



Inflammatory bowel disease and airway diseases

Maria Vutcovici, Paul Brassard, Alain Bitton

Maria Vutcovici, Alain Bitton, Division of Gastroenterology, McGill University Health Centre, Montreal General Hospital, Montreal, Québec H3G 1A4, Canada

Paul Brassard, Division of Clinical Epidemiology, McGill University Health Centre, Montreal, Québec H3A 1A1, Canada

Paul Brassard, Alain Bitton, Department of Medicine, McGill University, Montreal, Québec H3G 1Y6, Canada

Author contributions: Vutcovici M, Brassard P and Bitton A contributed equally to the conception and design of the manuscript; Vutcovici M conducted the literature review and drafted the manuscript; Bitton A and Brassard P contributed to the critical revision and editing; all authors approved the final version.

Supported by Financial support for this study was provided through internal funding from the McGill University Health Centre.

Conflict-of-interest statement: None of the authors has any conflict of interest to declare.

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Manuscript source: Invited manuscript

Correspondence to: Maria Vutcovici, MD, MSc, Division of Gastroenterology, McGill University Health Centre, Montreal General Hospital, 1650 Cedar Avenue D16-125, Montreal, Québec H3G 1A4, Canada. maria.vutcovici@mail.mcgill.ca
Telephone: +514-340-8222-3678
Fax: +514-843-2891

Received: March 24, 2016

Peer-review started: March 25, 2016

First decision: May 12, 2016

Revised: June 14, 2016

Accepted: July 6, 2016

Article in press: July 6, 2016

Published online: September 14, 2016

Abstract

Airway diseases are the most commonly described lung manifestations of inflammatory bowel disease (IBD). However, the similarities in disease pathogenesis and the sharing of important environmental risk factors and genetic susceptibility suggest that there is a complex interplay between IBD and airway diseases. Recent evidence of IBD occurrence among patients with airway diseases and the higher than estimated prevalence of subclinical airway injuries among IBD patients support the hypothesis of a two-way association. Future research efforts should be directed toward further exploration of this association, as airway diseases are highly prevalent conditions with a substantial public health impact.

Key words: Inflammatory bowel disease; Ulcerative colitis; Asthma; Chronic obstructive pulmonary disease; Crohn's disease

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Core tip: Recent evidence of inflammatory bowel disease (IBD) occurrence among patients with airway diseases and the higher than estimated prevalence of subclinical airway injuries among IBD patients support the hypothesis of a two-way association between these conditions. Future research efforts should be directed toward further exploration of this association, as airway diseases are highly prevalent conditions with a substantial public health impact.

Vutcovici M, Brassard P, Bitton A. Inflammatory bowel disease and airway diseases. *World J Gastroenterol* 2016; 22(34): 7735-7741
Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/>

INTRODUCTION

An association between inflammatory bowel disease (IBD) and airway diseases has long been described in the literature. The majority of studies have addressed the topic from the perspective of airway diseases as an extraintestinal manifestation of IBD^[1-7]. However, there is growing evidence regarding an increased risk of IBD occurrence among patients with airway diseases such as asthma^[8-11], chronic obstructive pulmonary disease (COPD)^[12,13] and bronchiectasis^[13]. There are several similarities between these conditions, ranging from the multifactorial complex etiology to the chronic remitting-relapsing disease course and the presence of low-grade systemic inflammation. It is, therefore, likely that the complex relationship between IBD and airway diseases is not merely unidirectional, and the new evidence from population-based studies supports this hypothesis.

In this paper we review the similarities between airway diseases and IBD and address the epidemiological evidence for the association, focusing on IBD occurrence in patients with airway diseases.

SIMILARITIES IN PATHOGENESIS AND RISK FACTORS

Genetic factors

Genome-wide association studies have shown an overlap of regions of genetic linkage for asthma, IBD, and other autoimmune disorders^[14]. Several gene loci, such as DENND1B, SMAD3 and SLC22A4/5 (5q31/IBD5), were found to be associated with both asthma and Crohn's disease (CD), while the ORMDL3 gene variants present in CD and ulcerative colitis (UC) were also found in childhood-onset asthma^[15]. The association between NOD2 gene polymorphism and the development of both CD^[16] and COPD^[17] supports the hypothesis of a shared genetic susceptibility. NOD2 proteins recognize peptidoglycan components of the bacterial wall, contributing thus to bacterial recognition and the activation of immune defense pathways^[17].

