REVIEW

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Association Between Particulate Matter Exposure and Chronic Rhinosinusitis

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Chronic rhinosinusitis (CRS) is a relatively common inflammatory disease of the nasal and paranasal sinus mucosa. Several epidemiological studies have established an association between particulate matter (PM) and CRS. Based on those data, PM has emerged as an important environmental factor in the development of CRS. Recent research has investigated the mechanisms and treatment options for CRS caused by PM through cellular experimentation. Therefore, the authors would like to explain the definition of PM, present research investigating the relationship between PM and CRS, and summarize the involved mechanisms reported to date.

Keywords: Particulate matter; Sinusitis; Mechanism.

INTRODUCTION

Airborne pollutants can pose significant risks to human health, and particulate matter (PM) is one of the most important pollutants. With industrialization, PM has become deeply embedded in our daily lives and has had a significant impact on our health and well-being. In contemporary Korean society, there is growing social concern about PM due to the increasing incidence of health-damaging concentrations of PM. The World Health Organization (WHO) estimates that exposure to PM is responsible for approximately 16% of lung cancer deaths, 11% of deaths from chronic obstructive pulmonary disease, and over 20% of deaths from ischemic heart disease and strokes [1]. Additionally, PM has been classified as a group 1 carcinogen by the International Agency for Research on Cancer under the WHO [2].

Chronic rhinosinusitis (CRS) is a common upper respiratory disease worldwide, with reported prevalence rates of around 10%; thus, it imposes a significant socioeconomic burden [3]. CRS can be diagnosed when clinical symptoms persist for more than 12 weeks and there is endoscopic or radiological evidence of sinus inflammation [4]. The nasal cavity is the first organ that encounters the external environment, and it plays a crucial role as a barrier by filtering inhaled air to protect the lower respiratory tract. Airborne pollutants, such as PM, initially encounter cells in the nasal cavity, leading to abnormal cellular changes. Consequently, studies investigating the effects of PM often utilize nasal epithelial cells as an experimental model. The aim of this paper was to review the definition of PM, as well as its impact on CRS and the underlying mechanisms involved.

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DEFINITION OF PARTICULATE MATTER

The composition of PM can vary depending on the location, season, weather conditions, and other factors influencing its development. PM is a heterogeneous mixture of solid, liquid, or mixed-phase particles suspended in the air that contains a complex array of organic, inorganic, and organometallic compounds [5]. PM is generated from both natural and anthropogenic sources. Human-related sources of PM include combustion processes, automobile exhaust, and cigarette smoking, as well as emissions from mechanical and industrial processes. Natural sources of PM include volcanic eruptions, wildfires, sandstorms, and aerosolized sea salt [6,7]. PM can be classified according to its size as follows: total suspended particles, less than 50 μm; PM10, less than 10 μm; fine particulate matter (PM2.5), less than 2.5 μm; and ultrafine particles (UFPs), less than 0.1 μm. The other components

of PM10 after PM2.5 is excluded are referred to as coarse particles or coarse PM (PM2.5-10) [5]. Coarse PM is primarily generated by crushing and grinding processes and tends to deposit in the nasal cavity, oropharynx, extra-thoracic, and upper tracheobronchial regions. PM2.5, which primarily originates from combustion sources such as vehicle emissions, coal burning, and industrial processes, can be inhaled deeply into the lungs and deposited in the alveoli, entering both the pulmonary and systemic circulations. UFPs are predominantly emitted by vehicle exhaust and can translocate from the alveoli to the circulatory system. PM2.5 accounts for approximately 50% of the total mass of PM10 [8].

