Review Article

Tobacco Consumption as a Risk Factor for Coronavirus Disease 2019?

Snehal Yerne

Department of Pharmacology and Toxicology, Swargiya Dadasaheb Kalmegh Smruti Dental College and Hospital, Nagpur, Maharashtra, India

Abstract

In December 2019, a novel coronavirus, now named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused a series of acute atypical respiratory diseases in Wuhan, Hubei Province, China. After virus identification and isolation, the pathogen for this pneumonia was originally called 2019 novel CoV-2, but has subsequently been officially named SARS-CoV-2 by the WHO. On January 30, 2020, the WHO declared the outbreak of SARS-CoV-2 a Public Health Emergency of International Concern. Compared with the SARS-CoV that caused an outbreak of SARS in 2003, SARS-CoV-2 has a stronger transmission capacity. The rapid increase in confirmed cases makes the prevention and control of coronavirus disease 2019 (COVID-19) extremely serious. The virus is transmittable between humans and has caused pandemic worldwide. The number of death tolls continues to rise, and a large number of countries have been forced to do social distancing and lockdown. Lack of targeted therapy continues to be a problem. Studies have shown that SARS-CoV-2 infects host cells through angiotensin-converting enzyme 2 receptors, leading to COVID-19-related pneumonia, while also causing acute myocardial injury and chronic damage to the cardiovascular system. The gastrointestinal symptoms include abdominal pain, diarrhea, appetite loss, nausea, and vomiting, and neurologic symptoms include cerebrovascular strokes and encephalitis.

Keywords: Angiotensin-converting enzyme 2, coronavirus disease 2019, Guillain–Barre syndrome, severe acute respiratory syndrome coronavirus 2

Introduction

Coronavirus is a zoonotic virus which has crossed species to infect the human populations. Globally it has created a havoc and millions have summed to death. Unlike its other two counterparts namely the severe acute respiratory syndrome corona virus (SARS- CoV) and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) the SARS-CoV causes disease which leads to severe respiratory distress and has more virulence potential additionally its rate of spread is approximately ten times faster as compared with its other two counterparts due to its ability to preferentially attack the Angiotensin-converting enzyme 2 receptors. Currently no vaccine is available and the patients are essentially been treated with anti-viral drugs whereas plasma therapy is reserved for severe cases. In such a global emergency it is essential to identify the high risk population in order to decrease the health burden. This article suggests that tobacco consumption in smokeless as well as smoked form may act as a risk factor for the novel coronavirus disease due to the common pathway of action which involves ACE2 receptors.

Biology of Coronavirus Disease 2019

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense single-stranded RNA virus with a single linear RNA segment.[1] It belongs to the family *Coronaviridae*, genus *Betacoronavirus*. Its RNA sequence is approximately 30,000 bases in length. SARS-CoV-2 is unique among known Betacoronaviruses in its incorporation of a polybasic cleavage site, a characteristic known to increase pathogenicity and transmissibility in other viruses.[2] Each SARS-CoV-2 virion is

Address for correspondence: Dr. Snehal Yerne, Swargiya Dadasaheb Kalmegh Smruti Dental College and Hospital, Ameya Apartment, Gopal Nagar, Nagpur - 440 022, Maharashtra, India.
E-mail: sweetsnehal2929@gmail.com

Access this article online

Quick Response Code:

Website: www.ijcommdent.com

DOI: 10.4103/ijcd.ijcd_4_20

How to cite this article: Yerne S. Tobacco consumption as a risk factor for coronavirus disease 2019? Int J Comm Dent 2020;8:9-12.

