




## The relationship between COVID-19 and smoking

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### ABSTRACT

Smoking leads to the development of many respiratory system diseases, including chronic obstructive pulmonary disease and lung cancer. By hindering the protective mechanisms of our non-respiratory tract, it provides convenient conditions for respiratory infections. Smoking is an important risk factor for the infection and spread of COVID-19. Our historical information demonstrates that the use of tobacco products negatively affects patients' chances of survival during MERS-CoV and SARS-CoV, outbreaks of the same family as COVID-19. Considering the harms of smoking, it can be predicted that its exposure negatively affects the course of COVID-19 disease, both directly and indirectly. The aim of this review is to evaluate the relationship between smoking and COVID-19 in the light of current literature.

**Keywords:** COVID-19, lung, smoking.

COVID-19 is a disease caused by a novel Coronavirus, that emerged in China's province of Hubei, Wuhan, at the end of 2019. Coronaviruses, a subtype of the Coronaviridae family, are enveloped viruses containing positive-sense RNA genome. Three serologically different coronavirus groups have been identified. Coronaviruses have been identified in mice, rats, chickens, turkeys, pigs, dogs, cats, rabbits, horses, cattle, and humans and can cause a variety of severe illnesses such as gastroenteritis and respiratory diseases.

The causative virus, initially referred to as the novel coronavirus-2019 (2019-nCoV), was later named "Severe Acute Respiratory Syndrome-Coronavirus-2" (SARS-CoV-2) by the World Health Organization (WHO), and the disease it caused was called COVID-19 (Coronavirus Disease 2019).<sup>[1]</sup>

Apart from SARS-CoV-2, the new member of coronaviruses which are zoonotic pathogens, SARS-CoV, MERS-CoV, human pathogenic coronaviruses (HCoV) HCoV-HKU1, HCoV-NL63, HCoV-OC43, and HCoV229E can also infect humans and cause respiratory infections.<sup>[1]</sup> Human pathogenic coronaviruses are responsible for 5-30% of mild seasonal colds, and >90% of the population carry antibodies against mild HCoV.<sup>[1,2]</sup>

On March 11, 2020, the WHO declared COVID-19 as a pandemic. According to the official data of the World Health Organization, on May 19, 2020, the number of confirmed cases worldwide was 4,696,849, while the number of reported deaths was 315,131.<sup>[3]</sup>

After the virus was officially detected in our country on March 11, 2020, the number of cases increased rapidly, and by May 20, 2020, 152,587

**Received:** January 05, 2021 **Accepted:** January 18, 2021 **Published online:** May 05, 2021

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### Cite this article as:

Durgun M, Dindar Demiray EK, Alkan Çeviker S. The relationship between COVID-19 and smoking. D J Med Sci 2021;7(1):77-81.

patients were diagnosed with the disease, while 4,222 patients died.<sup>[3]</sup>

The virus can easily bind to the angiotensin-converting enzyme 2 (ACE2) receptor in humans, particularly in type 2 alveoli cells of the lungs, as well as in myocardium, vascular endothelial cells, proximal tubules of the kidneys, esophagus, epithelial cells of the ileum, urothelial cells of the bladder, and may directly cause a cytotoxic effect in these cells.<sup>[1,2]</sup>

## SMOKING AND COVID-19

Smoking, biomass smoke exposure, and air pollution are the main etiological factors of chronic obstructive pulmonary disease (COPD). The aim of the WHO Chronic Respiratory Diseases Programme is to support efforts to reduce the morbidity, disability, and the rate of premature death associated with asthma and COPD.<sup>[4]</sup>

Smoking leads to the development of COPD, and lung cancer, and many respiratory illnesses. By blocking the protective mechanisms in the respiratory tract, smoking facilitates the progression of respiratory tract infections to illness. Smoking is an important risk factor for the infection and spread of the COVID-19 epidemic. With the quitting of smoking, lung and cardiovascular health begins to improve. The weakened immune system, which allows coronavirus to cause illness in the respiratory tract, begins to be repaired.<sup>[3,4]</sup>

According to previous data from during the MERS-CoV and SARS-CoV epidemics, which are in the same family as COVID-19, tobacco use negatively affects patients' chances of survival. Considering the harms of smoking, it can be predicted that its exposure negatively affects the course of COVID-19 disease, both directly and indirectly.

