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Association between Irritable Bowel Syndrome and Allergic Diseases: To Make a Case for Aeroallergen

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Abstract
Irritable bowel syndrome (IBS) is a functional gastrointestinal disease and the most common cause of prolonged abdominal pain and bowel disturbances in the developed world. While initially thought to be functional or psychosomatic in nature, IBS is now recognized as a heterogeneous group of conditions. A subset of IBS patients and patients with allergic diseases share some characteristic inflammatory features. In fact, atopic children show an increased likelihood of developing IBS as adults. Given these findings, a subset of IBS may be suffering from allergy-related gut diseases. In this review, we present the allergy-related comorbidities of IBS, including genetic, environmental, and immunologic factors. We discuss studies demonstrating an increased sensitization of IBS patients to aeroallergens compared to food allergens. We then postulate potential pathophysiological mechanisms underlying both IBS and aeroallergens in the gut, followed by potential implications in the screening and treatment of allergies in IBS patients.

Introduction

Irritable bowel syndrome (IBS) is a multifactorial gastrointestinal disorder affecting 5.2–22% of the population [1]. It is not a single disease, but a name given to a group of gastrointestinal symptoms that commonly present together. IBS is diagnosed according to symptom-based criteria (e.g., Manning criteria to ROME IV criteria). While these criteria have changed over time, the essential feature remains unchanged: recurrent and intermittent abdominal pain or discomfort that is associated with irregular bowel habits [2]. IBS likely represents a diverse group of disorders with a similar presentation but different pathophysiologies, such as post-infectious mucosal inflammation, food intolerance, hypersensitivity, or allergic disease. In fact, there is an increased prevalence of IBS in people with allergic diseases, suggesting a possible link between the two diseases [3, 4].

Allergy or atopy is an immediate hypersensitivity, or type I hypersensitivity reaction, caused by the release of

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mediators from mast cells. This release is often triggered by the binding of an immunoglobulin E (IgE) antibody (specific to an environmental antigen) to mast cells in various tissues. Allergic diseases range in severity, from life-threatening anaphylactic reactions to a certain food or insect bite to recurrent asthma, allergic rhinitis (AR), and atopic dermatitis (AD). The diagnosis of an allergic disease depends on the identification of allergen-related symptoms and the relevant allergen-specific IgE [5].

Mucosal immune activation and inflammation may contribute to the development of IBS. IBS may involve a mast cell-mediated inflammatory reaction [6] that affects epithelial cells. In turn, this would affect the epithelial barrier's permeability, causing inflammation [7]. In 2008, Tobin et al. [8] proposed the term "atopic IBS" to describe a novel subgroup of IBS associated with allergic diseases. They reported that the prevalence of IBS, compared to the general population, was significantly higher in patients with AR (2.67 times) and AD (3.20 times). In this review, we present relevant epidemiological and clinical studies that link IBS and allergic diseases as well as postulate the possible mechanisms linking the two diseases.

Epidemiology

IBS and Asthma

Asthma is a chronic respiratory disease characterized by recurrent airway inflammation, obstruction, and hyperresponsiveness. There are multiple epidemiological studies that show asthma and IBS often co-exist in a single patient (Table 1; Fig. 1). A link between IBS and asthma was first suggested by White et al. [9]. They observed that IBS patients, like asthmatic patients, show increased respiratory hyperresponsiveness – as measured by forced expiratory volumes in 1 s after inhalation of increasing concentrations of methacholine. Similar findings were made by Kennedy et al. [10], who showed that IBS, gastroesophageal reflux symptoms, and bronchial hyper-responsiveness occurred more frequently together than expected (2.5% of the sample having all 3 conditions compared with an expected prevalence of 0.7%). Another large study with 91,237 asthmatic subjects and 24,518 non-asthmatic subjects, found a 20% increase in the likelihood of asthmatic subjects developing IBS following their initial diagnosis with asthma. The development of IBS following a diagnosis of asthma was not associated with the use of oral steroids [11]. Similarly, Roussos et al. [12] observed an increased prevalence of IBS among asthmatic patients compared to subjects with other pulmonary disorders (41.3 vs. 22.3%) and showed again that asthma medications were not associated with the development of IBS. In another study from the United Kingdom that reviewed medical records of 23,471 patients from primary care practices across the country, an increased prevalence of atopy in patients with functional gastrointestinal disorders (FGIDs) was found. The association between FGIDs and atopic conditions remained statistically significant even after controlling for demographic factors and mood disorders [13]. Cohen et al. [14] reviewed the medical records of 314,897 consecutive 17-year-old males, undergoing comprehensive medical evaluation prior to recruitment for military service in Israel. Again, IBS was significantly more prevalent in asthmatics compared to non-asthmatics (1 vs. 0.5%); IBS was also significantly more prevalent in subjects with persistent asthma compared to those with intermittent asthma ($p < 0.001$). There was no difference observed between asthmatic and non-asthmatic and the incidence of inflammatory bowel disease (IBD) or peptic ulcers.

