Review Article

Air Pollution and Inflammatory Bowel Disease

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Abstract

The exact mechanisms through which IBD occurs are currently not known. There are several genetic and environmental factors that are implicated. What is known is that the incidence of IBD is commoner in Industrialised countries and in countries which are becoming more industrialised, the incidence of IBD is increasing. Pollution is one of the environmental factors that could be implicated in the increase in its incidence. In this review article we analyse the effects of pollution on the gut and the studies which try and shed light on the association between IBD and air pollution.

Key words

air; pollution; particulate matter; Crohn`s Disease; Ulcerative colitis; Inflammatory bowel disease

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Introduction

The incidence of inflammatory bowel disease (IBD),which consist of Crohn's disease (CD), ulcerative colitis (UC) and IBD unclassified (IBDU) is subject to considerable variation worldwide. IBD is commoner in industrialized countries. Recent data on the overall incidence rate ratios in all Western European centres was 1.9 (95% CI 1.5 to 2.4) for CD and 2.1 (95% CI 1.8 to 2.6) for UC when compared to Eastern European centres. The median crude annual incidence rates per 100,000 in 2010, for CD were 6.5 (range 0-10.7) in Western European Centres, compared to 3.1 (range0.4-11.5) in Eastern European Centres. For UC, the crude annual incidence rates were 10.8 (range 2.9–31.5), in Western European Centres compared to 4.1(range 2.4–10.3). Similar data was also present for IBDU.[1]

Although, over the last decade, the discovery of genes linked to susceptibility to IBD was thought to be a major breakthrough, current studies demonstrate that that this only explains approximately 20-25% of the hereditary variance. Thus, environmental factors are likely to contribute significantly to disease pathogenesis.[2]

Furthermore, currently the role of microbiome in IBD is being investigated world-wide. IBD is linked to changes in the composition of intestinal microbiota. It was noted that there is an increased proportions of Anctinobacteria and Proteobacteria, together with a decrease in the diversity and proportions of Firmicutes. Furthermore, the microbiota of patients in remission was found to be different than that of active IBD patients.[3]

The fact that the incidence of IBD increased rapidly during the past decades and that the increase has been particular in several developing countries, where the incidence of IBD was considered to be low, led to the suggestion of the importance of environmental factors, one of them being pollution.[4]

Environmental factors and IBD

Exposure to cigarette smoking is the best characterised among the environmental factors potentially contributing to CD, but other

environmental factors such as lack of exposure to pets and gardens as well as living in an urban area are also associated with an increased risk.[5]

Multiple sclerosis shares features with IBD, including the role of environmental, microbial factors and genetic factors. With regards to environmental factors both diseases are possibly associated with poor air quality.[6] Currently, no study has directly assessed how genes and air pollution interact in IBD. This is mostly in view of the difficulty to quantify the contribution of air pollution and IBD susceptibility. However, smoking and common IBD-related genes have been evaluated in this setting.[7]

Theoretically, there is a good rationale for gene-environment interactions in these patients. [8] This is due to the fact that may genes associated with IBD are involved in bacterial recognition and handling, and air pollution may modulate this effect. This is well demonstrated in patients with polymorphisms in NOD2 and autophagy genes which possibly enhance the effects of pollution.[9]

Although studies are limited with regards to the role of air pollution as a risk factor for IBD, studies of the effect on cardiorespiratory system have shown that there would be an increase in the circulating inflammatory cytokines, such as tumour necrotising factor alpha[10] and leukocytes.[11]

Ambient air quality had been associated with flares in multiple sclerosis, a disease which shares pathogenic mechanisms with IBD. In a study carried out by Oikonen *et al*. the relationship between the occurrence of multiple relapses and ambient air quality was observed. The results were that the odds of relapse were 4-folds higher during months with highest quartile of airborne particulate matter. In view of these results the authors stated that poor ambient air quality may lead to increased susceptibility to communicable infections or augment already existing peripheral inflammation leading to disease flare.[5]

Therefore, this study shed light on the possibility a similar systemic inflammatory response to poor air quality exposure may play a role in IBD flares, leading to increased hospitalisations.[12-13]

Components of Air pollution

Air pollution is a mixture of chemicals which are well known to cause adverse health effects. This heterogeneous mixture of substances commonly consists of gases such as sulphur dioxide, nitric oxide, nitrogen dioxide, carbon monoxide, carbon dioxide and ozone, volatile organic compounds and particulate matter.[15] The components of air pollution depends mainly on the source of the pollution itself ranging from fuel combustion such as home furnaces and vehicles to livestock 'emissions'.[16] Therefore, depending on where a person lives, travels and work; s/he is exposed to a unique mixture of pollutants.

