INFLAMMATORY BOWEL DISEASES AND AIR POLLUTION

Al. C. Moldoveanu¹,³*, Anca Maria Moldoveanu³, M. Diculescu²,³
¹. University Hospital, Internal Medicine II and Gastroenterology Clinic Bucharest
². Fundeni Clinical Institute, Department of Gastroenterology, Bucharest
University of Medicine and Pharmacy “Carol Davila” Bucharest
³. Faculty of Medicine
*Corresponding author. E-mail: alexandru.c.moldoveanu@gmail.com

INFLAMMATORY BOWEL DISEASES AND AIR POLLUTION (Abstract). Air pollution is responsible for the increase in mortality, morbidity and a high number of hospitalizations for respiratory and cardio-vascular diseases. Recently, several studies have shown that air pollution can also affect the digestive system. The major impact was observed on inflammatory bowel diseases (Crohn’s disease and ulcerative colitis). Air pollutants that have the great impact on the digestive system health are: gases, especially ozone, particulate matter and heavy metals like lead, cadmium.

Material and Methods: Forty-six articles and one book were evaluated for the purpose of this study. The articles are indexed in international databases, including PubMed, PMC, Scholar Google, and MEDLINE. Results: We present here the current understanding of the mechanisms by which air pollution can affect intestinal tissues. There are three mechanisms that can be taken into consideration: the direct effect of pollutants on epithelial cells; the alteration of the immune response and the influence of air pollution on the intestinal microbiota. The gene – environment relationship was also discussed in the case of the inflammatory bowel diseases. Conclusions: Up to this moment there are several indicators which show that pollution can have a negative impact on the intestinal tract, but the evidence is limited. The current studies have many limitations and confusion factors that must be measured and corrected so that the specific factors can be correctly evaluated for intestinal diseases. Studies on animals must verify the biologic plausibility of obtained data. Keywords: INFLAMMATORY BOWEL DISEASES, AIR POLLUTION, CYTOKINES, MUCOSAL INFLAMMATION, GUT MICROBIOTA, GENE-ENVIRONMENT RELATION.

The concept of air pollution refers to the presence of substances in air that can have a negative effect on human health.

The most famous incident related to the effect of acute air pollution on human health is the toxic fog accident in London in 1952. There were two previous episodes where air pollutants have determined increased mortality and morbidity: in 1928, in the Meuse Valley and in 1948 in Donora. The sources that have released pollutants in these areas were mostly stationary sources represented by industrial facilities. It was the meteorological conditions that have led to the increase in mortality and morbidity due to the phenomena of thermic inversion. Several studies have proved that long-term exposure to pollutants can reduce average lifespan by a few years and increase mortality. Thus, the APHEIS and APHEA study (1, 2), which investigated the impact of air pollution with particles and other air pollutants in Europe has demonstrated that, in Bucharest, the age standardized mortality rates (per 100,000 people) will be equal to 1127 if the level of air pollution with PM_{10} (particulate matter)
is in a range 14 –73 μg/m³. If the air pollution level will drop by 5 μg/m³, between 3,300 to 7,700 early deaths annually will be prevented, 500 to 1000 of which are associated with short term exposure (1). After the acute episodes of pollution mentioned above, legislative measures have been adopted, which have considerably lowered air pollution levels. A study conducted in U.S.A. assessed the changes registered in the life expectancy in relation with the levels of air pollution with fine particulate in the period between 1980 and 1990. The result of the study showed that, when the level of pollution with fine particle was lower than 10 μg/m³, there was an increase in the mean of life expectancy of 0.61±0.20 year (p=0.004) (3).

**OBJECTIVE**

This article tries to find connections between air pollution and the potential effects on human health especially between air pollution and intestinal diseases, especially inflammatory bowel diseases.

**MATERIAL AND METHODS**

Forty-seven articles and one book were evaluated. The articles are indexed in international databases, including PubMed, PMC, Scholar Google, and MEDLINE.

**Effects of air pollution on human health**

Studies have shown an increase in morbidity, number of hospitalizations and mortality during and immediately after an episode of acute air pollution.

a) Increased levels of air pollution can have impact on respiratory system with decreased ventilatory function in healthy individuals, modified ventilatory performance in exposed children, worsening of respiratory symptoms in pulmonary diseases like chronic obstructive pulmonary disease and acute attacks of asthma.

b) Also, recent studies have proven a consistent relation between air pollution with particles and cardio-vascular pathology. Exposure to an increased level of particles in ambient air can determine an increased rate of mortality by rhythm abnormalities and coagulation modifications, increasing the chance of myocardial infarction and stroke (4).

c) Another type of pathology that can be induced by air pollutants is significant intestinal pathology. There are very few studies in this regard.

**The influence of air pollutants on intestines**

In case of air pollutants exposure, the substances that enter the organism by inhalation are mostly eliminated. The main elimination path of particles and gases dissolved in mucus is done using the mucociliary system. By using the mucociliary escalator, the pollutants are taken towards the buccal cavity, where they are coughed or swallowed. By swallowing, the air pollutants can rapidly reach the intestines. Gaseous pollutants and particles can induce systemic inflammation that can have significant impact on intestines.