Asthma has also been associated with childhood-onset FGIDs. In an Italian study including 75 children with bronchial asthma and age- and sex-matched controls, asthmatic children showed a significantly greater frequency of gastrointestinal symptoms, particularly diarrhea, vomiting, and abdominal pain [15]. Colman et al. [16] in the United States showed a high prevalence of FGIDs (16.4%) among young patients (4–20 years old) with persistent asthma. Similarly, the BAMSE (Swedish abbreviation for Children, Allergy, Milieu, Stockholm, Epidemiology) study found that asthma and food hypersensitivity in the first 2 years of life were significantly associated with the development of abdominal pain at 12 years of age. BAMSE study also found a direct relationship between a 12-year-old's risk for abdominal pain and the number of allergic conditions they had (i.e., asthma, rhinitis, eczema, and food allergy) [17]. Another study found the prevalence of IBS to be significantly higher among young asthmatics compared to elderly asthmatics and healthy, age-matched controls [18]. Several pathogenic mechanisms may explain the observed relationship between IBS and asthma, including an age-related decrease in the number of neurons in the myenteric plexus, increase in collagen deposition in the distal colon, and age-related perceptual changes [19, 20].

In contrast, several studies have shown no association between allergic diseases and IBS. Two cross-sectional studies found no association between asthma and IBS in teenagers/adolescents [21] and adults [22]. Results from the Dunedin Multidisciplinary Health and Develop-

Table 1. Epidemiological study of IBS and asthma

Author, country	Number		IBS criteria	% IBS		OR (95% CI)	*p* value	Note
				non-asthma	asthma			
Huerta et al. [106], UK	479	Prospective	Doctor diagnosis	2.0	2.5	1.3 (1.1–1.5)		Risk of IBS could be reduced by the use of oral steroids
Roussos et al. [12], Greece	400	Prospective	ROME II	20.8	41.3		0.001	None of the asthma medications were associated with increased or decreased likelihood of IBS
Amra et al. [107], Iran	4,762	Prospective	ROME II	3.3	9.5	1.79 (1.06–3.03)		No relation between IBS and chronic bronchitis
Cole et al. [11], USA	115,775	Retrospective	Doctor diagnosis	6.8	9.7	1.4 (1.3–1.6)		No association with oral steroids
Ekici et al. [18], Turkey	131			16.8	27.5	1.8 (1.0–3.4)	0.04	Young asthmatic but not old asthmatic
Ozol et al. [43], Turkey	220	Prospective	ROME II	12.7	29.6		<0.005	No relation with food allergy
Panicker et al. [108], Kuwait	283	Prospective	ROME II	7.93	39.13		<0.001	Female > male asthmatics; Bloating and diarrhea were the most common IBS symptoms
Yilmaz et al. [109], Turkey	168	Prospective	ROME II	17.9	36.6		0.009	Not associated with psychiatric disorders
Jones et al. [13], USA	23,471	Retrospective	GP codes	11.0	15.0	1.40 (1.29–1.52)	0.0001	
Siddiqui et al. [22], India	140	Prospective	ROME II	20.00	17.14	0.828 (0.320–2.121)	0.664	Negative study
Koloski et al. [62], Australia	3,542	Prospective, postal survey	Modified ROME III	12.1	20.0	1.82 (1.44–2.30)	<0.001	Only IBS-C and IBS-M. A pollen allergy was also significantly associated with IBS including IBS-D and PI-IBS but not IBS-C or IBS-M; There was a substantial moderate significant effect size of 4.68 for pollen allergy in PI IBS; a self-reported animal allergy was significantly associated with IBS, IBS-M, and PI-IBS but not IBS-C or IBS-D
Nybacka et al. [24], Sweden	270	Prospective	ROME III	9	18		0.19	Negative study
Cohen et al. [14], Israel	314,897	Medical record review	Doctor diagnosis	0.5	1	1.2 (1.14–1.32)	0.001	All 17-year-olds, IBS significantly more prevalent in persistent compared to intermittent asthma ($p < 0.001$)
Kumari et al. [21], India	1,101	Cross-sectional	ROME III	3.1	4.5	1.7 (0.7–4.0)	0.2	Negative study

IBS, irritable bowel syndrome.