Embryologic origin, anatomical structure and function

The epithelia of the intestine and airways derive from the same embryological structure, the foregut region of the endoderm^[18]. Their anatomical structure is, therefore, very similar, with a columnar type epithelium, goblet cells and mucous glands^[4,19,20]. The lymphoid tissue in the submucosal layer is composed of antigen-presenting cells and lymphocytes capable of releasing pro-inflammatory cytokines^[21], and plays an important role in both innate and adaptive immune defense as part of the barrier organ function of the

respiratory and gastrointestinal tracts^[4].

Pathogenesis

Several similarities in the underlying pathological mechanisms have been described and may explain the association between IBD and airway diseases^[1,2,22-24]. Dysbiosis and an inappropriate immune response to intestinal microbiota are considered key components of the pathophysiological process in IBD^[25]. Similarly, an immune response to lung microbiota seems to occur in airway diseases such as bronchiectasis^[26]. A dysregulation of protease activity is present in both IBD^[27] and COPD^[28], and is associated with the breakdown of connective tissue components and the ensuing remodeling process^[1,29]. Alterations in immune cell homing function^[1,22] may explain the low grade chronic systemic inflammation that is present in IBD^[30], COPD^[31], asthma^[32-34] and bronchiectasis^[35-38]. The hygiene hypothesis, proposing that a lack of exposure to microorganisms during childhood contributes to abnormal immune reactions later in life, may also constitute a common factor linking asthma, IBD and a variety of other conditions^[39].

Environmental factors

Tobacco smoking is an important risk factor associated with the development of both airway diseases^[40,41] and CD^[42]. In asthmatic patients, smoking is associated with a decline in lung function^[43] and increased morbidity rates^[41,44]. A relative resistance to corticosteroid therapy was reported in smoking asthmatic and COPD patients^[41], and the hospitalizations and mortality rates were higher than in non-smoking asthma and COPD controls^[40,45]. Smoking has been associated with a poor response to treatment and a more severe disease course in CD patients^[42,46,47]. In contrast, ulcerative colitis seems to be a disease of non-smokers or former smokers^[48], and a more benign disease course was observed in UC smokers compared to non-smokers^[49]. This suggests that the association between UC and airway diseases goes beyond the confounding effect of smoking. Several potential underlying mechanisms that may explain the effect of cigarette smoke in IBD have been advanced, including alterations in cellular and humoral immunity, alterations in mucosal blood flow, gut permeability and motility, as well as a pro-thrombotic and a reduced anti-oxidant effect^[42], but the relationship with the dichotomous impact on CD and UC is still unclear.

Air pollution is another environmental risk factor associated with both airway diseases and IBD. Air pollutants such as particulate matter, ozone or nitrous oxides were associated with an increase in number of hospitalizations for asthma^[50], COPD^[51-53] and IBD^[54], and with an increased risk of mortality in COPD patients^[55]. The gastrointestinal tract is exposed to air pollutants through contaminated food and water^[56]. There appears to be a dose-response association

between long term exposure to air pollutants, such as nitrous oxides and particulate matter, and the risk of early onset CD^[57]. Exposure to sulfur oxides was associated with an increased risk of early onset UC, but no dose-response effect could be demonstrated^[57]. Gastrointestinal injury may be the result of alterations in gut microbiota induced by exposure to air pollutants, as demonstrated in animal models^[58], of an increased intestinal permeability, or of a pro-inflammatory effect^[56].

Vitamin D is an environmental factor with a pleiotropic role in immune regulation^[59], from inhibiting cytokine production to enhancing innate immunity by facilitating the transcription of peptides with antimicrobial effects^[60]. Low serum levels of Vitamin D in asthmatic patients were associated with impairments in lung function, a poor response to corticosteroid therapy and an increased airway hyper-reactivity^[61]. In children with mild to moderate asthma, vitamin D deficiency is relatively common and associated with an increased risk of severe exacerbations^[62]. Vitamin D deficiency in IBD patients may be a consequence of malabsorption, low dietary intake or reduced bioavailability^[63], but the suboptimal serum levels observed in newly diagnosed patients^[64] suggest that the deficiency may also be associated with IBD development^[59,63]. A randomized control trial of Vitamin D supplementation in CD patients showed a reduced number of relapses compared to the placebo group^[65]. Further studies are needed to confirm this effect.

AIRWAY DISEASE IN IBD

Airway diseases were first described in IBD patients four decades ago in the case series of Kraft *et al.*^[66]. There is an extensive literature documenting airway diseases as an extraintestinal manifestation of IBD. Approximately 6%-47% of patients develop at least one extraintestinal manifestation^[67-69] during the course of IBD, but the true prevalence of lung involvement is unknown due to the presence of subclinical pulmonary injury. It is estimated that 40%-60% of IBD patients have some degree of subclinical lung involvement evidenced through alterations in pulmonary function tests and high resolution tomographic imaging (HRCT)^[70-73].

