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Smoking and COVID-19: Renin-Angiotensin System the Hidden Link

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Abstract

The emergence of COVID-19, the global pandemic is originated from the Nobel member of the coronavirus family, i.e. SARS-COV-2 initially seen at Wuhan city of China since December 2019 have deeply impacted the lives of people and changed the way of our living. The pandemic has led to the death of thousands of people mostly seen in old age people, people having co-morbidity like cardiovascular disease, diabetes mellitus, obesity, kidney disease, etc. and cigarette smokers. It is found that cigarette smokers are more prone to the COVID-19 infection and have more severity of the disease when infected. From various studies, it has been revealed that there is increased pulmonary ACE2 expression in ever smokers and virus leading to an imbalance in the RAS appears to be an important cause for cigarette smokers which is being impacted more in this pandemic. This review article explains the underlying mechanism why smokers are more prone to COVID-19? and why higher severity of the disease is higher in them?

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INTRODUCTION

The World Health Organization identified a Nobel member of coronavirus in early 2020, which is named as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2). At present, it has infected more than 24 million and killed more than 831,000 across the world after its outbreak in china in December 2019. SARS-COV-2 fall in the coronaviridae family, and it is a positive sense, single-stranded RNA virus. This family commonly causes 10-30% of upper respiratory infections in humans. The virus is spread mainly through respiratory droplets from an infected person when coughing, sneezing and talking. The symptoms which are mostly seen in COVID-19 are pyrexia, dry cough and dyspnea, tiredness, scratchiness in throat, body aches, nasal congestion, headache, loss of taste or smell, diarrhoea. People of all ages, with certain underlying disease conditions such as asthma, heart disease etc. seem to be more susceptible and have severe illness or complications from COVID-19 infections.

Cigarette smoking is a prominent aetiology for chronic disease and death due to many pulmonary infections. Several observational studies found 1.4-18.5% of hospitalised adults who are smokers among coronavirus infected patients (Rajko, 2020). And certain investigators observed a pooled prevalence of 6.5-7.6% of smokers in hospitalised adults with this infection (Emami *et al.*, 2020; Farsalinos *et al.*, 2020). Approximately, smokers were 2.4 times higher chances to get admitted in the intensive care unit, needed Ventilator or die compared to

non-smokers with coronavirus infection (Vardavas and Nikitara, 2020). Liu et al., also found that the infected people with adverse outcomes had 27.3% of patients with a history of smoking (Liu *et al.*, 2020). Hence, recently WHO has reported that smoking increases risk as well as increasing the poor prognosis of disease and death among hospitalised SARS-COV-2 infected patient. It is peremptory to understand the underlying mechanism behind smokers being more susceptible to severe coronavirus infections to alleviate such transmissibility of this disease. This review paper focuses explicitly on pathophysiology between smoking and COVID-19 and the critical role played by the RAS pathway in this link as well as in the severity of this disease.

Renin-angiotensin system (RAS)

Our understanding of Renin-angiotensin system has changed radically after the identification of angiotensin-converting enzyme 2 (ACE2) since 2000. The circulating RAS has well-defined importance in maintaining normal blood pressure. Local RAS have now been explained for many tissues which appear to play a role in the inflammatory response (Marshall, 2003). SARS-COV-2 interrupts the RAS pathway by utilising the ACE2 receptor, which plays a vital role in the pathogenesis of the COVID-19.

Classically, juxtaglomerular cells of kidney secrets the inactive prorenin, which is cleaved into renin by the activation of juxtaglomerular cells. When renin is circulated in the blood, it acts on the angiotensinogen which is in the blood produced by the liver. Renin cleaves the angiotensinogen into angiotensin I which is functionally inactive but is an essential protein for the production of angiotensin II. The conversion of the Angiotensin I into Angiotensin II is catalysed by Angiotensin-Converting Enzyme (ACE). Angiotensin-Converting Enzyme 2 (ACE2) is involved in the conversion of angiotensin II into Angiotensin $_{(1-7)}$ (Ang $_{(1-7)}$) and Angiotensin $_{(1-9)}$ (Ang $_{(1-9)}$).