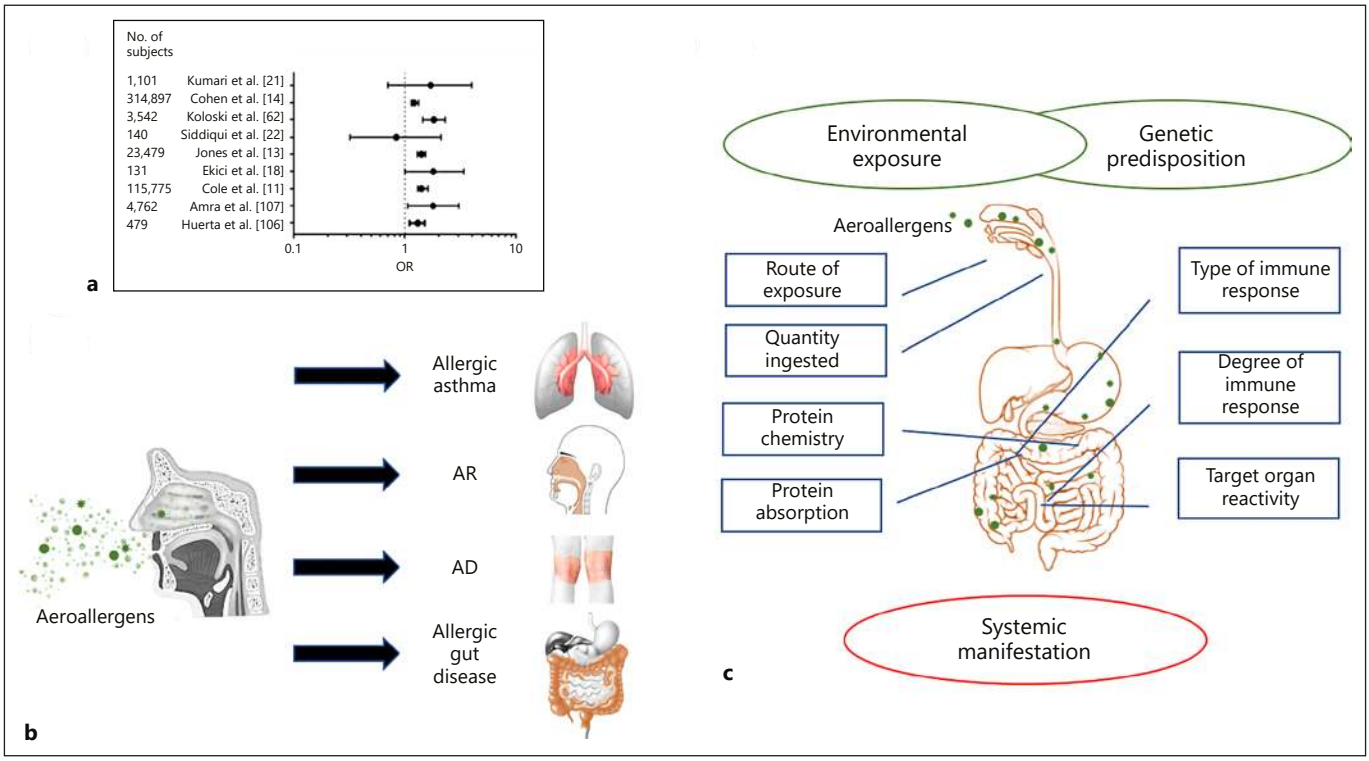

Fig. 1. a Forest plot of the association between asthma and IBS. **b** Sensitization to aeroallergen leads to asthma, AR, AD, and postulated allergic gut disease. **c** The possible role of genetic and environmental factors determining allergic reaction of aeroallergen in the gastrointestinal tract. AR, allergic rhinitis; AD, atopic dermatitis.

