Pulmonary function tests, high-resolutıon computed tomography findings and inflammatory bowel disease

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Abstract

Aim : **The association between inflammatory bowel disease and pulmonary involvement has not been clearly established. The aim of this prospective study was to define the features of pulmonary function tests and high resolution computed tomography in inflammatory bowel disease patients and the relation between these and disease activity.**

Method : **Fifty-two patients with inflammatory bowel disease (20 with Crohn's disease and 32 with ulcerative colitis) were enrolled. The standard pulmonary function tests and thorax high resolution computed tomography findings were investigated with respect to inflammatory bowel disease activity. Crohn's disease activity index and the Rachmilewitz endoscopic activity index for ulcerative colitis were used to assess disease activity. Medications used and smoking status were also documented.**

Results : **Among the patients with ulcerative colitis, 6.25% had an obstructive and/or restrictive ventilatory defect compared with 25% of the patients with Crohn's disease. Fifty percent of the patients with ulcerative colitis and 60% of the patients with Crohn's disease showed abnormal findings in high resolution computed tomography. Pulmonary function tests and high resolution computed tomography abnormalities did not differ significantly between Crohn's disease and ulcerative colitis. No significant difference related to inflammatory bowel disease activity was found ($P > 0.05$).**

Conclusion : **Findings of high resolution computed tomography and the pulmonary function tests did not differ between ulcerative colitis and Crohn's disease. Bowel disease activity did not seem to affect these measurements.** (Acta gastroenterol. belg., **2006**, 69, **255-260**).

Key words : inflammatory bowel disease, pulmonary function tests, thorax high-resolution computed tomography.

Extraintestinal manifestations are common, with a frequency of 45% in patients with inflammatory bowel disease (IBD) (1), whereas pulmonary involvement seems to be rare. In a survey of 1274 patients with ulcerative colitis (UC), only 7 patients (0.6%) had pulmonary complications. In addition to the adverse pulmonary effects of sulfasalasine and mesalamine, different bronchopulmonary manifestations, including obstructive airway diseases like chronic bronchitis or bronchiectasis, interstitial lung diseases, pulmonary granulomatosis, pulmonary vascular diseases, and pleural effusions were described in case reports and case series (2-10). However, subclinical pulmonary dysfunction in IBD patients is still not well defined. Pulmonary abnormalities in UC and Crohn's disease (CD) can present years after the onset of bowel disease. Early recognition is important as they can be steroid responsive (11). Investigations of pulmonary function in IBD patients by standard lung function tests have yielded inconsistent results. While some authors detected no differences in routine pulmonary function tests between IBD patients and controls, others documented a reduced lung transfer factor for carbon monoxide, especially in patients with active IBD (6-14). Recently, high resolution computed tomography (HRCT) scans have been used to show emphysema, bronchiectasis, and interstitial fibrosis even in the absence of recognisable morphologic abnormalities by conventional CT (16,17). This prospective study investigated differences in pulmonary function tests (PFT) patterns and HRCT findings of patients from age, sex, disease duration, disease activity, and smoking duration matched groups of CD and UC. Any possible relation between PFT and HRCT findings and disease activity was also investigated.

Patients and methods

Patients

Patients attending the IBD outpatient clinic were consecutively asked to participate. Informed consent was obtained from all participants.

Disease Activity

Crohn's disease activity was assessed by the Crohn's disease activity index (CDAI) (17). The index was based on an assessment of general well-being and the number of liquid stools per day, and an evaluation of the presence or absence of abdominal pain, an abdominal mass or extraintestinal complications of CD, as well as measurement of haematocrit, weight, and any antidiarrhoeal use. Clinical remission was indicated by an index score of less than 150. For each UC patient, endoscopic findings such as oedema, hyperaemia, erosion, ulceration, fragility, submucosal vessel distortion, granularity, mucus or blood within the lumen, and spontaneous bleeding were recorded and scored on a scale from 1 to 12. A score of 4 points and less was regarded as remission, whereas

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5 points and more indicated active disease (Rachmilewitz endoscopic activity index).

Pulmonary involvement

A questionnaire was used to collect data on respiratory symptoms. Once identified, patients with IBD underwent a series of examinations at the chest clinic by an experienced pneumologist (FB) regardless of the presence of respiratory symptoms. Patients were investigated for exposure to aero-contaminants or aero-allergens, toxic agents, and drugs (especially angiotensin converting enzyme inhibitor and nonsteroidal anti-inflammatory drugs), which could have accounted for the clinical picture, and those who had been exposed were excluded. Patients with a previous history of asthma, symptomatic gastro-oesophageal reflux, chronic bronchitis, emphysema, diffuse interstitial fibrosis, or tuberculosis were also excluded. Another reason for exclusion from the study was failure to perform the lung function tests. Smoking status was also recorded, but most of our patients were non-smokers. Symptoms (cough, sputum, and breathlessness) were evaluated as asymptomatic, intermittent or persistent.