Angiotensin II remain fully functional by promoting inflammation, thrombosis and pulmonary oedema with respiratory insufficiency. Angiotensin II (AngII) acts on the Angiotensin Type 1 receptor (AT1) promoting Reactive Oxygen Species (ROS) synthesis (Petcu *et al.*, 2020). Moreover, ROS along with Angiotensin II activates MAP kinase, protein, tyrosin Phosphatase, tyrosine kinase as well as RhoA/ Rho cellular kinase enhancing vascular contraction, vascular senescence and inflammation (Petcu *et al.*, 2020). Angiotensin II acting on Angiotensin Type 2 receptor (AT2) have opposite effect leading to platelet aggregation, vasodilation, promotes insulin action but an expression of AT2 receptor is low in healthy adults. Angiotensin $_{(1-7),}$ which is lung protective acts on the Mas receptor and have the opposite effect of Angiotensin II. It is involved in vasodilation, reducing fibrosis, inflammation and thrombosis.

Conceptually, grouping RAS system into ACE/ ANG II/ AT1 receptor pathway as an inflammatory pathway and ACE2/ Ang $_{(1-7)}$ / Mas receptor pathway as anti-inflammatory pathway helps to understand better the countering force and consequences when an imbalance occurs. Disruption in the lung ACE2 expression can lead to direct blocking of pulmonary ACE2/ Ang $_{(1-7)}$ / Mas receptor pathway, which causes inflammation, vasodilation, fibrosis, thrombosis resulting in lung injury.

There seem to be the high possibilities for the local generation of Ang II in the lung by the activation of Pulmonary RAS in SARS-COV-2 infection. This theory is supported by the expression of Angiotensinogen (A_0), AT1 receptor, AT2 receptor, ACE, ACE2 and renin (Marshall, 2003; Kuba *et al.*, 2006; Montes *et al.*, 2012). A study conducted on 12 COVID-19 patients helped to find an increased plasma level of Ang II than a healthy individual. It was strongly associated with viral load and severity of lung injury (Sarzani *et al.*, 2020). Therefore, this evidence helps to conclude the involvement of both classic and pulmonary RAS in the pathogenesis of COVID-19.

Cigarette smoking and upregulation of ACE2

Coronavirus primarily spreads by viral inhalation, and the infection is predominantly seen in the lungs of humans and rodents, where the ACE2 is expressed as a RAS pathway regulator (Hoffmann *et al.*, 2020). It is well established that *Angiotensin-converting enzyme 2 (ACE2)* is the central receptor of SARS-COV-2 and SARS-COV to enter the cell (Hoffmann *et al.*, 2020). So aetiology, which affect the *ACE2* expression in lungs and other airway tissues are critical in coronavirus infection. Cigarette smoking is one among such factor that effects ACE2 expression. In a study done by Wang et al., they observed that there is an increase in ACE2 expression in the intrapulmonary airway and oral epithelial cells in smokers compared with non-smoker (Wang *et al.*, 2020). Experiments, such as with mice, showed a concentration-dependent rise in ACE2 activity with cigarette smoke exposure, in their lung tissues (Wang *et al.*, 2020). A similar concentration depended exposure was seen in patients who expressed high levels of ACE2 expressions as they had reported smoking the significant number of pack-years (Smith *et al.*, 2020). Cai et al. demon-

strated that the current smokers had the highest ACE2 gene expression followed by formers smokers and then non-smokers (Cai *et al.*, 2020). This altogether substantiates the fact that the activity of ACE2 receptor, especially in pulmonary parenchymal cells increases when exposed to cigarette smoking.