Exposure to smoking causes several harmful inflammatory processes in the body. It is clinically known that increased inflammation in the mucosa, expression of inflammatory cytokines and tumor necrosis factor  $\alpha$  can cause increased permeability in epithelial cells, excessive production of secretions, and disruption of mucociliary activity.<sup>[5]</sup>

Smoking is a risk factor for several chronic systemic illnesses including COPD, hypertension,

cardiovascular disease, atherosclerosis, Crohn's disease, and rheumatoid arthritis.<sup>[5]</sup>

Cigarette smoke contains over 4,500 components in its gas and particle phases.<sup>[6]</sup> These include carcinogens such as methylcholanthrene, benzo-a-pyrenes and acrolein; toxins such as carbon monoxide, ammonia, acetone, nicotine, and hydroquinone; and chemically catalytic surfaced reactive solids and oxidants such as superoxide and nitrogen oxides.<sup>[5,6]</sup>

In addition, cigarette smoke can affect the immune system by chemically modifying signaling pathways and the extracellular matrix through aspiration, nitrosylation, carbonylation, and oxidation, which may impact cell survival, activation, and differentiation.<sup>[5,6]</sup>

Approximately 500 mL of air is inhaled into the lungs with each breath. The air we breathe contains toxic substances, viruses, and bacteria. However, thanks to the immune and non-immune protective mechanisms of the lungs, we can be protected from harmful agents in the air we breathe. Various specialized epithelial cell types such as cilia, goblet, Clara cells, basal cells, and Type I and Type II cells are found in the respiratory tract.<sup>[7]</sup> The airway epithelium gradually thins and changes to simple cuboidal cells at the terminal bronchiole level. Another specialized cell, goblet cells, are found in the airways and their number decreases distally. The lower layer contains Clara cells which produce mucus. Mucus glands are most commonly found in the intermediate airways and disappear at the bronchiole level. Serous cells are also lined up in the mucous glands, and these cells secrete proteoglycans and antimicrobial substances that play a role in the natural defense of the lungs.

The negative effects of exposure to cigarette smoke on the immune system are known and have been proven by numerous studies. For instance, exposure to cigarette smoke has been shown to increase TNF- $\alpha$  expression.<sup>[8]</sup>

An imbalance between apoptosis and proliferation of alveolar epithelial and endothelial cells has been observed in the lungs of patients with COPD.<sup>[9]</sup>

Asthma and COPD are characterized by chronic inflammation in the airways. Studies using bronchoalveolar lavage (BAL) have shown a

higher rate of eosinophils in BAL fluid of asthma patients compared to normal subjects, while COPD studies have shown an increased number of neutrophils.

In a study published in the American Journal of Respiratory and Critical Care Medicine, sputum was induced in 14 COPD patients, 23 asthma patients, 12 healthy smokers, and 16 healthy non-smokers (control group). A significant increase was found in the number of neutrophils and concentrations of TNF- $\alpha$  and interleukin-8 (IL-8) in COPD patients compared to smoking and non-smoking control subjects. Interleukin-8 and TNF- $\alpha$  concentrations were significantly higher in the COPD group compared to the asthma group. It was concluded that the cytokines TNF- $\alpha$  and IL-8 may play a role in inflammation in COPD.<sup>[10]</sup>

In addition, another study showed that inflammation, oxidative stress, and apoptosis, which play a role in COPD pathogenesis, can activate the p38 subgroup of mitogen-activated protein kinases (MAPK). Increased activation of p38 MAPK was observed in alveolar walls and alveolar macrophages of COPD patients compared to smoking and nonsmoking controls.<sup>[11]</sup>

Cigarette smoke affects immune cells in the respiratory tract by inducing the production of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1, IL-6, IL-8, and granulocyte-macrophage colony stimulating factor (GM-CSF). A severalfold increase in the number of neutrophils, macrophages, and dendritic cells was observed in the airways of smokers and animals exposed to cigarette smoke compared to controls.<sup>[11]</sup>