Pulmonary function tests

Pulmonary function tests, including vital capacity (VC) and forced expiratory volume in 1 s (FEV1), were carried out according to the American Thoracic Society (ATS) criteria using a water seal spirometer (SensorMedics 2400, CA, USA). Spirometry was used to determine forced expiratory volume in 1 s (FEV1), the forced vital capacity (FVC), and the Tiffeneau value (FEV1/FVC). Results were expressed as the percentage of the normal value for gender, age, and height (percent predicted). Spirometric parameters were regarded as abnormal when FEV1 and FVC values were less then 70% of those predicted and if FEV1/FVC was less than 70% of that predicted. The reduction in both FEV1 and FVC without an alteration in the Tiffeneau value suggests a restrictive pattern of lung function impairment. An obstructive pattern was indicated if FEV1/FVC was less than 70% of that predicted.

High Resolution Computed Tomography

All patients with IBD underwent both inspiratory and expiratory HRCT within 1 week of the PFT study. All CT scans were obtained with a Somatom Plus scanner (Siemens, Germany). Images were acquired during inspiration and expiration from lung apices to basis with 2 mm collimation, and 10-mm intervals. All lung images were reconstructed algorithmically. Window levels appropriate for the assessment of bronchi and parenchyma (Window level :-500 HU ; Window width : 1500 HU) were used. CT scans were evaluated by one of the authors (KA) independently, who was blinded to the results of pulmonary function tests and clinical data. The individual features evaluated included the following : (a) bronchial wall thickening, (b) reticular opacity, (c) bronchiectasis, (d) interstitial fibrosis, (e) emphysema, and a combination of these findings. Emphysema was defined as the presence of localised areas of decreased attenuation with permeative destruction of the lung parenchyma and associated distortion of pulmonary vascularity.

Statistics

Statistical analysis was performed by analysis of variance. Data were tested for normal distribution (Levene's test for equality of variance). Fisher's exact probability test or Pearson's test was used for chi-square analysis ; a *P*-value less than 0.05 was considered significant.

Results

Fifty-two patients (26 male and 26 female) with IBD were enrolled in this prospective study. Of these, 20 had CD and 32 had UC. The two groups (CD and UC) were similar in terms of age, sex, disease duration, disease activity, smoking duration, and respiratory symptoms (Table 1). The mean age of IBD patients was 42.79 ± 14.05 yr (range 19-82 yr). The mean duration of disease in IBD patients was 7.2 ± 6.5 yr (range 0.1-35.0). Six patients with CD had isolated small bowel disease, 4 patients had large bowel disease only, and ten had evidence of both small and large bowel disease. Six patients with UC had total colitis, 8 had extensive colitis up to the hepatic flexure, 9 had left sided colitis up to the splenic flexure, and 4 had disease affecting only the rectum. Inactive disease was present in 34 patients (13 with CD), and active disease in 18 patients (7 with CD). No extraintestinal manifestation was noted in patients except for in two with CD and in one with UC having arthralgia. Four patients with CD but none with UC had a complication of bowel disease, namely an abscess or fistula. One patient with CD and one with UC were ex-smokers. The patients with CD did not differ from those with ulcerative colitis with regard to either anamnestic data or clinical findings concerning the IBD except for the complication of bowel disease. There was no difference in terms of gender, age, IBD activity or IBD duration between CD and UC patients. None of the patients reported having had a previous respiratory illness. Fourteen of the 52 (26.9%) IBD patients were smokers at the time of the study. Forty were receiving aminosalicylates (between 2 and 4 g/day) for at least 5 days, and 4 patients were on corticosteroids. None of the patients had ever received methotrexate. Some patients had taken more than one drug. Forty patients were asymptomatic for pulmonary disease. The physical examination was normal in all patients. The chest X-ray examination was normal in 50 patients. Two patients had visible reticular opacities in their chest X-rays. The pulmonary function tests were abnormal in 6 patients. Four of them had