ments study with a follow-up of 1,037 children to the age of 26 years also showed no association between IBS and respiratory syndromes [23]. Nybacka et al. [24] showed that IBS patients did not have more atopic diseases compared to healthy controls. They recruited 223 IBS patients and 47 controls, out of which, there were 55% of IBS patients with atopic diseases compared to 40% in the control group ($p = 0.07$). There are several possible reasons for the contrasting findings observed in these studies. First, the aforementioned studies applied different diagnostic criteria for IBS (including ROME and Manning criteria) which may have underestimated the heterogeneity of IBS patients, causing them to overlook the presence of a subset of patients with allergy-related IBS. This subgroup may be better understood through studies that directly compare atopic against non-atopic IBS patients or studies which look for IBS symptoms in atopic patients. Second, the studies varied in their definition of atopy, including atopic manifestations during childhood [24], seasonal allergies [8], and the presence of urticaria [25] or conjunctivitis [13]. Details of the studies are presented in Table 1.

IBS and AR

Several studies suggest a link between AR and IBS. In Taiwan, a retrospective study showed that children with antecedent allergic diseases had a greater risk of IBS than did control subjects. Among allergic conjunctivitis, AR, asthma, AD, urticaria, and food allergy, the highest adjusted odds ratio was observed among AR patients (OR 1.78) [26]. Similarly in UK, a retrospective chart review of 30,000 primary care records found that AR (OR 1.90, 95% CI 1.65–2.20) and eczema (OR 1.46, 95% CI 1.33–1.61) were significantly associated with IBS, even after controlling for age, gender, and mood disorders [13]. Tobin et al. [8] showed that AR and allergic eczema patients were 2.67 and 3.85 times more likely to develop IBS compared to healthy controls. In another retrospective case-control study of 7,235 adult patients, gastrointestinal problems were found to be significantly more common in patients with AR (7.9%) compared to those with chronic illnesses (4.9%) and the healthy population (5.5%) [3]. Data from the population-based Västerbotten Environmental Health Study also showed that IBS was comorbid with allergic asthma and AR [27].

IBS and Allergic Dermatitis

IBS has also been highly associated with AD. In a Taiwanese cohort study involving 24,208 AD-diagnosed children and controls, children with AD had a 1.45-fold greater risk of developing IBS than non-AD children [28]. Nybacka et al. [24] also showed that IBS patients recruited in a Swedish hospital had a higher prevalence of AD (31 vs. 21%, $p = 0.019$) as compared to healthy controls. In another study involving 125 adult patients in Chicago, 51% of patients with IBS reported having allergic dermatitis compared to only 18% of non-IBS patients. In fact, the presence of AD is an independent predictor of IBS diagnosis [8]. Bansal et al. [29] also reported an increased prevalence of IBS in patients with AD, suggesting that AD may precede the development of IBS or be a marker for IBS.

Genetics

Several studies have explored the genetic risk factors shared between atopic diseases and IBS. Walker et al. [30] reviewed genome-wide association studies that looked at overlapping loci between atopic diseases, IBD, and gastrointestinal disorders. There were 7 nucleotide polymorphisms in the genes (*IL-2, DENND1B, SMAD3, ORMDL3, HLA B, TNFSF15*) that were shared between atopic diseases and IBD, suggesting the involvement of the immune response in both condition's biological pathways. Patients with allergic disease, IBS, and IBD also show polymorphisms at loci encoding Toll-like receptors and the nucleotide-binding oligomerization domain like family of intracellular pattern recognition receptors. These findings suggest an involvement of genetic polymorphisms affecting the innate, immunological recognition of microbes [31, 32]. Another review by Lee and Park [33] has also shown the involvement of the TNFSF15 gene (identified in genome-wide association studies) to bring about mucosal inflammation in IBS and IBD [34]. Similar findings were made in cohort studies in the United States, United Kingdom, and Sweden [35, 36]. Like IBS, TNFSF15-TNFRSF25 signaling is also implicated in allergic diseases, suggesting the involvement of a shared inflammatory pathway [37]. TNFSF15 is a TNF family cytokine (TL1A) that is involved in the co-stimulation of type 2 innate lymphocytes and T cells by binding to the TNFRSF25 (DF3) receptor, inducing both the production of T helper 2 cytokines and Th9 differentiation with the subsequent promotion of allergic immunopathology [38, 39].