Received: 03-05-20; **Accepted:** 11-07-20; **Web Published:** 12-07-21

approximately 50200 nm in diameter.[3] Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins; the N protein holds the RNA genome, and the S, E, and M proteins together create the viral envelope.[4] The spike protein, which has been imaged at the atomic level using cryogenic electron microscopy,[5,6] is the protein responsible for allowing the virus to attach to and fuse with the membrane of a host cell.[7]

Protein modeling experiments on the spike protein of the virus soon suggested that SARS-CoV-2 has sufficient affinity to the receptor angiotensin-converting enzyme 2 (ACE2) on human cells to use them as a mechanism of cell entry.[8] By January 22, 2020, a group in China working with the full virus genome and a group in the United States using reverse genetic methods independently and experimentally demonstrated that ACE2 could act as the receptor for SARS-CoV-2.[9,10] Studies have shown that SARS-CoV-2 has a higher affinity to human ACE2 than the original SARS virus strain.[11,12] SARS-CoV-2 may also use basigin to assist in cell entry.[13]

Initial spike protein priming by transmembrane protease, serine 2 (TMPRSS2) is essential for entry of SARS-CoV-2.[14] After a SARS-CoV-2 virion attaches to a target cell, the cell's protease TMPRSS2 cuts open the spike protein of the virus, exposing a fusion peptide. The virion then releases RNA into the cell and forces the cell to produce and disseminate copies of the virus, which infects more cells.[15]

SARS-CoV-2 produces at least three virulence factors that promote shedding of new virions from host cells and inhibit immune response.[16]

Location of Angiotensin-Converting Enzyme 2 Receptors in the Body

This virus enters the human body through ACE2 receptors, which are attached to the cell membrane of mainly lung Type II alveolar cells. Apart from the lungs, expression of the ACE2 receptor is also found in many extrapulmonary tissues including heart, kidney, endothelium, and intestine.[17,18] Importantly, ACE2 is highly expressed on the luminal surface of intestinal epithelial cells, functioning as a coreceptor for nutrient uptake, in particular for amino acid resorption from food,[19] also involved in amino acid transportation. We, therefore, predict that the intestine might also be a major entry site for SARS-CoV-2 and that the infection might have been initiated by eating food from the Wuhan market, the putative site of the outbreak. As the source of outbreak is a market place therefore a strong possibility of coronavirus infecting the gut epithelium exists. A study showed that the ACE2 protein is abundantly expressed in the glandular cells of gastric, duodenal, and rectal epithelia, supporting the entry of SARS-CoV-2 into the host cell and therefore has important implications for fecal–oral transmission and containment of viral spread. The key findings of the study published online in gastroenterology suggest that:

- A significant portion of coronavirus patients experience diarrhea, nausea, vomiting, and/or abdominal discomfort before the onset of respiratory symptoms
- Viral RNA is detectable in fecal samples from suspected cases, indicating that the virus sheds into the stool
- Viral gastrointestinal infection and potential fecal–oral transmission can last even after viral clearance from the respiratory tract.[20]

Here, we consider the ability of SARS-CoV2 to enter and infect the human gastrointestinal tract (GIT) and nervous system based on the strong expression of the ACE2 target throughout the GIT and brain. Moreover, we predict that nicotine exposure through various kinds of tobacco consumption (smokeless form and smoked form) can increase the risk for coronavirus disease 2019 (COVID-19). The gastrointestinal system,brain,respiratory system can also get affected by COVID-19 due to the presence of ACE2 receptors within them. The coronavirus can damage the innate and adaptive immune arms. Cigarette smoke is shown to augment the production of numerous proinflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor which are also involved in hyperinflammatory syndrome which leads fulminant and fatal hypercytokinemia with multiorgan failure in COVID-19 patients. Hence, smoked forms of tobacco not only affect the binding of the virus to the receptor but also may contribute to increased mortality associated with hyperinflammatory syndrome.