Table 1. — **Features of patients and findings of PFT and HRCT**

	Total	*Crohn's Disease*	*Ulcerative colitis*	*P significance*
Age	42.79 ± 14.05	43.70 ± 10.18	42.22 ± 16.13	ns
Male/Female	26/26	9/11	17/15	ns
Disease duration (yr)	7.20 ± 6.53	7.86 ± 7.70	6.78 ± 5.77	ns
Active/inactive bowel disease	18/34	7/13	11/21	ns
Smoker/Non-smoker	14/38	7/14	7/24	
Smoking duration (yr)	19.64 ± 8.99	18.61 ± 7.92	19.96 ± 9.42	ns
Medication				0.04
Mesalamine/Sulfasalasine	40	12	28	
Corticosteroid	1	1	0	
Azathiopyrine	3	2	1	
Mesalamine + corticosteroid	3	1	2	
Mesalamine + azathiopyrine	5	4	1	
Chest symptom				ns
None	40	17	23	
Intermittent	10	3	7	
Persistent	2	0	2	
FEV1 (litres)	97.02 ± 11.38	92.05 ± 10.98	100.28 ± 10.60	ns
FVC (litres)	93.90 ± 11.29	90 ± 12.38	96.41 ± 9.95	ns
FEV1/FVC	112.68 ± 13.69	108.79 ± 11.17	115.32 ± 14.77	ns
HRCT findings				ns
Normal	24	8	16	
Peribronchial thickening	2	1	1	
Reticular opacity	4	1	3	
Bronchiectasis	5	2	3	
Interstitial fibrosis	6	3	3	
Emphysema + reticular opacity	2	2	0	
Interstitial fibrosis + Reticular opacity	7	2	5	
Peribronchial thickening + Bronchiectasis	1	0	1	
Peribronchial thickening + Bronchiectasis + Emphysema	1	1	0	
Pulmonary function tests pattern				ns
Normal	46	16	30	
Obstructive	0	0	0	
Restrictive	4	2	2	
Mixed pattern	2	2	0	

restrictive, and two of them mixed ventilatory defects. High resolution CT was abnormal in 28 (53.8%) patients. The ground glass appearance observed in the dependent (lower) areas of both lungs in 6 out of 15 patients was interpreted as interstitial fibrosis. No correlation was found between HRCT abnormalities, disease activity and pulmonary function tests between the groups of patients with CD and UC ($P > 0.05$). The overall results are shown in Tables 1-4. Four of the 20 CD patients (20%) and 2 of the 32 UC patients (6.25%) showed pathological pulmonary function tests. In the CD group, lung function tests seemed to be lower than those in the UC group, but the difference was not statistically significant. This could be shown for FEV1 92.05 ± 10.98 litres in CD and 100.28 ± 10.60 litres in UC ($p > 0.05$). Moreover, according to the analysis of variance, disease activity had no influence on pulmonary function. Regarding the two groups, IBD patients with active disease (CDAI $\geq$ 150, Rachmilewitz index $\geq$ 4) and patients in remission (CDAI < 150, Rachmilewitz index < 4), chi-square analysis was performed to evaluate the influence of disease activity on lung function. There was no significant difference between patients with active disease and those in remission. There were no significant differences between the two groups regarding the Tiffeneau value. The diagnosis of IBD-associated pulmonary disease was based on the development of persistent and otherwise unexplained bronchopulmonary symptoms.

Discussion

Respiratory involvement in patients with IBD should clearly be separated from interstitial lung disease due to sulfasalazine or mesalamine, although the distinction may be difficult in some cases. In several cases, the exact diagnosis and the relation between the bronchopulmonary disease and IBD had not been established for many years, thus delaying effective treatment with steroids. Patterns of involvement included :

1) Airway inflammation, in the form of subglottic stenosis, chronic bronchitis, severe chronic bronchial

Table 2. — **Relation between bowel disease activity, pulmonary function tests and HRCT findings**

	Active bowel disease	*Bowel disease in remission*	*p*
PFT normal PFT abnormal	16 2	30 4	ns
HRCT normal HRCT abnormal	10 8	14 20	ns

Table 3. — **Relation between HRCT and pulmonary function tests**

	HRCT normal	*HRCT abnormal*	*p*
PFT normal PFT abnormal	22 2	24 4	ns

Table 4. — **Independent samples test if equal variances assumed**

	HRCT normal	*HRCT abnormal*	*P*	*F*	*Significance*
Disease duration	6.01 ± 4.82	8.21 ± 7.64	0.229	0.631	ns
FEV1 (litres)	97.92 ± 8.04	96.27 ± 13.72	0.624	4.187	ns
FVC (litres)	94.55 ± 8.71	93.35 ± 13.25	0.709	2.503	ns
FEV1/FVC	111.86 ± 14.3	113.40 ± 13.38	0.705	0.004	ns

suppuration, bronchiectasia, and chronic bronchiolitis. In patients with large airway involvement, endoscopy showed exuberant inflammatory tissue in the airways and narrowing of the tracheal and/or bronchial lumen. Histologically, airways may be heavily infiltrated by a dense aggregate of inflammatory cells, and there may be mucosal ulcerations.