Environmental Factors

The impact of environmental factors on chronic diseases and human health has been gaining attention in the past decade. Worsening air quality, for example, has been associated with a growing incidence of IBS and allergic diseases. In a Taiwan-based study involving 254, 207 children (<18 years of age), the increase in the number of newly diagnosed cases of IBS was associated with increases in the concentration of carbon monoxide, non-methane hydrocarbons, nitrogen dioxide, and methane, as detected from air quality monitoring stations nationwide [40]. In a meta-analysis of 12 birth cohort studies in Europe and North America, increased exposure to nitrogen dioxide and particulate matter was found to be associated with an increased incidence of asthma [41]. Similarly, Lee et al. [42] found a positive association between AR and air pollutants (such as carbon monoxide and nitrogen oxides) in children who attended schools within 2 km of air monitoring stations in Taiwan. These studies suggest that exposure to air pollutants may contribute to the pathogenesis of both IBS and allergic diseases.

Aeroallergen and GI Tract

While the role of food allergy in IBS has been studied extensively [43–45], the role of aeroallergens has not. Aeroallergens, such as house dust mites (HDM), pollens, mold, and animal dander, can reach our respiratory tracts through inhalation or our gastrointestinal tract through ingestion [46]. Based on the aerodynamics of human nasal airflow, over 80–90% of small particles in the inhalant air are trapped on the surface of the nasal mucosa [47] and are transported by the mucociliary apparatus to the pharynx where they are either swallowed or coughed out. However, aeroallergens can still contaminate the food that we eat. Foods containing aeroallergens can cause allergic reactions such as oral mite anaphylaxis. Oral mite anaphylaxis is a relatively new hypersensitivity syndrome characterized by an immediate allergic reaction to mite contained in food. It is normally found in patients with IgE-mediated hypersensitization to HDMs [48, 49]. Food can also be easily contaminated by aeroallergens from furred animals and pollen grains [50].

Aeroallergens may contribute to the pathogenesis of asthma and IBS. For example, AD, food allergy, and asthma are each associated with the development of eosinophilic esophagitis (EoE): an esophageal disease characterized by eosinophil-predominant inflammation [51]. Re-

peated exposure to aeroallergens in EoE can produce esophageal eosinophilia [52]. An experimental animal study showed that EoE could be induced by intranasal instillation of dust mite, *Aspergillus fumigatus*, and cockroach [53]. In patients allergic to birch pollen, exposure to birch pollen produces local duodenal inflammation with increased eosinophils and IgE-carrying mast cells [54]. In a retrospective cohort study by Wauters et al. [55], duodenal eosinophils counts were higher in FD patients compared to controls. Of note, the incidence of atopic diseases in this study was higher in FD patients compared to controls.

A number of studies have shown that IBS patients are more sensitized to aeroallergens. A study by Vivinus-Nébot et al. [56] showed that IBS patients with atopic diseases had more severe disease and diarrhea-predominant symptoms. In the same study, it was shown that IBS patients had a higher sensitivity to inhalant allergens, but not food allergens, as compared with controls. In Sweden, Nybacka et al. [24] assessed the prevalence of self-reported atopy in IBS patients. They found a higher prevalence of IBS in atopic patients compared to controls, albeit without statistical significance (55 vs. 40%, $p = 0.07$). They also found that atopic IBS patients had higher levels of total serum IgE ($p < 0.001$) and aeroallergen allergy (but not food allergy) than non-atopic IBS patients ($p < 0.001$) [24]. Fang et al. [57] performed a retrospective case-control study of 108 atopic patients in China and observed that atopic patients with HDM-specific IgE were more likely to have abdominal bloating (OR 3.640; 95% CI 1.228–10.790, $p < 0.05$). The severity of abdominal bloating was directly related to total IgE levels [57]. Another small clinical study in the US reported significant differences in sensitization rates towards *Dermatophagoides pteronisimus* and *Dermatophagoides farinae* for patients with IBS compared to the control group [58]. In addition, more IBS patients were sensitized to both dust mites compared to control (38.8 vs. 10%, $p < 0.005$). These results indicate a possibility that aeroallergens may potentially be a key environmental trigger in the pathogenesis of IBS.