**Pollutants that can induce intestinal pathology**

Regarding the evaluation of the impact of environmental pollutants on digestive diseases, a relatively small number of studies have been done.

Pollutants that can induce intestinal pathology include:

- Gaseous pollutants like ozone, sulfur dioxide, nitrogen oxides and nitrogen diox-
Inflammatory Bowel diseases and air pollution

ide in particular, carbon monoxide and carbon dioxide,
- Volatile organic substances like benzene,
- Particles. These represent a mix of biological elements like bacteria, fungi, pollen as well as particles with a high absorbent capacity for different gases like polycyclic aromatic hydrocarbons like benzo(a)pyrene. The particle composition can also have nitrates, sulfates, organic carbon or metals like lead, cadmium, etc. The particle structure depends on the source that releases the pollutants in the air.

The pollutants sources can be either fixed or mobile. The pollutants can result from the burning of fossil fuels in industry, for thermal energy, from the combustion of biomass or from traffic.

Of all air pollutants, it appears that ozone and particles have the greatest impact on intestinal pathology. It was determined that exposure to ozone can induce inflammation in both humans and animals, which will cause an increased cellular permeability and the destruction of mucosal barrier integrity (5). Important effects have also been identified for particles, as presented earlier. Regarding the exposure to nitrogen oxides, important intestinal effects have been identified, both in humans and animals, in case of exposure to very high concentrations.

Mechanisms by which air pollution can affect intestinal tissues
Multiple mechanisms can be taken into consideration, which could explain the impact of air pollution on bowels. Because there are few elements that evaluate the effect of air pollution on bowels, the proposed mechanisms for analysis are extrapolated starting from research on other organs and systems like the respiratory and cardiovascular systems.

a. The direct effect of air pollutants on epithelial cells
The direct effect of pollutants on epithelial cells could be considered. There is aggression, especially of particulate matter, against epithelial cells of the respiratory system. Modifications were found in exposed individuals that have pre-existing lesions as well as healthy individuals. These modifications have been seen on animal experiments as well as in vitro studies (9-13). A study done by Manzo et al. has demonstrated that in case of exposure of healthy cells, from the tracheal pathways or at the alveolar levels to diesel type air particles, have not registered a notable effect. However, if the pulmonary epithelial cells are already in a state of inflammation through the action of exogenous cytokines, like TNF-α (tumor necrosis factor α), IL-1β (interleukin 1β), and IFN-γ (interferon γ), due to previous exposure to diesel particles, they become incapable of responding to the increased level of oxidative stress, which will cause injury and dysfunc-
tion of the epithelial barrier and increased permeability (14). The action of environmental pollutants like diesel particles will, thus, have a greater effect on individuals with genetic predispositions and other conditions that induce inflammatory afflictions like Inflammatory Bowel Diseases (IBDs) (14).

Another study has evaluated the effect of administering a single oral dose of diesel particles on rats and has observed DNA injuries in colonic epithelial cells (15).

The effect on epithelial cells caused by exposure to air pollutants is the same, regardless of the exposed zone, respiratory or digestive. Epithelial cells generate radical oxygen species (ROS) as a response to exposure to particulate matter from air, inducing epithelial barrier disruption and increasing gut permeability (16).

b. The alteration of the immune response

In both Crohn’s disease and ulcerative colitis, there is a modified and over reactive immune response (17). Air pollution has an immunomodulation effect, of inducing systemic inflammation, which causes an increased risk for autoimmune diseases and related diseases like type 1 diabetes, neuro inflammation or increased cardiovascular risk by systemic inflammation. This means it has a significant effect on inflammatory bowel diseases as well (18-21). Many of these effects are associated with urban development and industrialization, which would be favorable elements in the hygiene hypothesis of inflammatory bowel disease (22). This hypothesis suggests that persons with a decreased exposure to infections developed in childhood and at more precarious hygienic conditions in adulthood can have a deficit of „friendly” microorganisms or elements that stimulate the development of T regulatory cells, or they do not develop sufficient immune mechanisms due to the fact that they did not encounter harmful microorganisms. Individuals in this category have a higher incidence in chronic immune diseases, including inflammatory bowel diseases.

Zanobetti et al. (2009) and Ritz (2010) have shown that, at least in part, autoimmune diseases can be explained by the effect of air pollutants (23, 24).

The mechanisms used could be systemic oxidative stress, the stimulation of hematogenic medulla, the increase in the cytokine levels in blood and the increase in number of white blood cells The effect demonstrated in vitro (9, 25-33) of cellular immune activation could support this theory (34, 35). For example, IL-6 and TNF-α produced by peritoneal macrophages in mice are induced by the exposure to particles (both fine particles and large diameter particles). TLR2 (toll-like receptor 2) and TLR4 appear to mediate differently the response to air pollution. However, the exposure of alveolar macrophages in humans to particles in the urban air and diesel type particles induce a suppression of TNF-α and secretion of IL-6 and IL-8 (36).