2) Varied patterns of interstitial lung disease, mainly bronchiolitis obliterans with organising pneumonia, and pulmonary infiltrates and eosinophilia.
3) Miscellaneous other forms of involvement including striking neutrophilic necrotic parenchymal nodules (corresponding histologically to sterile aggregates of neutrophils), and serositis. Steroids seem to be very effective in the majority of cases. Patients with IBD can develop several inflammatory complications in the lung, and a sizable fraction of these complications are steroid sensitive (9-15).

Circulating cytokines (tumour necrosis factor, interleukin-6) may be responsible for pulmonary and other systemic manifestations of IBD. On the other hand, lymphocytes sensitised from the GI tract may induce inflammation of the mucosal surfaces of other organs. It is important to recognise that extensions of the inflammatory process are not restricted to the development of organ-based events but may be responsible for some of the most frequent systemic abnormalities detected in IBD patients (10-14). Despite the tremendous developments concerning the pathophysiological mechanism of IBD, the association between inflammatory bowel disease and pulmonary involvement has not been well defined since respiratory involvement in patients with IBD was first reported in 1976 (1,3) (Table 5). Some authors stated that subclinical pulmonary dysfunction was more frequent in IBD, dependent on disease activity, but persists even during remission. However, others found no influence of disease activity (18-25).

We investigated features of PFT and HRCT in IBD patients. It may be difficult to distinguish between disease-related pulmonary dysfunction and the influence of general well-being on these tests because patients with severe disease activity may perform worse because of general sickness and fatigue. We obtained abnormal results in pulmonary function tests (obstructive, restrictive or mixed) in 6.25% of patients with UC and in 20% of patients with CD. At first sight the incidence of disorders seems to be lower in UC than in CD, but we did not identify any difference in the PFT pattern between the diseases as described by Sommers *et al.*, who found a predominance of obstructive disorders in UC and of restrictive defects in CD (11). However, the small sample size may have precluded the detection of any subtle difference. We also did not observe any difference in symptoms, FEV1, FVC, FEV1/FVC ratio (Tiffeneau value), or HRCT findings between the two disease entities.

The influence of disease activity on pulmonary function tests in IBD patients is still a subject of debate. PFTs of patients with active disease were not significantly different from those of patients in remission. Kuzela *et al.* stated there was no apparent correlation between PFT abnormalities and bowel disease activity (21). Accordingly, in the present study, the lung function tests showed no significant difference between patients with active disease and those in remission. In a recent study, PFT abnormality was reported as 8/51 (15.7%), 7 of whom had a restrictive pattern. In our

Table 5. — **Major comments from previous studies**

Author	*Comment*
Kuzela *et al.* 1999	No apparent correlation between pulmonary function tests abnormalities and either bowel disease activity or drug administration (sulphasalazine, mesalazine)
Tzanakis *et al.* 1998	No difference in routine PFTs between UC and CD patients
Spira *et al.* 1999	Large airway disease (bronchiectasis and bronchitis) diagnosis in all of 7 patients, in the absence of factors, other than IBD, that could account for pulmonary disease
Tzanakis *et al.* 1998	Function of the small airways of the lungs are affected in patients with IBD
Godet *et al.* 1997	Smoking status was not predictive of these abnormalities
Munck *et al.* 1995	Latent pulmonary involvement is also present in a paediatric population with active Crohn's disease, despite a short disease history and absence of smoking

study, 11.5% (6/52) of patients had an abnormal PFT pattern. Interestingly, four of them were restrictive while the other two had mixed function abnormality.

Twelve patients had mild respiratory symptoms. Half of them had restrictive or mixed PFT abnormality. Four of the patients had intermittent mild symptoms and two had persistent mild complaints. The remaining six patients with symptoms had normal ventilation function. Because the pulmonary symptoms were mild, these patients were advised to give up smoking and to be available for close follow-up.