How can aeroallergens withstand the digestive process? Strong evidence on the stability of aeroallergens in the gut is provided by Tulic et al. [59]. They found Der p1 antigen (a major HDM antigen) in the duodenal fluid of participants as well as in all regions of the gut including the large bowel. Besides bringing about gastrointestinal inflammation, HDM is capable of weakening intestinal barrier function in participants with IBS [59]. Exposure and sensitization to aeroallergens are closely linked to allergic diseases, particularly asthma. In fact, aeroallergen sensitization is a risk factor for poorly controlled diseases. We often link exposure to aeroallergens to certain environmental conditions, such as HDM with dusty environments and cat dander with animal exposure. We know that HDM exposure is related to asthma severity [60]. While there is currently no study linking HDM exposure to IBS, several studies have linked pet exposure to IBS. In an epidemiological study in Singapore, Siah et al. [61] showed that pet owners were 2.5 times more likely to develop IBS compared to those without pets. Similarly, Koloski et al. [62] found that exposure to herbivorous pets was a risk factor for both IBS and FD.

Sublingual Immunotherapy and Associated Gastrointestinal Problems

Sublingual immunotherapy refers to repeatedly exposing patients to small doses of allergen by placing it under the tongue. Substantial evidence has been presented by several groups on gastrointestinal problems associated with sublingual immunotherapy. A meta-analysis of randomized controlled trials on the efficacy of sublingual immunotherapy in the treatment of pediatric AR reported that gastrointestinal problems were one of the most common adverse effects of treatment [63]. In a sublingual immunotherapy trial involving *Dermatophagoides farinae* (a HDM antigen) in the United States, gastrointestinal symptoms were reported as one of the adverse side effects. Of note, one subject with IBS experienced an increase in diarrheic symptoms while receiving a low dose of sublingual immunotherapy treatment [64]. In another multisite, randomized trial in France and Spain that included 219 subjects with AR with or without asthma, one of the most frequent immunotherapy-related adverse reactions reported was upper abdominal pain [65].

Pathophysiology

Possible Mechanisms Linking IBS and Allergic Diseases

Immune Responses

Both allergic diseases and IBS are brought about by immune dysregulation in genetically susceptible hosts [66]. IBS has been linked to defects in intestinal permeability and subsequent diarrhea. Mucosal immune activation results in the production of immune mediators such as cytokines, histamine, and prostaglandins which stimu-

late epithelial ion secretion. In addition, mast cell proteases activate downstream effects by cleaving protease-activated receptors, which in turn results in the secretion of ions in colonic mucosa [6, 67].

Besides being involved in IBS pathogenesis, mast cells also play a central role in allergic inflammation. Exposure to environmental allergens in the environment will lead to the synthesis of allergen-specific IgE in susceptible individuals. Newly synthesized IgEs will bind to FcεRI receptors on mast cells and basophils. On re-exposure to the specific allergen, mast cells and basophils produce mediators that result in allergic reaction. Mast cells and basophils are central to the initiation and propagation of immediate hypersensitivity reactions. Principal among the cells drawn to sites of mediator release is the eosinophil.

Multiple studies report increased numbers of mast cells and mast cell products (including tryptase, histamine, and prostaglandins) in the small and large bowel of IBS patients. Weston et al. [68] reported high levels of mast cells in the terminal ileum of IBS patients as early as 1993. Many other studies have revealed the role of mast cells in immune activation and causing symptoms such as abdominal pain and altered GI motility in IBS patients [69–72]. Barbara et al. [69] performed a seminal study in this area. They compared the colonic mucosa of IBS and healthy controls and showed that IBS patients had increased mast cells with a higher release of tryptase and histamine. Furthermore, they showed that in IBS patients, masts cells located closer to mucosal innervation were significantly correlated with the severity and frequency of abdominal pain or discomfort [69]. In another study, Cremon et al. [73] showed that mucosal mast cell infiltration in IBS patients was significantly associated with abdominal bloating frequency and symptoms of dysmotility-like dyspepsia. Barbara et al. [74] also showed that biopsy supernatants from patients with IBS contained higher amounts of mast cell mediators, including proteases and histamines. Bashashati et al. [75] performed a systematic review and meta-analysis of colonic immune cells in IBS and found that mast cells were increased in the sigmoid rectum and descending colon in IBS patients. There are many postulated pathophysiological mechanisms regarding the involvement of mast cells in IBS exist, including undetected food allergies, stress, and post-infectious IBS [72, 74, 76–79]. Findings of anti-mast cells treatment in IBS patients are presented in Table 2.