ASSOCIATION BETWEEN PARTICULATE MATTER AND CHRONIC RHINOSINUSITIS

A multitude of research has exhibited a clinical correlation between CRS and PM. According to recent studies, patients with higher PM2.5 exposure were more likely to be diagnosed with CRS. In an epidemiological study using the National Health Interview Survey, a significant association was observed between ambient PM2.5 concentrations and the self-reported prevalence of sinusitis (odds ratio=1.18) [9]. In another study using a case-control approach with 6,102 subjects, long-term PM2.5 exposure was found to be significantly associated with CRS diagnosis, particularly in the ethmoid sinus, which has the most airflow [10]. A study by Park et al. [11] reported a significant association between PM10 exposure and the prevalence of CRS. Specifically, an increase of 1 $\mu g/m^3$ in PM10 was found to be associated with a significant increase in CRS prevalence, with an odds ratio of 1.22.

Historically, CRS has been classified into two main phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). Studies have investigated the association between PM and these two phenotypes. Mady et al. [12] found a significant association between PM2.5 exposure and the need for additional surgery in CRSsNP patients, with a 1.89-fold increase in risk for each unit increase in PM2.5. This association may be influenced by exposure levels, with a more pronounced impact on patients with CRSsNP. However, CRS inflammation is primarily characterized by three endotypes, which are distinguished by elevated levels of representative lymphocyte cytokines [13]. In a recent study, it was found that for each increased unit of the average concentration of PM2.5, there was a 1.047-fold increased risk of the endotype of eosinophilic CRSwNP [14].

PATHOGENIC PROCESSES OF CHRONIC RHINOSINUSITIS CAUSED BY PARTICULATE MATTER

CRS is hypothesized to be caused by multiple factors, including environmental factors, abnormalities in the physical immune barrier (e.g., epithelial tight junctions and mucociliary clearance), and innate and adaptive immune dysregulation [15]. Dysbiosis is one of these factors, suggesting that changes in the sinus microbiota may have an impact on the development of CRS [16]. A study found that higher levels of PM2.5 were associated with a lower relative abundance of *Corynebacterium* in both CRS patients and controls, implying that PM exposure may have an impact on the nasal microbiota of the human nasal cavity [17].

In cell experiments, PM exposure reduced the viability of human nasal epithelial cells and increased cytotoxicity [18]. When cells are exposed to PM, the expression of inflammatory mediators (e.g., tumor necrosis factor-alpha, interleukin [IL]-1β, IL-4, IL-6, IL-8, and monocyte chemoattractant protein-1) increases in a time- and dose-dependent manner through various pathways [19-21]. In nasal tissue samples exposed to PM, cilia demonstrated pronounced disorientation and morphological alterations, and changes in the expression of genes related to cilia were even observed [22-24]. PM-induced dysfunction of the epithelial barrier is also considered an important mechanism in the development of CRS. PM exposure reduced transepithelial electrical resistance and the expression of tight junction proteins in human nasal epithelial cells [25-27]. Furthermore, PM exposure resulted in reactive oxygen species (ROS) production in cells, while pretreatment with an antioxidant (N-acetylcysteine) restored tight junction protein expression [25,28,29]. Diesel exhaust particles, a type of PM, induced the epithelial-to-mesenchymal transition (EMT), which is a process involving the loss of epithelial polarity and junctional proteins, in the sinonasal mucosa [30]. Nasal airway lavage fluid after PM exposure in a mouse model contained higher numbers of macrophages, neutrophils, and eosinophils than observed in controls [15,31]. Recent research has also indicated that PM2.5-induced damage to nasal epithelial cells is caused by ferroptosis [32]. Thus, PM has been shown to cause CRS through various mechanisms, such as immune responses, oxidative stress, and dysfunction of the epithelial barrier in nasal cells (Table 1).