Although previous studies showed the most frequent HRCT finding to be air trapping, bronchiolitis and bronchiectasis, the most frequent HRCT finding in our study was interstitial fibrosis and the combined form of interstitial fibrosis and reticular opacity (24-29). We may speculate that our results of "interstitial fibrosis and restrictive type PFT" showed good concordance. However, the relation between HRCT and PFT was not significant, and hence we think that is not appropriate to say that there was an apparent harmony.

The time interval between the onset of CD and pulmonary involvement was reported to be approximately 8.3 years (4,6). Although our study group had bowel disease duration close to that value, the majority of patients had normal ventilation function. However, we recommend a sufficiently long follow-up to allow clinically relevant abnormalities to become apparent.

Most of our patients had used sulfasalasine or mesalamine. Although we may suggest that fibrosis was caused by these drugs, it might also have had an immunologic basis because it is seen in rheumatoid arthritis or ankylosing spondilitis (13,24-27). However, it was interesting that there was no effect of disease duration on HRCT abnormality. The issue arising from that point is whether pulmonary involvement is a sequela independent of disease duration.

This was an observational study on pulmonary function tests and CT abnormalities in a series of IBD patients. We conclude that disease type, duration and activity were not predictive of pulmonary function or HRCT features in patients with IBD. Accordingly, although no significant differences were observed between CD and UC patients, or between active and inactive patients, we think that the most interesting characteristic is the extremely high prevalence of pulmonary abnormalities in a population of asymptomatic IBD patients. How aggressive routine surveillance for pulmonary abnormalities in IBD patients should be is another question remaining to be answered. Pathophysiological mechanisms and clinical relevance are to be further clarified and new epidemiological studies should be performed.

References

1. GREENSTEIN A.J., JANOWITZ H.D., SACHAR D.B. The extraintestinal complications of Crohn's disease and ulcerative colitis : a study of 700 patients. *Medicine*, 1976, **55** : 401-412.
2. MONSEN U., SOSTAD J., HELLERS G., JOHANSSON C. Extracolonic diagnoses in ulcerative colitis : an epidemiological study. *Am. J. Gastroenterol.*, 1990, **85** : 711-6.
3. KRAFT S.C., EARLE R.H., ROESLER M., ESTERLY J.R. Unexplained bronchopulmonary disease with inflammatory bowel disease. *Arch. Intern. Med.*, 1976, **136** (4) : 454-9.
4. HOFFMANN R.M., KRUIS W. Rare extraintestinal manifestations of inflammatory bowel disease. *Inflamm. Bowel Dis.*, 2004, **10** (2) : 140-7.
5. OMORI H., ASAHI H., INOUE Y., IRINODA T, SAITO K. Pulmonary involvement in Crohn's disease report of a case and review of the literature. *Inflamm. Bowel Dis.*, 2004, **10** (2) : 129-34.
6. SETHY P.K., DUTTA U., AGGRAWAL A.N., DAS R., GULATI M., SINHA S.K., SINGH K. Pulmonary and hematological alterations in idiopathic ulcerative colitis. *Indian J. Gastroenterol.*, 2003, **22** (5) :176-9.
7. MAHADEVA R., WALSH G., FLOWER C.D., SHNEERSON J.M. Clinical and radiological characteristics of lung disease in inflammatory bowel disease. *Eur. Respir. J.*, 2000, **15** (1) : 41-8.
8. TZANAKIS N., BOUROS D., SAMIOU M., PANAGOU P., MOUZAS J., MANOUSOS O., SIAFAKAS N. Lung function in patients with inflammatory bowel disease. *Respir. Med.*, 1998, **92** (3) : 516-22.
9. CAMUS P., PIARD F., ASHCROFT T., GAL A.A., COLBY T.V. The lung in inflammatory bowel disease. *Medicine (Baltimore)*, 1993, **72** (3) : 151-83.
10. DOUGLAS J.G., MC DONALD C.F., LESLIE M.J., GILLON J., CROMPTON G.K., MC HARDY G.J. Respiratory impairment in inflammatory bowel disease : does it vary with disease activity ? *Respir. Med.*, 1989, **83** (5) : 389-94.
11. SOMMER H., SCHMIDT M., GRUBER K.D. Pulmonary functional disorders in ulcerative colitis and Crohn's disease. *Dtsch. Med. Wochenschr.*, 1986, **111** (21) : 812-5.
12. BONNIERE P., WALLAERT B., CORTOT A., MARCHANDISE X., RIOU Y., TONNEL A.B., COLOMBEL J.F., VOISIN C., PARIS J.C. Latent pulmonary involvement in Crohn's disease : biological, functional, bronchoalveolar lavage and scintigraphic studies. *Gut*, 1986, **27** (8) : 919-25.
13. FOSTER R.A., ZANDER D.S., MERGO P.J., VALENTINE J.F. Mesalamine-related lung disease : clinical, radiographic, and pathologic manifestations. *Inflamm. Bowel Dis.*, 2003, **9 (**5) : 308-15.
14. LEVINE J.B., LUKAWSKI-TRUBISH D. Extraintestinal considerations in inflammatory bowel disease. *Gastroenterol. Clin. North Am.*, 1995, **24** (3) : 633-46.