As described above, IgE is known to play a central role in the pathophysiology of type I hypersensitivity reactions [80]. Multiple studies have shown that higher level of IgEs is associated with IBS [81]. Fang et al. [57] showed that atopic patients had higher IgE levels and were more likely to have abdominal bloating; total IgE level was also independently associated with bloating in atopic patients. Atopic patients also had increased intestinal permeability and density of IgE-bearing mast cells compared with non-atopic patients [82].

Structural Defects

Adherens junctions, tight junctions, and desmosomes govern the integrity of the intestinal epithelial barrier. Evidence from a few studies has shown the involvement of increased intestinal permeability and defective epithelial barrier in the pathogenesis of IBS [83–85]. Jejunal biopsies from IBS-D patients show differential expression in genes related to mast cells and the intercellular apical junction complex compared to healthy subjects [86]. Besides, structural abnormalities at the apical junction complex have also been found in jejunal mucosa of IBS-D subjects [87]. E-cadherin is a major component of adherens junctions and tight junctions. Defects in E-cadherin have also been found in people with AD [88, 89]. These findings highlight a possible link between IBS and eczema that could possibly be mediated through an impaired epithelial barrier. Other than defects in E-cadherin in eczema, loss of E-cadherin has also been found in bronchial epithelial cell biopsies from asthmatic subjects [90]. Bronchial biopsies from asthmatic subjects have revealed tight junction disruption. Differentiated bronchial epithelial cultures show significant reductions in tight junction formation from asthmatic subjects (n = 43) compared to normal subjects (n = 40) [91]. This disruption in tight junction formation correlates with macromolecular permeability, suggesting that this defect may facilitate the entry of allergens into the host.

Gut Microbiota

It is known that patients with IBS and allergic diseases have alterations in gut microbiome composition, including an increased abundance of *Firmicutes* and reduced abundance of *Bacteroides* [92]. Lower abundance of members of the *Bifidobacterium* genera has been reported in children with IBS-D (diarrhea-predominant IBS) compared to healthy volunteers [93]. Similarly, children with asthma were also found to have a lower abundance of members of *Bifidobacterium adolescentis* [94]. In another study in Turkey, stool samples from allergic and non-allergic children (0–3 years old) were compared. It was found that *Bifidobacterium longum* was detected in only 11.1% of the allergic children as compared to 30.3%

Table 2. Anti-allergic drug trials in IBS

	Drugs	Mechanism	Results	Remarks
Placebo-controlled randomized control trial	Ketotifen	Anti-histamine 1 receptor and mast cell stabilizer	Positive	Decreases visceral hypersensitivity and IBS symptoms
Randomized control trial	Sodium Cromoglycate	Inhibit mast cell degranulation	Positive	Combination of dietary exclusion and cromoglycate better than dietary intervention alone for IBS-D with food intolerance (by SPT)
Open label	Sodium Cromoglycate	Inhibit mast cell degranulation	Positive	Decreased mucosal mast cells activation in jejunal biopsies, reduced abdominal pain and bowel habits in IBS-D
Case report	Omalizumab	Anti-IgE monoclonal antibody	Positive	Treatment of chronic urticaria also improved IBS
Case report	Omalizumab	Anti-IgE monoclonal antibody	Positive	Treatment of asthma also improved IBS
Placebo-controlled randomized control trial	Ibodutant	Neurokinin receptor 2 antagonist	Positive	Dose-dependent efficacy response in IBS-D, reaching statistical significance at the 10 mg dose in female patients
Placebo-controlled randomized control trial	Ebastine	Histamine 1 receptor antagonist	Positive	Reduced visceral hypersensitivity, increased symptom relief (and reduced abdominal pain scores)

IBS, irritable bowel syndrome.

of the healthy children [95]. This shows that alterations in gut microbiota may occur early in life and may later drive the development of IBS and allergic diseases.