Goblet cell hyperplasia induced by smoking

A differentiated human respiratory epithelium contains various cell types such as 50-70% of ciliated cells, 11% of club cells formerly known as Clara cells, 25% of goblet cells (secretory cells) and 30% of basal cells (Schamberger *et al.*, 2015). Till terminal bronchioles, humans have pseudostratified epithelium which mainly consists of ciliated, basal and secretory cells: that is predominantly goblet cells, which produces mucus to protect airways (Schamberger *et al.*, 2015). Alveolar compartment consists of pneumocytes such as *alveolar type 1* and alveolar type 2 cells alveolar cells. Cigarette smoke contains more than 5000 chemicals, many of which are toxic to the respiratory epithelium. An increase in the number of goblet cells and, an increase in upper respiratory tract secretion and, metaplastic alterations to the respiratory mucosa are caused by this smoke (Tamashiro *et al.*, 2009). Schamberger et al. illustrated that chronic exposure to CSE (cigarette smoke extract), alters basal cell differentiation and function (Schamberger *et al.*, 2015). Goblet cell number was increased, when bronchial cells were exposed to this CSE during the cell differentiation process (Schamberger *et al.*, 2015). Apart from this in an invitro respiratory tract tissue model of human, cigarette whole smoke solutions induced dose – time related hypersecretion of mucins 5AC and 5B, together with upregulation of respective mucin genes (Cao *et al.*, 2018). Increased goblet cells and mucin gene expression also occurs with increased mucin secretion. Duclos et al. did a study., found that smoking cigarette remodelled tissue with loss of club cells and extensive hyperplasia of goblet cells in their bronchial epithelium, which attributes to the fact that smoking leads to increase in the population of goblet cells (Duclos *et al.*, 2019).

ACE2 Expression in goblet cells

Normally, mammalian lung epithelium, ACE2 expression is in high levels in secretory club and goblet cells and Alveolar type 2 cells. It is to be noted that ACE2 expression was seen in goblet cells of current smokers and club cells of non-smokers in bronchial epithelium and expressed in remodelled alveolar type 2 cells of former smokers in alveoli (Cai *et al.*, 2020). In the recent study conducted by Smith et al., observed that the smoker's airways had a significant expansion of secretory cell compartment and that ACE2 was highly expressed in MUC5AC+ secretory cell cluster in a single cell transcriptase collected from the trachea of both current and never smokers (Smith *et al.*, 2020). The number of ACE2+ positive cells and ACE2 expression within ACE2+ cells was increased due to smoking (Cai *et al.*, 2020). This increase is due to the hyperplasia of the secretory cell compartment. The expression of mucus-secreting goblet cells that co-express ACE2 caused an increase in ACE2 expression in smoker's respiratory tract. Hence altogether, cigarette smoking induces the expansion of a subset of lung secretory cell, which expresses coronavirus receptor ACE2, which is said to be increased clearly.

Upregulation of ACE2 due to lung protective action

The possibility of upregulation of ACE2 expression due to its lung-protective action cannot be ruled out. Pulmonary ACE2 plays a crucial role in maintaining the balance of circulation Angiotensin II / $Angiotensin_{(1\text{-}7)}$ levels. Angiotensin II-mediated cell signalling is antagonised by $angiotensin_{(1\text{-}7)}$. ACE promotes severe lung failure by upregulating Angiotensin II through Angiotensin type 1 receptor in the pathogenesis of acute lung injury. In contrast, ACE2 and Angiotensin type 2 receptor protect against lung injury. Yilin et al. demonstrated a similar theory, where they established lung injury due to smoke inhalation in rats, who expressed high levels of ACE and ACE2 in their lungs after smoke inhalation (Yilin *et al.*, 2015). According to their explanation, there would be a gradual increase in Angiotensin II due to generation of ACE. And the body would have increased the expression of ACE2 to cease Angiotensin II reactions which can lead to severe lung injury, thereby counterbalancing the ACE effects, caused by smoking (Yilin *et al.*, 2015).

Smokers are more prone to covid-19

The meta-analysis conducted by Amos et al. showed that ever smoking increased pulmonary ACE2 expression by 25% (Cai *et al.*, 2020). It was also found upregulation of pulmonary ACE2 gene activity in ever-smoking while comparing with non-smokers irrespective of tissue subset or COPD status and suggesting a dose-dependent response (Cai *et al.*, 2020; Leung *et al.*, 2020).

