

# Angiotensin Converting Enzyme-2 (ACE2) Receptors, Asthma and Severe COVID-19 Infection Risk

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To editor,

Asthma is one of the most common chronic respiratory diseases in the world and it is possible that asthma-related factors may influence susceptibility to coronavirus disease (COVID-19) or infection severity. There is a great concern about the effect of asthma on COVID-19 morbidity: Centers for Disease Control and Prevention (CDC) stated that people with moderate to severe asthma may have an increased risk for COVID-19 and infection may lead to an asthma attack, pneumonia, or acute respiratory disease. However, available data is limited and there is no concrete evidence that asthma is a risk factor for COVID-19. In Zhang et al. study including 140 community-infected COVID-19 patients, asthma or other allergic diseases were not reported by any of the patients<sup>1</sup>. Although the prevalence of asthma in China was 4.2% and allergic rhinitis in Wuhan was 9.7%, allergy or asthma was not detected as a risk factor for COVID-19 infection [1]. In another article from Wuhan, Li et al. reported the prevalence of asthma as 0.9% in 548 patients with COVID-19 and the asthma rate did not differ between severe and non-severe COVID-19 cases<sup>2</sup>.

Angiotensin converting enzyme-2 (ACE2) receptors mediate the entry of SARS-coronavirus 2 (SARS-CoV-2) into host cells and the virus uses the transmembrane protease serine 2 (TMPRSS2) for S protein priming<sup>3</sup>. ACE2 receptors are expressed in the heart, vessels, gut, lung, kidney, testis, and brain<sup>4</sup> and binding of SARS-CoV-2 to ACE2 receptors markedly down-regulates ACE2 receptors which have protective biological effects on human body. With the loss of the protective effect of these receptors interstitial fibrosis, endothelial dysfunction, enhanced inflammation, oxidative stress and increased coagulation can be seen<sup>5</sup>. It is interesting to note that severity of the COVID-19 disease is associated with several conditions which may have ACE2 deficiency such as older age, male gender, hypertension, diabetes, or cardiovascular disease.

There may be a link between asthma and ACE2 deficiency and based on this hypothesis Peters et al. investigated differences in ACE2 and TMPRSS2 gene expression in sputum cells of 330 asthma patients and 79 healthy controls<sup>5</sup>. Gene expression of ACE2 and TMPRSS2 was similar in asthma and health. Among asthma patients, higher expressions of ACE2 and TMPRSS2 were observed in males, African Americans, and patients with diabetes mellitus. High expression of ACE2 in the lungs facilitate the entry of corona virus into lungs and may result with down-regulation of ACE2 receptors which make these subgroups more susceptible to severe SARS-CoV-2 infection. Interestingly, use of inhaled corticosteroids was associated with lower expression of ACE2 and TMPRSS2 after adjustment for asthma severity.

This is an important study giving clues about possible factors explaining the low prevalence of asthma among COVID-19 patients. Asthma itself or the use of inhaled steroids may have protective effect against SARS-CoV-2 infection. However, there are some limitations. ACE2 receptors are particularly expressed in type 2 pneumocytes which have an effective role on triggering a cascade of inflammation in the lower respiratory tract. Sputum may not reflect the amount of ACE2 receptors in the lower respiratory tract including type 2 pneumocytes. Many of the inhaler steroids have less peripheral airway deposition and so inhaler steroids might not effect ACE2 expression of type 2 pneumocytes. Although direct evidence regarding the role of

ACE2 in chronic obstructive pulmonary disease (COPD) and smokers is limited, studies have shown that accumulation of inflammatory cells and the release of proinflammatory cytokines in COPD were mediated by angiotensin II in which ACE2 has an active role in degradation of angiotensin II<sup>6</sup>. There are also rat studies indicating that ACE2 deficiency may have a role in the pathogenesis and progression of COPD. It is reasonable to infer that ACE2 deficiency in COPD may have a negative effect on severity of SARS-CoV-2 infection like diabetes and hypertension. Smoking status of the patients and asthma endotypes (eosinophilic or neutrophilic, atopic, non-atopic) were not provided in Peters et al study. ACE2 and TMPRSS2 expression in sputum may be different in smokers, neutrophilic asthma, or asthma-COPD overlap (ACO) subgroups and inhaled steroids may not influence ACE2 expression in these subgroups.

Asymptomatic nasal carriage of COVID-19 is more common in children, asthmatic children seems to have most likely asymptomatic COVID-19 infection. Therefore to understand the basic underlying mechanisms related with childhood asthma and mild COVID-19 infection may help to understand the possible mechanistic links for adult asthma and severe COVID-19 infection. Sajuthi et al. used nasal airway transcriptome and network co-expression analysis to identify the cellular and transcriptional factors in COVID-19 infectivity<sup>7</sup>. They used a children cohort including 695 subjects with asthma and healthy controls between the ages of 8 and 21. They mainly focused on ACE2 and TMPRSS2 expression. Interestingly, 43% of non-asthmatics in this study were scored as T2-high like asthmatics based on their expression profile. They found that interleukin (IL)-13 mediated T2 high inflammation had a major role in ACE2 downregulation and TMPRSS2 upregulation. The results of this study can be interpreted as T2 rich inflammation may have protective role against COVID-19 by causing ACE2 downregulation or exacerbates COVID-19 infection by causing TMPRSS2 over expression. They showed that ACE2 was expressed in secretory cells and ciliated cells while TMPRSS2 was expressed by all epithelial cell types<sup>7</sup>. Virus behavior may be different depending on ACE2 and TMPRSS2 expression variations in different part of the airways such as nasal and peripheral airways and TMPRSS2 may have more effective role in peripheral airways compared to ACE2.

In conclusion, it is yet to be proved that asthma is a risk factor for COVID-19 infection. Whether there is a link between asthma and COVID-19 infection remains to be determined. The heterogeneous nature of asthma may cause interindividual variation in COVID-19 infection immunology. More clinical studies focusing ACE2 and TMPRSS2 expression in central and peripheral airways are warranted to understand the role of individual factors such as atopy, obesity and smoking habit and treatment related factors such as inhaled/systemic steroid use in different asthma groups (mild/severe, T2-high and T2- low asthma) for the risk of COVID-19 morbidity.

## References:

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