The microbial metabolites produced may also play a role in the pathogenesis of IBS [96, 97]. Recent evidence shows that the regulatory functions of intestinal macrophages by butyrate [98], a short-chain fatty acid, are altered in IBS and AD/allergic disease [99, 100]. This finding highlights the implication of gut microbiota and immunomodulatory pathways in the pathogenesis of both IBS and allergic diseases.

Rodent studies have shown that the ingestion of particulate matter induces changes in the gut microbiota's composition and function [101]. Similar to the altered microbiota composition seen in IBS and allergic patients, $IL10^{-/-}$ mice were also found to have significantly increased abundance in *Firmicutes*, decreased abundance in *Bacteroides*, and a lower concentration of butyrate [101]. Reduction in butyrate is known to bring about a decrease in barrier function as well as reduce defense against inflammation [102, 103].

Five Criteria to Establish a Pathomechanism: Role of Aeroallergen in IBS

In 2016, a group of international experts on FGIDs (together with the publication of ROME IV criteria for FGIDs) proposed criteria to be considered for potential, pathophysiological mechanisms for FGIDs [104]. To establish a causal relationship between a particular mechanism and FGID symptoms, several criteria needed to be met, including the presence, temporal association, a correlation between the level of impairment and symptom severity, induction in healthy subjects, and treatment response or congruent natural history. Based on the strength of evidence for these 5 criteria, a plausibility score can be calculated for each mechanism. As an example of a potential, pathophysiological mechanism, Table 3 presents the role of acid in gastroesophageal reflux disease.

There have been many studies showing an increased sensitization to aeroallergens in IBS patients. However, it is unknown how long it takes for an aeroallergen to produce a reaction (ingestion vs. direct inoculation) and illicit anticipated symptoms (pain vs. motility). Unlike other allergic diseases, the link between allergy and IBS still requires ex-

Table 3. Five criteria to establish a pathomechanism: role of aeroallergen in IBS

	Meaning	Role of acid in GERD	Role of aeroallergen in IBS
1 Presence	The presence of abnormality in a subset of patients	The finding of increased esophageal acid exposure on pH monitoring in patients with heartburn	The finding of increased aeroallergen sensitization in IBS patients
2 Temporal association	Temporal association between proposed mechanism and symptom(s)	The temporal association between reflux events and heartburn occurrence	No evidence
3 Correlation	Correlation between the level of impairment of the mechanism and symptom(s)	The worsening of heartburn scores with increasing severity of esophageal acid exposure	Indirect evidence. The association of bloating in IBS patient with HDM sensitization and worsening of bloating with increasing IgE level. Worsening of IBS symptoms with allergic factors
4 Induction	Induction of the symptom(s) by provoking the pathophysiological abnormality in healthy subjects	The induction of heartburn by esophageal acid perfusion	No evidence
5 Treatment response	Treatment response by a therapy specifically correcting the underlying disorder or congruent natural history of symptoms and dysfunction in the absence of specific therapy	The response of symptoms to acid-suppressive therapy	The response of IBS symptoms to anti-histamine or anti-allergy therapy

IBS, irritable bowel syndrome; HDM, house dust mite.

tensive research on temporal association (the ability to observe or detect immediately delayed symptoms), correlation (to determine a dose-response relationship, both internally and externally), and induction (the direct observation of an inflammatory reaction alongside the elicitation of IBS symptoms) [105]. Even though the development of allergies to aeroallergens may not be the only pathophysiological mechanism which explains IBS symptoms, it is plausible that aeroallergens may act like a catalyst that impairs gut barrier function and facilitates the pathogenic mechanisms of other pathogens or gut microorganisms.

Clinical Implications

Allergic diseases and IBS are two very common conditions in the community. It is not unusual to find them co-existing in a single patient. However, our review shows that perhaps there might be a connection between a subset of IBS patients and allergic diseases. Due to the chronic and complex nature of IBS, all avenues that may lead to better treatment must be carefully explored. No stone should be left unturned.

Conclusion

There is suggestive and supportive evidence with regard to the link between irritable bowel disease and allergic diseases. Future work should focus on confirming the underlying biological mechanisms that are involved in the pathogenesis of these diseases so as to derive preventive and treatment strategies for better patient care.

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Author Contributions

E.X.L.L. and D.Y.W. were involved in the writing and critical review of the manuscript. K.T.H.S. conceptualized the idea and was involved in the writing of the manuscript.

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