%/FVC	84.1318±3.09364	92.9594±3.30837	NS
MMEF75%-25%	83.5884±3.22490	90.7529±3.73120	NS
FEF75%-85%	83.9419±5.50035	92.8265±6.38625	NS

NS= Not significant

Table 2. PFT findings.

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some of the earliest changes in the airways of patients with IBD would affect primarily the small airways, and thus it is of importance to assess the function of the peripheral airways. It can be another cause of not earning significant pulmonary function difference between UC patients and controls in our study despite the presence of some pulmonary problems in IBD patients.

It is also known that high IgE levels are common in IBD despite the absence of atopic symptoms [15]. These observations suggested the probability of higher prevalence of allergic reactions and BHR in IBD patients in comparison with normal controls. In our study history of allergy was higher in UC patients in comparison with controls. However, it did not reach a significant difference. Other studies also showed higher levels of allergy in IBD patients [15,16,17,18,19].

In addition, it is noteworthy that there are similarities between colonic and bronchial epithelium: both originate from the primitive gut and both are sensitive to inhaled and ingested irritants.

In our study, there was a positive correlation between duration of UC and RV, history of pulmonary problems, allergy and male gender and a negative correlation with FEF75%. It has been shown that the incidence increases with duration of intestinal disease and is greater in CD than in UC [20].

Pulmonary disease has been described much less frequently than other organ systems associated with IBD. Although the cases with IBD and pulmonary manifestation may be incidental findings, it seems that some are directly associated with CD and UC. However, our methodology of comparing the UC patients with a matched control group, emphasize on not having an association between UC and major pulmonary diseases that are found by PFT. In all IBD cases, drug-induced pulmonary disease, a rare side effect of sulfasalazine, mesalamine, and methotrexate, must be ruled out. Pulmonary disease in IBD ranges from interstitial fibrosis (which can be lethal) to subclinical pulmonary function abnormalities.

Sixteen studies of pulmonary function tests (including> 600 patients with IBD) revealed a spectrum of restrictive disease, small airway disease, bronchial hyper-responsiveness, and hyperinflation during acute exacerbations associated with IBD [8, 9]. Although some studies are negative ones [21,22], two large trials [7, 23] and another new study [24] showed that more than 50% of patients with UC had abnormal pulmonary function tests compared with healthy matched controls. The most commonly described abnormality is a decrease in diffusion capacity of the lungs. In most reports, no relationship was found between these abnormalities and 5-ASA usage or disease activity. There was significant correlation between the severity of disease with smoking, allergy, hemoglobin, MCH, MCV, and MCHC in our study. According to the authors' search, there was no congruent study about smoking and severity of UC. Our assumption is that according to publication bias, some (or maybe many) congruent studies with our finding (positive association between smoking and severity of UC) are not published. However, we do not have another view about it.

Pulmonary function test studies in IBD suggest that subclinical pulmonary disease may be present in a large subpopulation of patients [22].

Pulmonary manifestations of IBD may be more common than originally thought. In a review article, more than 150 reports of active lung disease, with an even greater number of patients demonstrating subclinical pulmonary findings was found.

Although in most reported cases IBD predates respiratory symptoms, this may represent a reporter bias, because patients who present with preceding pulmonary disease may be overlooked [2].

Many authors who describe pulmonary disease in the setting of IBD stress the relationship

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between colectomy and the onset of symptoms. In our review of the literature, we have not found this to be the case. The overall incidence of colectomy in patients with UC is 5% to 10% in patients with a severe first attack and 1% per year in the remainder [25]. The incidence of colectomy among patients with pulmonary manifestations of IBD is similar. Colectomy has never been shown to be a curative treatment of extraintestinal pulmonary disease.

Most of our patients had a mild disease and were inactive at the time of measurement of lung volumes which can be other causes of lack of association between lung abnormalities and UC.

These controversies about the relation between UC and lung disease can be due to different sample sizes, activity of UC at the time of measurement of lung volumes, methods of measuring lung capacities at the time of PFT and different nationalities. Finally, according to our findings and similar studies, we recommend more exhaustive pulmonary evaluation in UC patients in order to find pulmonary abnormalities.

Simple spirometry is not capable of determining significant pulmonary function differences between UC patients and healthy controls. More detailed, basic, structural, mechanical and functional evaluation with higher sensitivity is needed to rationalize pulmonary abnormalities in cases with UC.

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