Role of Nicotine

Tobacco contains a number of toxicologically significant chemicals and groups of chemicals, including polycyclic aromatic hydrocarbon (benzopyrene), tobacco-specific nitrosamines (NNK and NNN), aldehydes (acrolein and formaldehyde), carbon monoxide, hydrogen cyanide, nitrogen oxides, benzene, toluene, phenols (phenol and cresol), aromatic amines (nicotine, 4-aminobiphenyl), and harmala alkaloids. Nicotine constitutes approximately 0.6%–3.0% of the dry weight of tobacco, and it acts as a receptor agonist at most nicotinic acetylcholine receptors (nAChRs).[21]

COVID-19 has the ability to bind the ACE2 on epithelial cells as a primary mechanism of entry into the host.[22] Critical cases of COVID-19 infection commonly manifest as cardiopulmonary symptoms and, in severe cases, advance into organ failure and sepsis as a result of a "cytokine storm" over activation of the immune system.[23]

Nicotine, the psychoactive component of tobacco smoke, has profound immunological effects. It is an agonist at nAChRs, which causes it to interfere with immune responses in a receptor-mediated manner.[24]

Nicotine suppresses the migration of leukocytes to the inflammation/infection site; the decreased inflammation correlates with lower chemotaxis/chemokinesis of

peripheral blood mononuclear cells (PBMCs) toward formyl-methionyl-leucyl-phenylalanine and monocyte chemoattractant protein-1 without affecting the density of their respective receptors. However, nicotine suppressed the chemokine-induced Ca^2 + response in PBMC, indicating impaired chemokine signaling. Thus, because nicotine suppresses leukocyte migration, it might contribute to the increased incidence of respiratory infections among smokers.[25] This proves that, although nicotine may serve as an anti-inflammatory agent, it may, in turn, increase the incidence of COVID-19 infections.

Functional interactions between nicotine exposure and ACE2 expression in the lungs and other organ systems such as heart and kidneys as well as nicotine and other components of the renin–angiotensin system suggest that nicotine can promote COVID-19 cellular entry through nAChR signaling. Notably, nAChRs are known to be on many of the same cells that express ACE2 in the lungs, kidneys, circulation, and brain.[26-28] Thus, nicotine can impact COVID-19 pathophysiology and clinical outcome in several organ systems.

Differential host factors such as age, health, simultaneous infection, and genetics are known determinants of susceptibility to a viral infection. Smoking tobacco is a strong factor in predicting an individual's likelihood of developing and managing a viral infection and especially a respiratory infection.[25,29] The mechanism of increased susceptibility to infections in smokers is multifactorial and includes alteration of the structural and immunologic host defenses. Here, we try to establish a link between nicotine-associated comorbidity to COVID-19 in the context of the brain, GIT, and respiratory system based on published evidence that the viral target receptor ACE2 is expressed in the various extrapulmonary sites and functionally interacts with nAChRs.[30,31] We consider if neural cells, such as epithelial cells, are more vulnerable to infection in smokers as well as people consuming smokeless forms of tobacco because nicotine stimulation of the nAChR can increase ACE2 expression within them.[32] This issue is critical because evidence shows that mRNA from the closely related SARS virus, which also binds ACE2 as a mechanism of cell entry, was detected in brain and cerebrospinal fluid of infected individuals.[33-35] Moreover, SARS ability to enter neurons is established in experimental systems using recombinant human ACE2 as the point of entry,[36,37] as SARS-CoV-2 can actively infect and replicate in the GIT. It has important implications for the disease management, transmission, and infection control.