The most frequently observed alterations in pulmonary function tests are decreases in forced expiratory volume in 1 s (FEV₁)^[72,73] and FEV₁/forced vital capacity (FVC) ratio, in forced expiratory flow 25%-75%^[72,73] as well as in the transfer coefficient for carbon monoxide (DLCO)^[73]. The severity of the observed alterations in pulmonary function tests was found to be in correlation with the endoscopic and clinical activity in UC patients^[73,74] and independent of the effect of smoking^[73].

HRCT imaging techniques allow the detection of lung involvement in IBD patients without overt respiratory symptoms. The most common findings are an enlarged bronchial internal diameter, peribronchial wall thickening, air trapping or the identification of

airways in the extreme lung periphery^[6,75]. The imaging appearance of small airway involvement in UC patients, with the "tree in bud" aspect and cellular bronchiolitis, was described as indistinguishable from the imaging findings in patients with rheumatoid arthritis or in transplant recipients, indicating thus an immunological mechanism of small airway injury^[75].

In IBD patients with respiratory symptoms, airway diseases are the most commonly reported respiratory condition^[4,11,73,76]. Bronchiectasis was found to occur in 22% of symptomatic cases^[4,5], followed by chronic bronchitis in 20% of cases^[5] and suppurative airway disease without bronchiectasis^[4]. Furthermore, evidence from population-based epidemiologic studies indicates an association with asthma, bronchitis and COPD. A large matched-cohort study involving more than 8000 IBD patients found asthma to be the second most common comorbidity after arthritis in both CD and UC^[11]. The prevalence of bronchitis was also significantly increased in IBD patients compared to healthy controls^[11]. Studies of survival and cause of death reported a significant increase in mortality due to COPD among IBD patients^[77,78].

Lung involvement in IBD can also result from the effect of IBD-specific medications. The most commonly reported associations were with interstitial lung diseases, such as interstitial pneumonitis (for Mesalamine, thiopurines and biologics) or diffuse interstitial lung disease (for Methotrexate)^[3], or with diseases affecting the lung parenchyma, such as eosinophilic pneumonia (for Mesalamine and biologics)^[79,80], but not with airway diseases.

IBD OCCURRENCE IN AIRWAY DISEASES

Despite the substantial evidence of an IBD-airway disease association and of the complex interplay between the two groups of conditions, an interest toward the possibility of IBD occurrence in patients with pre-existing airway diseases has only recently emerged. In the last decade, a handful of population-based studies have addressed the risk of developing IBD, its incidence or prevalence in patients with asthma, bronchitis, bronchiectasis and COPD (Table 1).

Four studies have reported an increased prevalence of IBD in patients with airway diseases. In the study of Bernstein *et al.*^[11], the prevalence of CD and UC among patients with asthma and bronchitis was significantly increased compared to the prevalence in the general population of Manitoba, Canada. A four-fold increase in IBD prevalence was observed in a cohort of patients with airway diseases in the United Kingdom. The prevalence of UC was significantly increased in all types of airway disease investigated; CD prevalence was increased in patients with COPD and bronchiectasis^[13]. A study of COPD patients and their first degree relatives identified from the Swedish Multigeneration Register showed an increased prevalence of both CD and UC among the patients

Table 1 Population-based studies of inflammatory bowel disease occurrence in patients with airway diseases

Ref.	Country	Airway disease	Cohort size	Results		
				Crohn's disease	Ulcerative colitis	IBD
Bernstein <i>et al</i> ^[11]	Canada	Asthma	12397	PRR = 1.38 (95%CI: 1.23-1.53)	PRR = 1.56 (95%CI: 1.4-1.74)	
		Bronchitis	3092	PRR = 1.72 (95%CI: 1.15-2.58)	PRR = 1.92 (95%CI: 1.35-2.73)	
Ekbom <i>et al</i> ^[12]	Sweden	COPD	180239	HR = 2.72 (95%CI: 2.33-3.18)	HR = 1.83 (95%CI: 1.61-2.09)	
Raj <i>et al</i> ^[13]	United Kingdom	COPD	588	OR = 5.26 (95%CI: 1.71-16.19)	OR = 3.57 (95%CI: 1.3-9.38)	OR = 3.87 (95%CI: 1.19-12.62)
		Bronchiectasis	215	OR = 7.21 (95%CI: 1.62-32.2)	OR = 7.88 (95%CI: 2.71-22.91)	OR = 8.38 (95%CI: 2.43-28.89)
		Asthma	893	OR = 1.74 (95%CI: 0.39-7.65)	OR = 2.81 (95%CI: 1.15-6.90)	OR = 2.54 (95%CI: 0.78-8.26)
		Airway disease, total	2192	OR = 5.96 (95%CI: 1.94-18.31)	OR = 4.21 (95%CI: 1.71-10.41)	OR = 4.26 (95%CI: 1.48-11.71)
Virta <i>et al</i> ^[9]		Finland	Asthma	185	OR = 2.33 (95%CI: 1.41-3.86)	OR = 1.11 (95%CI: 0.68-1.80)
Hemminki <i>et al</i> ^[8]	Sweden	Asthma	148295	SIR = 1.64 (95%CI: 1.42-1.87)	SIR = 1.54 (95%CI: 1.36-1.73)	
Brassard <i>et al</i> ^[10]	Canada	COPD	143904	IRR = 1.55 (95%CI: 1.49-1.62)	IRR = 1.30 (95%CI: 1.24-1.37)	
		Asthma	136178	IRR = 1.27 (95%CI: 1.22-1.31)	IRR = 0.99 (95%CI: 0.94-1.04)	