15. STAS P., DHOORE A., VAN ASSCHE G., GEBOES K., STEENKISTE E., PENNINCKX F., RUTGEERTS P., VERMEIRE S. Miliary tuberculosis following infliximab therapy for Crohn disease : A case report and review of the literature. *Acta gastroenterol. Belg.*, 2006, **2** : 217-220.
16. STERN E.J., SWENSEN S.J., HARTMEN T.E., FRANK M.S. CT mosaic pattern of lung attenuation : distinguishing different causes. *AJR*, 1995, **165** : 813-816.
17. ARAKAWA H., WEBB W.R., MC COWIN M. *et al*. Inhomogenous lung attenuation at thin section CT : diagnostic value of expiratory scans. *Radiology*, 1998, **206** : 89-94.
18. BEST W.R., BECKTEL J.M., SINGLETON J.W. *et al.* Development of a Crohn's disease activity index. National Cooperative Crohn's disease Study. *Gastroenterology*, 1976, **70** : 439-444.
19. KARADAG F., OZHAN M.H., AKCICEK E., GUNEL O., ALPER H., VERAL A. Is it possible to detect ulcerative colitis-related respiratory syndrome early ? *Respirology*, 2001, **6** (4) : 341-6.
20. MARVISI M., BORRELLO P.D., BRIANTI M., FORNARSARI G., MARANI G., GUARIGLIA A. Changes in the carbon monoxide diffusing capacity of the lung in ulcerative colitis. *Eur. Respir. J.*, 2000, **16 (**5) : 965-8.
21. KUZELA L., VAVRECKA A., PRIKAZSKA M., DRUGDA B., HRONEC J., SENKOVA A., DRUGDOVA M., OLTMAN M., NOVOTNA T., BREZINA M., KRATKY A., KRISTUFEK P. Pulmonary complications in patients with inflammatory bowel disease. *Hepatogastroenterology*, 1999, **46** (27) : 1714-9.
22. SPIRA A., GROSSMAN R., BALTER M. Large airway disease associated with inflammatory bowel disease. *Chest*, 1998, **113 (**6) : 1723-6.
23. TZANAKIS N., SAMIOU M., BOUROS D., MOUZAS J., KOUROUMALIS E., SIAFAKAS N.M. Small airways function in patients with inflammatory bowel disease. *Am. J. Respir. Crit. Care Med.*, 1998, **157 (**2) : 382-6.
24. GODET P.G., COWIE R., WOODMAN R.C., SUTHERLAND L.R. Pulmonary function abnormalities in patients with ulcerative colitis. *Am. J. Gastroenterol*., 1997, **92** (7) : 1154-6.
25. MUNCK A., MURCIANO D., PARIENTE R., CEZARD J.P., NAVARRO J. Latent pulmonary function abnormalities in children with Crohn's disease *Eur. Respir. J.*, 1995, **8** (3) : 377-80.
26. NEILLY J.B., MAIN A.N., MC SHARRY C., MURRAY J., RUSSELL RI., MORAN F. Pulmonary abnormalities in Crohn's disease. *Respir. Med*., 1989, **83 (**6) : 487-91.
27. WILCOX P., MILLER R., MILLER G., HEATH J., NELEMS B., MULLER N., OSTROW D. Airway involvement in ulcerative colitis. *Chest*, 1987, **92** (1) : 18-22.
28. SONGUR N., SONGUR Y., TUZUN M., DOGAN I., TUZUN D., ENSARI A., HEKIMOGLU B. Pulmonary function tests and high-resolution CT in the detection of pulmonary involvement in inflammatory bowel disease. *J. Clin. Gastroenterol.*, 2003, **37** (4) : 292-8.
29. GARG K., LYNCH D.A., NEWELL J.D. Inflammatory airways disease in ulcerative colitis : CT and high-resolution CT features. *J. Thorac. Imaging*, 1993, **8** (2) : 159-63.