LIMITATIONS AND FUTURE DIRECTIONS OF RESEARCH

Population-based studies have been largely retrospective, and there is insufficient clinical evidence to evaluate the long-

Table 1. Experimental studies on the cellular mechanisms of PM-induced chronic rhinosinusitis

Study	Tissue	Exposure	PM treatment method	Main pathogenesis
London et al., 2016 [26]	Human sinonasal epithelial cells obtained during endoscopic sinus surgery	PM10	Air-liquid interface culture	Sinonasal epithelial cell barrier disruption by Nrf2 activation
Lee et al., 2018 [19]	Human nasal fibroblasts obtained during partial turbinectomies	Urban PM	PM added directly to cell culture media	IL-6 and IL-8 expression by fibroblasts via p38 and NF-κB classical signaling
Ahmadzada et al., 2019 [23]	Human nasal epithelial cells from patients	DEP	PM added directly to cell culture media	Impairment of cellular barrier function due to abnormalities in ciliary beat frequency and transepithelial electrical resistance
Montgomery et al., 2020 [24]	Human nasal epithelial cells from patients	PM2.5 organic extract	Air-liquid interface culture	The expression of genes was modified to increase mucus secretory expression and decrease ciliated cell expression
Lee et al., 2020 [25]	Human nasal epithelial cells obtained during partial turbinectomies	Urban PM	PM added directly to cell culture media	Tight junction disruption by inducing oxidative stress via the Akt signal pathway
Shin et al., 2020 [18]	Primary human nasal epithelial cells from the inferior turbinate of patients	PM10	PM added directly to cell culture media	PM exposure induces changes in gene expression via exosomal miRNAs
Xian et al., 2020 [27]	Human sinonasal epithelial cells obtained during endoscopic sinus surgery	PM2.5	Air-liquid interface culture	Loss of barrier function through decreased expression of tight junction proteins
Lee et al., 2022 [30]	Human nasal epithelial cells from patients	DEP	Air-liquid interface culture	Epithelial-to-mesenchymal transition dependent on ZEB2 expression
Lee et al., 2022 [21]	Human nasal polyp-derived fibroblasts	PM10	PM added directly to cell culture media	IL-33/ST2 pathway-mediated immune response
Gu et al., 2023 [32]	Human nasal epithelial cell line	PM2.5	PM added directly to cell culture media	Ferroptosis of cells via AMPK-mediated autophagy

PM, particulate matter; DEP, diesel exhaust particles; IL, interleukin; miRNA, micro-RNA

term effects of PM. Cohort studies should be conducted to assess the long-term effects of PM exposure. While laboratory experiments continue to be conducted in various laboratories, cellular evidence alone cannot fully explain all clinical phenomena. Therefore, clinical studies must be conducted to support the correlations, clinical manifestations, and treatment of PM and CRS.

PM exposure has been shown to play an important role in the development of CRS by a substantial body of clinical research. However, there is a significant shortage of research on patient factors that predispose individuals to CRS due to PM exposure. Impaired immune function in response to environmental factors is a critical mechanism underlying the pathophysiology of CRS. Further cell-based and clinical research, taking into account patient-specific factors, is required to gain a comprehensive understanding of the relationship between PM and CRS. Furthermore, the effect of PM on CRS may vary depending on the phenotype and endotype, and more experimental evidence is needed to fully understand this relationship. It is an important challenge not only to identify the mechanisms of PM-induced CRS, but also to develop effective preventative and therapeutic strategies.

CONCLUSION

PM has been reported to exhibit a strong association with CRS. Multiple mechanisms, such as inflammation, ROS, tight junction disruption, and EMT, have been proposed as being involved in this relationship. The incidence of health-damaging concentrations of PM is currently increasing, accompanied

by a consequent increase in the incidence of CRS. Therefore, further research is needed to investigate the impact of PM on CRS, as well as the underlying mechanisms and potential treatments.

Ethics Statement

Not applicable

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Dong Chang Lee. **Data curation:** Dong Chang Lee. **Funding acquisition:** Dong Chang Lee. **Investigation:** Ji-Sun Kim, Dong Chang Lee. **Supervision:** Dong Chang Lee. **Validation:** Ji-Sun Kim, Dong Chang Lee. **Writing—original draft:** Ji-Sun Kim, Dong Chang Lee. **Writing—review & editing:** Ji-Sun Kim, Dong Chang Lee.

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