Conclusion

Therefore, we conclude that, due to this interaction between ACE2 and nAChR, the chances of acquiring COVID-19 infection might be significantly high among people consuming tobacco either in smoked or smokeless form. As nicotine present in the tobacco may enhance the severity of respiratory infection due to its immunomodulatory mechanisms, it might lead to increased chances of acquiring acute respiratory distress syndrome in COVID-19 infections. According to recent studies, Guillain–Barre syndrome can be considered as neurological complications of infection with COVID-19, which indicates that infection with COVID-19 can result in long-term neural damage in both symptomatic and asymptomatic individuals, and if, in such cases, history of chronic nicotine exposure through smoked and smokeless forms of tobacco is present, it increases the risk of developing COVID-19-associated neuropathology through interactions between nAChRs and ACE2 in neurons and glia,[38] contributing to lifelong morbidity.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Oves M, Ravindran M, Rauf MA, Omaish Ansari M, Zahin M, Iyer AK, Ismail IMI, Khan MA, Palaniyar N. Comparing and Contrasting MERS, SARS-CoV, and SARS-CoV-2: Prevention, Transmission, Management, and Vaccine Development. Pathogens. 2020 Nov 26;9(12):985. doi: 10.3390/pathogens9120985. PMID: 33255989; PMCID: PMC7761006.
2. Shu, Yuelong, and John McCauley. "GISAID: Global initiative on sharing all influenza data - from vision to reality." Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin vol. 22,13 (2017): 30494. doi:10.2807/1560-7917.ES.2017.22.13.30494.
3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15;395(10223):507-513. doi: 10.1016/S0140-6736(20)30211-7. Epub 2020 Jan 30. PMID: 32007143; PMCID: PMC7135076.
4. Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, *et al*. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sin B. 2020 May;10(5):766-788. doi: 10.1016/j.apsb.2020.02.008. Epub 2020 Feb 27. PMID: 32292689; PMCID: PMC7102550.
5. Sironi M, Hasnain SE, Rosenthal B, et al. SARS-CoV-2 and COVID-19: A genetic, epidemiological, and evolutionary perspective. Infect Genet Evol. 2020;84:104384. doi:10.1016/j.meegid.2020.104384.
6. Wong AC, Li X, Lau SK, Woo PC. Global epidemiology of bat coronaviruses. Viruses 2019;11:174.
7. Wang K, Chen W, Zhang Z, Deng Y, Lian JQ, Du P, *et al*. CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. Signal Transduct Target Ther. 2020 Dec 4;5(1):283. doi: 10.1038/s41392-020-00426-x. PMID: 33277466; PMCID: PMC7714896.
8. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, *et al*. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci 2020;63:457-60.
9. Letko M, Munster V. Functional assessment of cell entry and receptor usage for lineage B β-coronaviruses, including 2019-nCoV. bioRxiv [Preprint]. 2020 Jan 22:2020.01.22.915660. doi: 10.1101/2020.01.22.915660. Update in: Nat Microbiol. 2020 Apr;5(4):562-569. PMID: 32511294; PMCID: PMC7217099.
10. Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, *et al*. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect. 2020 Jan 28;9(1):221-236. doi: 10.1080/22221751.2020.1719902. Erratum in: Emerg Microbes Infect. 2020 Dec;9(1):540. PMID: 31987001; PMCID: PMC7067204.
11. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, *et al*. Cryo-EM structure of the 2019-nCoV spike in the