Most of the attention has been given to ozone and particulate matter (PM). Ozone has been linked with induction of airway inflammation and damage, resulting in increased cell permeability and breakdown of tight junction integrity, and a similar process may take place in IBD.[17] PM leads to a number of effects. Nitrogen dioxide is linked with adverse health outcomes.[18] PM is defined according to the aerodynamic diameter, being divided into either fine particles, these being smaller than 2.5μm or coarse particles, the latter having a diameter which is more than 2.5μm but less than 10μm.[19]

Other components of air pollution may be linked with health effects, however only selective ones are used as surrogate markers of quality of air. Therefore such components may be missed due to lack of data.[20]

Pollution exposure to gut mucosa

The gastrointestinal tract is exposed to high concentration of pollutant PM, as they are quickly cleared from the lungs by the muco-ciliary system and transported to the gut. Another source of intake is the oral route due to contaminated food and water supply. It is estimated that 10^{12}-10^{14} particles are ingested per day.[19]

Current treatment strategies, of using thiopurines, methotrexate and anti-TNF-alpha are targeted to reduce the effects of the immune system.[21] Thus dysregulation and over reactivity of intestinal immune responses are potential mechanisms for IBD.[22]

As demonstrated in various studies, air pollutants lead to a systemic immunomodulatory/ inflammatory effect, and therefore many autoimmune diseases are linked with urban living and industrialisation, as seen in the hygiene hypothesis.[23] This states that the decrease of infectious burden, in industrialised countries, has led to a rise in the incidence of autoimmune diseases. It was first proposed by Strachan in 1958. [24] Several epidemiological studies have investigated

this link. These have demonstrated that exposure to cowsheds and farming at a young age can prevent the development of atopic diseases, especially if this is during pregnancy.[25] However, up to date there is still little research that studies autoimmune disease and air pollution directly.[26] Most data about the possible mechanisms such as systemic oxidative stress and increased cytokine levels in the blood come from respiratory and cardiovascular research.[27-28]

Environmental effects on the Gut Microbiota

Microbiota plays an important key role in IBD, and therefore another effect of air pollution may be the disruption of this balance.[29]

Microbial imbalance reported in IBD may be a result of changes in the environment, including hygiene and food. This results in imbalance in microbial-host relationship leading to mucosal barrier dysfunction and a decrease in the microbiota diversity.[30] Dysbiosis leads to an increase in the pathological bacteria including *Mycobacterium avium paratuberculosis ssp (*MAP) and a decrease in beneficial bacteria such as Lactobacilli and Bifidobacteria.[31]

Several studies have highlighted the high prevalence of MAP in CD patients.[32] However, although a number of microbes have been associated with the disease, no single agent was identified. Many of the features of modern lifestyle have been linked with IBD including crowding, domestic hygiene and antibiotic usage in childhood.[33]

Geographical variation in IBD and the living environment

Northern Europe and North America have the highest incidence rates of IBD worldwide. This may indicate common aetiological factors. Studies demonstrate that in countries (e.g. South Korea, China, India, North Africa, French West Indies and Thailand) which are becoming more westernised, the incidence of IBD is increasing.

Within Europe, there are also marked differences in the rates of IBD between different countries. These differences may be due to difference in the cohorts, organisation of health care and methodology of data collection. However, in the European Collaborative Study on IBD, the rate difference between Northern and Southern Europe decreased and similarly there is a sharp increase in IBD diagnosis in Eastern European countries. Over the past two decades, these populations have 'westernised' their lifestyle, leading to increase in pollution. Immigration has also shown to leave an impact on the prevalence of IBD. It was shown that individuals who have emigrated to westernised countries and then returned back to their native country, demonstrated an increase an increase in developing IBD, especially UC, suggesting that environmental factors related to industrialisation may play an important factor.[34]

Relationship between smoking and pollution-relevance to IBD

Smoking is associated with the severity of CD; however it is inversely associated with UC, occurring more in non-smokers and ex-smokers. The similarities in exposure between air pollution and smoking, brings to relevance the possibility that air pollution may also have an important effects on the development of IBD. Some mechanism involved in mediating the intestinal effects of cigarette smoking might play a role on how air pollution affects the intestines.[4]

One obvious difference is that air pollution does not contain nicotine, which is found in cigarettes. Although nicotine appears to cause some of the clinically relevant effects, nicotine replacement alone does not seem to replicate smoking in terms of impact on IBD. [20] Particulate matter is the common component between air pollution (from other sources) and smoking.

Effects of Pollution on the Gut

In between the external luminal environment and the internal body proper, lies the highly regulated epithelial monolayer, which besides the function of absorption also provides important immune and barrier surveillance mechanisms. Mutlu *et al*. showed that with exposure to PM, there was a decrease in the epithelial barrier, associated with rearrangement of epithelial tight junction proteins. This is linked to the generation of free radical oxygen species (ROS). The increase in permeability has been associated with intestinal inflammation. This may be due to the fact that there is an influx of the PM and microbial products into the lamina propria, thus increasing interactions with immune cells.[19]

The microbial entry will induce an inflammatory response by dendritic cells and

macrophages leading to systemic inflammation, altering the luminal environment of the gut, thus allowing for growth of particular microbial strains. The latter would be suited to survive in an inflammatory environment. These changes may also lead to production of altered metabolites such as butyrate which further increases the intestinal permeability.[19]