The most important known cause of COPD is cigarette exposure which includes a series of abnormal inflammatory responses towards inhaled particles and gases in the lung. Other processes such as chronic inflammation, abnormal cell repair, apoptosis, extracellular matrix destruction (protease/antiprotease imbalance) and oxidant/antioxidant imbalance caused by smoking also play a role. Subsequent chronic inflammatory responses lead to mucus hypersecretion, airway remodeling, and alveolar destruction. Smoking not only causes airway inflammation, but also causes lung parenchymal destruction. It causes emphysematous spaces as a result of alveolar wall destruction. It also causes a significant decrease in the first second of forced expiration and lowers

the forced vital capacity. The harmful effects of cigarette exposure is not limited to epithelial damage, it can progress from a series of changes in cellular immune response to visible major alveolar destruction. Tobacco exposure causes significant damage to the body's response to infection.<sup>[11,12]</sup>

The SARS-CoV-2 spike (S) protein uses ACE-2 receptors for host cell entry, as in SARS and MERS coronaviruses.<sup>[12]</sup> The main target cells of the virus are type II pneumocytes and enterocytes with high ACE-2 expression.<sup>[13]</sup> S protein binds to ACE-2 then undergoes structural changes by TMPRSS2, a host transmembrane serine protease, and viral RNA enters the cell through endocytosis or fusion to the cellular membrane, infecting the cell.<sup>[13]</sup>

Another study investigated the gene expression levels of ACE-2 in the respiratory tracts of individuals with and without COPD and found that ACE-2 expression was significantly increased in COPD and active smokers. ACE-2 is expressed in various tissues, including the respiratory tract, myocardium, and gastrointestinal mucosa.<sup>[14]</sup> Although its role in human health and disease has not been fully enlightened, it appears to have an important regulatory role regarding blood pressure and cardiac function. The physiological role of ACE-2 in the respiratory tract is largely unknown. However, ACE-2 has been shown to provide protection against pulmonary damage due to aspiration and sepsis in mice.<sup>[15]</sup>

While increase in ACE-2 is beneficial in protecting the host against acute lung injury, this may predispose individuals to an increased risk of coronavirus infection, which utilizes this receptor to enter epithelial cells. This may partially explain the risk of viral respiratory infections in active smokers and virus-related exacerbations in COPD patients.<sup>[16,17]</sup>

Previous studies have reported that smokers had twice the risk of contracting influenza than non-smokers, with smokers having a higher mortality in the previous MERS-CoV outbreak.<sup>[16,17]</sup>

In a study by Zhou et al.<sup>[18]</sup> which examined 191 individuals infected with COVID-19, 54 of the patients died and 137 survived. While 9% of the patients who died and 4% of the survivors

were active smokers, in terms of COVID-19 mortality, it was observed that there was no statistically significant difference between the smoking rates of patients who died and survivors ( $p=0.21$ ).

However, contradicting our current knowledge and according to the results of a study conducted at the Pasteur Jean-Pierre Changeaux Institute in France, it was suggested that COVID-19 infections can be prevented with nicotinic agents such as nicotine patches, as nicotinic acetylcholine receptor (nAChR) plays an important role in the pathophysiology of COVID-19. It was hypothesized that nicotine may be a target for the prevention and management of COVID-19 infection, and that nicotine inhibits the binding of coronavirus to the ACE receptor and thus has a protective nature against the disease.<sup>[19]</sup> The French researchers stated that their results did not comply with the results of research conducted in China, and indicated that the rate of smokers among the COVID-19 patients in their study sample was very low.

A similar result was found in another previous study conducted by Giuseppe Lippi and Henry<sup>[20]</sup> in Italy. The results of this study, published in the European Journal of Internal Medicine, demonstrated that smokers contracted the disease less than nonsmokers.<sup>[20]</sup>

### Conclusion

Although some recent studies indicate that nicotine prevents COVID-19 from entering cells, considering all of the toxins found in tobacco smoke, its negative effects on immunity, and the irreversible damage caused in the lung parenchyma, overall, smoking makes us more vulnerable to COVID-19.

### Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

### Funding

The authors received no financial support for the research and/or authorship of this article.

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