The virus main entrance is through the nose, mouth, upper respiratory tract and affects the respiratory system initially lead to viral pneumonia, acute lung injury, dyspnea, etc. The respiratory system contains abundant of ACE2 expression. The research article published by Hoffman et al. pro-

vided the unambiguous evidence that SARS-COV-2 enters through the ACE2 receptor, which is also used by SARS-COV (Hoffmann *et al.*, 2020). SARS-COV-2 initially affects the pulmonary system and ACE2 expression in this region is highly increased in the ever-smokers as per the various studies conducted and compared with healthy individuals or former smokers (Cai *et al.*, 2020) Therefore, increased ACE2 Expression in lungs appears to play the role for a higher rate of infection in ever smokers. Since ACE2 receptor appears to be the main receptor for the SARS-COV-2 for entry in the host cells, long term cessation of smoking can help to reduce the probability of getting infected.

Severity of disease in smokers

Smoking has been linked as an etiological factor for poor prognosis in COVID-19. Current smoking is found to have low recovery in patients with sepsis and septic shock along with the development of Acute Respiratory Distress Syndrome (ARDS) in a hospitalised patient (Lang, 2020). A study conducted by lang et al. found that smokers were two times more prone to die compared to non-smokers in a hospitalised patient when suffering from viral pneumonia which includes coronavirus (Lang, 2020).

However, according to WHO, there are no proper studies available which directly describes the severity of disease linking with COVID-19 in smokers. The meta-analysis conducted by the Zheng et al. and Zhao et al. found a prominent association between smokers and chronicity of disease in COVID-19 patient (Rajko, 2020).

Generally, the expression of ACE2 is low in a healthy individual and decrease with age, due to smoking, there is a dose-dependent increase in ACE and ACE2). Chronically, elevated ACE2 expression evidence suggests compensation rather than causal. Based on the studies conducted in the animal model, have revealed the SARS-COV-2 down regulates the ACE2 functional receptor only found in the lung (Petcu *et al.*, 2020). The down regulation of ACE2 leads to inhibition of ACE2/Ang$_{(1-7)}$/Mas receptor pathway and over activity of ACE/Ang II/ AT1 receptor pathway, this imbalance leads to promoting inflammation, thrombosis, fibrosis, pulmonary oedema with respiratory insufficiency. Similarly, an experiment conducted on the mouse using SARS-COV infection model, it showed that when ACE2 knockout mice are infected, they became resistant to virus and the viral load was 10^5 times lower than that of the lung of infected wild type mice (Kuba *et al.*, 2006). This study helps to understand that reason for low severe cases in non-smoker or former smokers than ever smokers in COVID-19 patients.

Additionally, it is found that cigarette smokers have higher serum Tissue Necrosis Factor-α (TNF-α) and Interleukin-6 (IL-6) compared with non-smokers (Voican, 2010; Jamil *et al.*, 2017). It suggests an imbalance in the pro-inflammatory and anti-inflammatory factor as a result of tobacco smoke exposure. IL-6 is involved in inflammation, the immune response and hematopoiesis, TNF-α is involved in the regulation of the inflammatory process, infectious disease and malignant tumour. In COVID-19 patient, various studies have revealed IL-6 and TNF-α is markedly higher in patients with poor prognosis with more severe symptoms (Costela-Ruiz *et al.*, 2020). It is seen that patient having higher IL-6 level had a higher mortality rate compared to those who recovered from COVID-19 (Costela-Ruiz *et al.*, 2020). SARS-COV-2 activates Interleukin-1β (IL-1β) which in turn activates IL-6 and TNF-α leading to an inflammatory process, contributing to cytokine storm and worsening the prognosis of the disease (Costela-Ruiz *et al.*, 2020).

CONCLUSION

From the various studies, it reveals increased pulmonary expression of ACE2 in ever smokers as an important cause for a higher rate of infection. Cessation of smoking for long-term can helps to reduce over expression of pulmonary ACE2, which reduces the susceptibility of infection compared to ever smokers. Down regulation of the pulmonary ACE2 by SARS-COV-2 leads to an imbalance in the RAS and smokers have higher expression of ACE which leads hyperactivity of inflammatory ACE/ AngII/ AT1 receptor pathway leading to thrombosis, fibrosis, oedema, respiratory insufficiency. The higher plasma level of IL-6 and TNF-α appears to play the synergistic role in the worsening prognosis of the disease.

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Conflict of interest

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