prefusion conformation. Science 2020;367:1260-3.
12. Kaur SP, Gupta V. COVID-19 Vaccine: A comprehensive status report. Virus Res. 2020;288:198114. doi:10.1016/j.virusres.2020.198114.
13. Matusiak, M., Schürch, C.M. Expression of SARS-CoV-2 entry receptors in the respiratory tract of healthy individuals, smokers and asthmatics. Respir Res 21, 252 (2020). https://doi.org/10.1186/s12931-020-01521-x.
14. Hoffman M, Kliene-Weber H, Krüger N, Herrler T, Erichsen S, Schiergens TS, *et al*. (16 April 2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271-80.e8.
15. Anatomy of a Killer: Understanding SARS-CoV-2 and the Drugs that Might Lessen its Power. The Economist; 12 March, 2020. [Last retrieved 2020 March, 14].
16. Masters, Paul S. "The molecular biology of coronaviruses." Advances in virus research vol. 66 (2006): 193-292. doi:10.1016/S0065-3527(06)66005-3.
17. Kabbani, Nadine, and James L Olds. "Does COVID19 Infect the Brain? If So, Smokers Might Be at a Higher Risk." Molecular pharmacology vol. 97,5 (2020): 351-353. doi:10.1124/molpharm.120.000014.
18. Rabi FA, Al Zoubi MS, Kasasbeh GA, Salameh DM, Al-Nasser AD. SARS-CoV-2 and coronavirus disease 2019: What we know so far. Pathogens 2020;9:231.
19. Hashimoto T, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paolino M, *et al*. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature 2012;487:477-81.
20. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. Gastroenterology 2020;158:1831-3000.
21. Kishioka S, Kiguchi N, Kobayashi Y, Saika F. Nicotine effects and the endogenous opioid system. J Pharmacol Sci 2014;125:117-24.
22. Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. Biochem Biophys Res Commun. 2020 May 21;526(1):135-140. doi: 10.1016/j.bbrc.2020.03.044. Epub 2020 Mar 19. PMID: 32199615; PMCID: PMC7156119.
23. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55(5):2000547. Published 2020 May 14. doi:10.1183/13993003.00547-2020.
24. Piao WH, Campagnolo D, Dayao C, Lukas RJ, Wu J, Shi FD. Nicotine and inflammatory neurological disorders. Acta Pharmacol Sin 2009;30:715-22.
25. Razani-Boroujerdi S, Singh SP, Knall C, Hahn FF, Peña-Philippides JC, Kalra R, *et al*. Chronic nicotine inhibits inflammation and promotes influenza infection. Cell Immunol 2004;230:1-9.
26. Changeux JP. Nicotine addiction and nicotinic receptors: Lessons from genetically modified mice. Nat Rev Neurosci 2010;11:389-401.
27. Olu S, Eddine R, Marti F, David V, Graupner M, Pons S, *et al*. Co-activation of VTA DA and GABA neurons mediates nicotine reinforcement. Mol Psychiatry 2013;18:382-93.
28. Nordman JC, Muldoon P, Clark S, Damaj MI, Kabbani N. The α4 nicotinic receptor promotes CD4+T-cell proliferation and a helper T-cell immune response. Mol Pharmacol 2014;85:50-61.
29. Eddleston J, Lee RU, Doerner AM, Herschbach J, Zuraw BL. Cigarette smoke decreases innate responses of epithelial cells to rhinovirus infection. Am J Respir Cell Mol Biol 2011;44:118-26.
30. Pacurari M, Kafoury R, Tchounwou PB, Ndebele K. The Renin-Angiotensin-aldosterone system in vascular inflammation and remodeling. Int J Inflam. 2014;2014:689360. doi: 10.1155/2014/689360. Epub 2014 Apr 6. PMID: 24804145; PMCID: PMC3997861.
31. Oakes JM, Fuchs RM, Gardner JD, Lazartigues E, Yue X. Nicotine and the renin-angiotensin system. Am J Physiol Regul Integr Comp Physiol 2018;315:R895-906.
32. Olds JL, Kabbani N. Is nicotine exposure linked to cardiopulmonary vulnerability to COVID-19 in the general population? FEBS J. 2020 Sep;287(17):3651-3655. doi: 10.1111/febs.15303. Epub 2020 Mar 28. PMID: 32189428; PMCID: PMC7228237.
33. Zhang QL, Ding YQ, Hou JL, He L, Huang ZX, Wang HJ, *et al*. Detection of severe acute respiratory syndrome (SARS)-associated coronavirus RNA in autopsy tissues with *in situ* hybridization]. Di Yi Jun Yi Da Xue Xue Bao 2003;23:1125-7.
34. Chong PY, Chui P, Ling AE, Franks TJ, Tai DY, Leo YS, *et al*. Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore: Challenges in determining a SARS diagnosis. Arch Pathol Lab Med 2004;128:195-204.
35. Inoue Y, Tanaka N, Tanaka Y, Inoue S, Morita K, Zhuang M, *et al*. Clathrin-dependent entry of severe acute respiratory syndrome coronavirus into target cells expressing ACE2 with the cytoplasmic tail deleted. J Virol 2007;81:872:2-8729.
36. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2 J Virol 2008;82:7264-75.
37. Kaparianos A, Argyropoulou E. Local renin-angiotensin II systems, angiotensin-converting enzyme and its homologue ACE2: Their potential role in the pathogenesis of chronic obstructive pulmonary diseases, pulmonary hypertension and acute respiratory distress syndrome. Curr Med Chem 2011;18:3506-15.
38. Kabbani N, Olds JL. Does COVID19 infect the brain? If so, smokers might be at a higher risk. Mol Pharmacol 2020;97:351-3.