Another study, performed in Seoul, has shown a dose dependence of the pro-inflammatory level of cytokines (IL-1, TNF-α, and IL-6), the type of cytokines Th0 (IL-2) and the type of cytokine Th1 (IL-12 and IFN-γ) in exposure to particles with the diameter of 2.5 μm. The activity of the oxidative stress related genes, like HSP 1a (heat shock protein 1a), HSP 8 (heat shock protein 8) and SOD (superoxide dismutase), and tissular lesions related genes, like MMP 15-19 (matrix metalloproteinases 15 and 19) and SLPI (secretory leukocyte peptidase inhibitor) were also influenced, dependent on exposure time.
Inflammatory Bowel diseases and air pollution

PM 2.5 can also induce an increase in the distribution of T cells in lymphocytes and a decrease of the CD4+/CD8+ ratio. Based on these results the authors of the Soul study suggest that the pollution of air with PM 2.5 can induce a Th1 type inflammatory response with oxidative stress, which can determine adverse effects on human health.

c. The effect on intestinal microflora

Another mechanism that can influence air pollutant action on intestinal mucosa is the effect on intestinal flora. The intestinal flora has a key role in inflammatory bowel diseases (38). It was proven in animal experiments that inflammatory bowel diseases do not appear if the mice are held in a sterile environment. The intestinal flora of patients with inflammatory bowel diseases is different than that of healthy subjects (39). The genetic loci associated with IBDs suggest the important role of the relation between the intestinal immune system and intestinal flora in the pathogenesis of inflammatory bowel diseases (40).

The structure of the intestinal flora can be affected by pollutants, especially heavy metals like lead and cadmium (39-42), which reduce taxonomic diversity.

Intestinal bowel diseases: gene – environment relationship

The discovery of the genetic implication in inflammatory bowel diseases etiopathogenesis represented an important element. Still, only 20% of the cases can be thus explained. It is suggested that environmental factors contribute more than the genetic component in IBD pathogenesis (43). The importance of environmental factors is proven especially in children (44).

Up to this moment there are no studies to directly link and describe how the genetic and environmental factors act together in IBDs.

A study was performed on 310 patients with Crohn identified NOD2 gene as the most significant gene associated with Crohn’s disease in smokers (45).

CONCLUSIONS

Up to this moment there are several indicators which show that pollution can have a negative impact on the intestinal tract. However, up to this moment the evidence is limited. The current studies have many limitations that must be eliminated and many confusion factors that must be measured and corrected so that the specific factors can be correctly evaluated for intestinal diseases.

This can include identifying and evaluating the interaction between genetic factors and environmental factors.

A careful interpretation must be done of the data that evaluates the relation between air pollution and inflammatory intestinal diseases and it must represent an incentive towards the continuation of research in this direction.

Studies on animals must verify the biologic plausibility of obtained data.

Air pollution with particles as well as gas and heavy metals can represent an element which cannot be ignored in determining the etiopathogenesis and evolution of inflammatory bowel diseases (46, 47).

ACKNOWLEDGEMENTS

This paper is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/159/1.5/S/137390/.
REFERENCES

Inflammatory Bowel diseases and air pollution


---

**BIOFILM-INHIBITORY COMPOUNDS AGAINST *PSEUDOMonas AERUGINOSA* FROM BURDOCK LEAF**

In a study by Lou Z *et al*, basic anti-biofilm profile data for the compounds in burdock leaf were analyzed and a convenient method for fast screening of anti-biofilm compounds from natural plants was provided. According to this study, 34% ethanol elution fraction of burdock leaf could completely inhibit biofilm formation of *Pseudomonas aeruginosa* at 1 mg·mL(−1). Ultra-performance liquid chromatography-mass spectrometry (UPLC-MS) was used to determine the chemical composition of burdock leaf fraction and to obtain the metabolic fingerprints of burdock leaf fractions before and after inhibiting *P. aeruginosa* biofilm. The analysis identified 11 active compounds: chlorogenic acid, caffeic acid, p-coumaric acid, quercetin, ursolic acid, rutin, cynarin, luteolin, crocin, benzoic acid, and Tenacissoside I. Partial least squares discriminant analysis (PLS-DA) of the metabolic fingerprints showed that, among 81 compounds that were screened as potential anti-biofilm ingredients, rutin, ursolic acid, caffeic acid, p-coumaric acid and quercetin are the main anti-biofilm compounds in burdock leaf (Lou Z, Tang Y, Song X, Wang H. Metabolomics-Based Screening of Biofilm-Inhibitory Compounds against Pseudomonas aeruginosa from Burdock Leaf. *Molecules*. 2015;20(9):16266-77. doi: 10.3390/molecules200916266).

Teodora Vremera