In a study conducted in Singapore, it was demonstrated that elevated atmospheric PM was associated with greater circulating polymophonuclear leukocytes. Healthy men who were exposed to diesel fumes, showed an increase in the level of plasma cytokines, particularly TNF-alpha, which is an important mediator in IBD. Currently one of the common drugs used in the management of both CD and UC is anti-TNF-alpha medications. Furthermore, Miller et al. also showed an impairment of vascular function on exposure to diesel exhaust. Such studies may continue to explain the link between pollution and the disease.[13]

Epidemiological studies have been performed as to assess the association between pollution and IBD. A study carried out by Kaplan *et al*, concluded that there is no association between pollution and IBD epidemiologically, for newly diagnosed cases. However, an association was revealed in some subgroups. Individuals, under the age of 23 years of age were more likely to be diagnosed with CD if they lived in regions of higher pollution (OR 2.31), with a linear association between risk and increased air NO levels. PM exposure was mostly associated with CD (OR 1.73), while UC was associated with higher sulphur dioxide levels for individuals under 25 years of age (OR 2.0). However, middle aged adults, between the age of 44 and 57 years, diagnosed with Crohn's disease were less likely to live in regions with elevated concentration of Nitrogen Dioxide.[35] Therefore this may indicate that traffic-related pollutants, such as nitric oxide and industrial based pollutants such as sulphur dioxide may have age specific effects on the development of IBD.

In another study, data from the Wisconsin Hospital Association, from the year 2002 was used to identify IBD related hospitalisation. Data regarding average annual emissions density was obtained from the Environmental Protection Agency. This study demonstrates that there is an association between adult hospitalisation (81.3 hospitalizations/ 100,000 people per year) and total pollutant density.[36] There was a mean of 81.3 IBD hospitalizations/100,000 population per county (range 0-174). The total criteria pollutant emissions density correlated significantly with adult IBD hospitalizations (Pearson's correlation coefficient (rho) 0.28, p=0.020). On Poisson regression, a 1-log increase in the density of total criteria pollutant emission was associated with a 40% increase in the rate of IBD hospitalizations (incidence rate ratio [IRR] 1.40, 95% confidence interval [CI] 1.31-1.50) This was similar for both ulcerative colitis (UC) (IRR 1.48, 95% CI 1.27-1.73) and Crohn's disease (CD) hospitalizations (IRR 1.39, 95% CI 1.26-1.52). Analysis of each of the individual criteria pollutant emission densities revealed a significant association for all the component criteria pollutants.[37]

Studies had also shown that an urban household was associated with a higher incidence of IBD, in light of the fact that urban regions are associated with higher air pollution levels.[38-40] A systematic review and meta-analysis demonstrated a positive association between the urban environment and both CD and UC. However due to the heterogeneity in the study design and results, the temporal link between urban environment and the risk of IBD development could not be concluded with confidence.[41]

Although the relationship between ambient air pollution and IBD appears plausible from an epidemiologic stand point, one should interpret them with caution, due to possible bias. In such studies, mixed air pollution is observed, where one measured pollutant may also serve as a marker of other confounding exposures.[20]

There are multiple other studies which had examined the relationship between urban living and IBD. A study carried out in Manitoba showed that individuals who had ever lived on a farm, were less likely to develop CD (OR 0.62, 95 % CI 0.46–0.85, p=.003), while urban living was associated with higher risk of both CD (IRR 1.29, 95 % CI 1.17–4.41) and UC(IRR 1.12, 95 % CI 1.04–1.21). Likewise, rural patients in the UK were less likely to develop early-onset CD (OR 0.36, 95% CI 0.14-0.95) and UC (OR 0.66, 95% CI 0.51-0.85).[42]

Li X et al., using a nationwide database linking the Swedish Census to the hospital discharge register, studied the link between education level and occupation and hospitalisation for IBD. The data obtained was on all first

hospitalisations for UC and CD. The results show that there was a significant decrease in the standard incidence ratio for Crohn's disease in both men and women who had an educational level of more than 12 years. However, a significant increase in the standard incidence ratio was seen amongst drivers in all cohorts. The reason for this is unclear but the probable daily exposure to pollutants has to be actively considered.[43]

Finally, in laboratory studies, where mice were fed particles sieved from an urban air filtration system developed increased pain,[44] had raised pro-inflammatory IL-8 levels and exhibited dysbiosis.[38]

Conclusion

Several environmental factors have been linked with IBD, including ambient air pollution. Though it might not be a leading cause, it can definitely be a significant contributor. The underlying mechanism and the interaction of all these risk factors to cause IBD have not yet been elicited. A limitation of these studies is the different methodological methods associated with studying environmental risk factors in IBD.[4]

Although data is suggestive of this association especially epidemiologically, further efforts should be done to determine the effects of pollution on the biological mechanisms.[20]

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