IBD: Inflammatory bowel disease; PRR: Prevalence rate ratio; COPD: Chronic obstructive pulmonary disease; SIR: Standardized incidence ratio; IRR: Incidence rate ratio; CI: Confidence interval; HR: Hazard ratio; OR: Odds ratio.

and their siblings compared to IBD prevalence in controls^[12]. Younger age at COPD diagnosis was found to be associated with a higher prevalence of UC. A case-control study of Finnish children with IBD showed that the risk of developing CD was significantly higher in children with asthma and with both asthma and cow milk allergy than in healthy controls^[9].

Unfortunately, prevalence studies are informative only from the point of view of disease coexistence, and cannot provide an insight into the temporal sequence of developing these conditions. Two population-based studies assessed IBD occurrence during the course of airway diseases, one in asthmatic patients only and the other in asthma and COPD.

A study of Swedish inpatients discharged with a diagnosis of asthma showed an increased incidence of CD and UC hospitalizations during the follow up period^[8]. To ensure incident IBD cases were captured, all subjects in which the diagnosis of CD and UC preceded that of asthma were excluded from the analyses. The standardized incidence rates for CD were significantly increased in all age groups, while the incidence increase of UC was only significant in subjects diagnosed with asthma after the age of 20 years.

More recently, a large retrospective cohort study of Québec patients with asthma and COPD showed a significantly increased incidence of both CD and UC in COPD patients and an increased incidence of CD in asthmatic patients compared to the IBD incidence in the general population^[10]. Similar to the results of Hemminki *et al*^[8], in asthmatic patients the incidence of CD was significantly increased in all age groups; the incidence of UC, although not significantly increased when all age groups were considered, was significantly increased in patients diagnosed with asthma after the age of 10 years. In COPD patients, the incidences of both CD and UC were significantly increased compared to the general population for all age groups. A follow

up study of the same COPD cohort revealed that new onset IBD was associated with an increased risk of all-cause mortality as well as from respiratory and digestive causes^[81].

FUTURE DIRECTIONS FOR RESEARCH

The existing evidence of IBD occurrence in patients with airway diseases is supported by population based studies. In clinical settings, the true prevalence of IBD or of digestive symptoms indicative of IBD is still unknown. If clinical studies confirm the association, it would be of importance to assess whether exacerbations in airway diseases are impacted by IBD disease activity.

Inversely, in IBD patients with lung manifestations, further assessment of prevalence of subclinical airway injuries is warranted, as recent evidence suggests it is much higher than previously expected. Such an assessment could shed more light into the temporal sequence of IBD-airway disease development.

CONCLUSION

There is a complex inter-relation between IBD and airway diseases and new evidence suggests that not only can airway diseases occur as an extraintestinal manifestation of IBD, but that IBD, in turn, can have a high occurrence in patients with airway diseases. This occurrence seems to also impact on key outcomes, such as mortality in COPD patients. While the importance of airway involvement as extraintestinal manifestation of IBD is amplified by the evidence of an increased prevalence of subclinical airway injuries, the impact of IBD occurrence in patients with airway diseases raises a substantially greater public health concern due to the worldwide high prevalence of airway diseases. Early detection of IBD may improve the treatment management and prognosis of airway disease patients.

ACKNOWLEDGMENTS

We thank librarian Tara Landry from the Montreal General Hospital branch of MUHC Libraries for assistance with the literature search.

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P- Reviewer: Maharshak N, Soares RLS, Vecchi M **S- Editor:** Ma YJ

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ISSN 1007-9327



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