Does Vaping Increase Susceptibility to COVID-19?

To the Editor:

We read with much interest the study by Zhang and colleagues (1) in which they show that ACE2, the gene encoding the receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is expressed throughout the human airway epithelium. They also show a relative increase in the expression of ACE2 in airway epithelial cells derived from smokers. In addition, men who smoke have a higher expression of ACE2 than women. TMPRSS2, a cellular protease that facilitates viral entry, is also increased in the small airways of smokers. These data support the notion that smoking may pose a greater risk of SARS-CoV-2 respiratory infection and subsequent development of coronavirus disease (COVID-19). However, whether this explains the higher male susceptibility to COVID-19 is not yet clear (1).

As of June 1, 2020, the COVID-19 pandemic has now spread to more than 180 countries, infecting 6 million people globally and resulting in more than 360,000 deaths (2). SARS-CoV-2 is highly transmissible and can spread readily from human-to-human, causing acute and severe respiratory failure, often followed by death. This scenario appears to be even more likely in patients with preexisting health conditions and other comorbidities, including diabetes and cardiopulmonary diseases.

We know that active smokers have an increased risk of respiratory tract viral infections and virus-related exacerbations in chronic obstructive pulmonary disease. Emerging research also suggests that current smokers and patients with chronic obstructive pulmonary disease have higher expression of ACE2 in the airway epithelium, type 2 pneumocytes, tissue macrophages, and ciliated airway epithelial cells (3, 4) and that this ACE2 expression may vary with sex and age (5).

Zhang and colleagues have further confirmed and extended these findings, showing that both ACE2 and TMPRSS2 expression are increased with smoking, and have provided new evidence that ACE2 expression is greater in the male population (1). Although new data are still emerging, earlier reports have suggested that COVID-19 mortality rates are higher in the male population (6). Of note, the upregulation of ACE2 may be useful in protecting the host against acute lung injury by producing proresolution peptides such as angiotensin 1–7; however, chronically elevated ACE2 in the lungs may predispose individuals to an increased risk of developing COVID-19.

Although it is becoming increasingly clear that ACE2 expression is induced by active smoking (1, 3), we are not aware of any studies that have evaluated exposure to electronic cigarettes (e-cigarettes), heat-not-burn devices (IQOS), or other electronic nicotine-delivery systems. Cigarette smoking appears to be an important risk factor that could further exacerbate this pandemic. We believe that new data on e-cigarette exposure both with and without nicotine may shed light on the nicotine-dependent effect, as suggested by Leung and colleagues (3), and the nicotine-independent effect, which we believe may also influence ACE2 expression in the airways. If there is a connection between such an exposure (i.e., electronic nicotine-delivery devices) and the risk of succumbing to COVID-19, then this risk extends to not only cigarette smoking but possibly also vaping via e-cigarette use.

Long-term safety studies with e-cigarette devices on humans are still lacking. However, the 2019 e-cigarette or vaping use-associated lung injury epidemic revealed the serious ill effects of vaping. Although many researchers have now shown the harmful effects of vaping, we first reported the deleterious effects of IQOS on human airway cells as compared with e-cigarettes and traditional cigarettes (7). Additional research is needed to investigate the relationship between smoking, other electronic delivery devices, and SARS-CoV-2 infection as well as its transmission and progression. This understanding will not only affect public health policies but may also shed light on important new therapeutic approaches.

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Reply to Sharma and Zeki

From the Authors:

We agree with Sharma and Zeki that the increased expression of ACE2 and TMPRSS2 in the small airway epithelium (SAE) in men and cigarette smokers may play a role in the increased susceptibility to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and that our findings are consistent with those of others (1–7). In response to their suggestion that exposure to electronic cigarettes (e-cigs) with or without nicotine may influence ACE2 expression in the airways, we evaluated our prior study assessing the SAE gene expression responses of healthy never-smokers after acute exposure to e-cigs (8). Ten nonsmokers matched for age, sex, and ethnicity with no history of exposure to tobacco products or e-cigs, were assessed at baseline; this included medical examination, routine blood studies, urine analysis, respiratory questionnaires, chest X-ray, and full lung function, followed by bronchoscopy to obtain SAE by brushing. All subjects were documented to be never-smokers on the basis of their self-reported smoking history and by the absence of urine tobacco metabolites. One week later, all subjects inhaled 10 puffs of a “Blu” brand e-cig (first exposure) and 30 minutes later inhaled 10 more puffs (second exposure). Subjects were randomized to inhale e-cigs with (n = 7) or without (n = 3) nicotine. Two hours after the second e-cig exposure, all subjects were reassessed as at baseline, including bronchoscopy to obtain SAE. SAE cell differentials were similar in both exposure groups at both time points and before and after exposure within the same exposure group. Total RNA was extracted, processed, and hybridized on Illumina HiSeq 2500 (Illumina) (8). Genome-wide fragments per kilobase per million expression values are publicly available in the National Center for Biotechnology Information Gene Expression Omnibus (accession number GSE85121).

The SAE transcriptome at baseline was compared with the SAE transcriptome after e-cig exposure within each group using a paired t test using Partek Genomics Suite Software version 6.6 (Partek). A genome-wide analysis of n = 16,044 genes identified 71 genes significantly modified in the SAE after exposure to e-cigs with nicotine and 65 genes significantly modified in the SAE after exposure to e-cigs without nicotine (8). Neither ACE2 nor TMPRSS2 were among the significant genes in either comparison. Gene expression analysis of only ACE2 and TMPRSS2 before and after exposure demonstrated no effect on either ACE2 or TMPRSS2 of e-cigs with or without nicotine (Table 1). Thus, at least for this brand of e-cigs, acute exposure does not affect ACE2 or TMPRSS2 expression, in contrast to cigarette smoke exposure (1). However, only one e-cig brand was evaluated, and e-cig smoke likely varies among brands and added flavorings (9–13). Thus, although our data related to acute e-cig exposure do not show an effect on ACE2 or TMPRSS2 expression, we agree with Sharma and Zeki that further studies of use of e-cigs are warranted because chronic use and different formulations could have an effect on SARS-CoV-2 expression.

Table 1. Expression of ACE2 and TMPRSS2 in the SAE of Healthy Nonsmokers before and after Acute Exposure to E-Cigarettes

| SAE Population | E-cig with Nicotine (FPKM) | E-cig without Nicotine (FPKM) |
|----------------|---------------------------|-------------------------------|
| ACE2§ | Preexposure 0.9 ± 0.5 | 0.7 ± 0.4 |
|       | Postexposure 0.6 ± 0.2 | 0.7 ± 0.1 |
|       | P value‡ >0.1           | >0.3 |
| TMPRSS2§ | Preexposure 22.5 ± 5.0 | 22.1 ± 2.2 |
|       | Postexposure 21.9 ± 4.3 | 23.4 ± 1.9 |
|       | P value‡ >0.6           | >0.05 |

Definition of abbreviations: E-cig = e-cigarette; FPKM = fragments per kilobase per million; SAE = small airway epithelium.

*SAE was assessed in never-smokers (n = 10) before and after acute exposure (2 × 10 puffs, 30 min apart) to “Blu” brand e-cigarettes.
†A random sample (n = 7) of the nonsmokers was exposed to e-cigarettes with nicotine.
‡A random sample (n = 3) of the nonsmokers was exposed to e-cigarettes without nicotine.
§The expression of each of the genes was compared before exposure (baseline) and after exposure (Day 7) within each group of exposure, separately.

P values were calculated using a paired t test.

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