ASSOCIATION OF ACE EXPRESSION AMONG HYPERTENSION PATIENTS IN COVID - 19 PANDEMIC

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ABSTRACT

The present review provides valuable information about the ACE expression and its association with hypertension in COVID-19 patients. The potent use of angiotensin converting enzyme inhibitors, found to increase the ACE expression in hypertension and cardiovascular diseased patients which leads to acute lung injury. Currently there is no clear evidence that impact use of ACEI or ARBs could increase the severity of COVID -19 infection in hypertensive patients.COVID -19 being an infectious disease increases the mortality and morbidity of patients with hypertension. Previous studies have been reported that hypertension is considered as a prognostic indicator in SARS nCov infection. Few studies have also reported that there is no significant association of ACE expression with Covid 19. Review data was collected using the recent articles searched from PubMed, the google scholar, core, Cochrane, from 2000 to 2020. The present review highlights all the possible factors between ACE expression among hypertension patients and covid disease.

Keywords: ACE expression, COVID -19, hypertension, SARS - COV

INTRODUCTION

The recent outbreak of novel coronavirus from Wuhan, China is an infectious disease also known as Severe acute respiratory syndrome (SARS). The transmission of virus from human to human through the respiratory droplets, appears to be asymptomatic with an incubation period of 14 days [1,2]. The clinical features of COVID -19 reported as cough, sore throat, fatigue, dyspnea, severe respiratory infection, in which a patient requires high intensive care treatments [3,4]. The COVID-19 infection leads to severe viral pneumonia, as the patient needed supportive care and oxygen supplementation [5,6]. The outer structure of a novel coronavirus consists of highly dense glycosylated spike S protein which binds to the angiotensin-converting receptor 2 in the lungs within the host cells [7,8]. A previous study has reported diabetes and hypertension were the two major risk factors associated in COVID-19 affected patients [9]. Systemic arterial hypertension is one of the major risk factors and mortality worldwide due to abnormal blood pressure mechanisms. Renin-angiotensin aldosterone system plays a pivotal role in regulating blood pressure [10].

An Angiotensin converting enzyme is a group of dipeptidyl carboxypeptidase which converts AngI to Ang II. Angiotensin converting enzyme 2 acts as a co-receptor for the viral entry of SARS - Cov2, plays a vital role in the progression of COVID-19 disease. A previous clinical study has reported that

Angiotensin converting enzyme inhibitors and receptor blockers were reported to increase the mortality rate of patients affected with COVID-19 infection. A similar study has been evaluated that diabetes and hypertension patients, who are treated with ACE2 stimulating drugs, will have increased risk of COVID-19 infection [11,12]. A similar study has been revealed that there is a significant link between the ACEI and SARS. It was found that ACE inhibitors and angiotensin receptor blockers are frequently used by the patients affected with heart disease and hypertension [13,14]. A previous study has reported that, apart from ACEI, N6- adenosine methylation (m6A) has been a new molecular target gene which affects hypertension and cardiovascular diseases [15,16]. The epidemiological study in China has revealed that hypertension is associated with increased mortality and morbidity of COVID-19 affected patients [17],[18]. The present review highlights the association of ACE expression among hypertensive patients in COVID -19 pandemic.

ROLE OF ACE IN HYPERTENSION

The angiotensin-converting-enzyme is a dipeptidyl carboxypeptidase significant in the Renin Aldosterone Angiotensin (RAA) system, which regulates blood pressure. This angiotensin system consists of a regulatory natriuretic peptide which stimulates diuresis and vasodilation. ACE 2 plays an important role in the conversion of Ang I to Ang 1-9. Angiotensin 1- 9 is a counter regulatory peptide that reduces adverse cardiovascular hypertrophy, fibrosis and hypertension [19,20]. Angiotensin-converting enzyme generates angiotensin II, a potent vasoconstrictor which acts to counterbalance the effect of ACE and releases angiotensin II , a vasodilator. The role of this vasodilatory effect as a link between the pathogenesis of COVID-19 is found to be unclear. But some animal studies have revealed that ACE 2 and angiotensin (1-7) found to be protective in different lung injury models [21]. The ACE 2 receptor which is present in epithelial cells of lungs, intestine, heart is the pathway for the entry of viruses. The chronic administration of ACE inhibitors was found to increase the ACE2 expression in pneumocytes of the lungs. A previous systematic review done by Caldeira et al has been proved that the effect of ACE inhibitors increases the risk of CAP and pneumonia in covid affected patients. Few studies have been reported that the administration of renin angiotensin system inhibitors found to make the symptoms of COVID-19 severe and resulted in increased expression of ACE 2 receptors in the lungs [22,23]. It has been proven that the ACE 2 receptor affected by ACE inhibitors causes differential regulation of ACE and AT1 receptors which leads to left ventricular failure in the hypertensive patients [24,25].

INTERACTION OF SARS n- COV IN RENIN ANGIOTENSIN SYSTEM

The spike protein present in the SARS nCov , facilitates the entry of virus into target host cells. The ACE 2 receptor has a broad expression pattern in the gastrointestinal system, heart, and kidney and liver tissues. ACE 2 and TMPRSS2 are the two receptors present in the epithelial cells of the respiratory tract , which supports the spread of viral infectious disease. The efficiency of SARS Cov interaction between S-protein and ACE-2 receptor is a key determinant factor for the viral replication and rate of spread and severity of the infection. Many studies have been reported that ACE inhibitors mainly, enalapril and lisinopril found to increase the risk of lung injury in covid affected patients. Few studies have been reported that activation of Ang II -AT1R , influences the pathogenicity of SARS -COV infection and down regulates the ACE 2 expression in lungs. There is no significant data related to down regulation of ACE 2 expression in human beings . But few experimental studies have indicated an age dependent decrease in the pulmonary ACE 2 expression with viral infection. A significant reduction in the inflammatory mediator and ACE 2 substrate in lungs, associated with the activation of bradykinin, resulted in severe lung inflammation due to the endotoxin inhalation in an experiment mice models. There is considerable evidence in animal models as well as in human beings, showing the increased expression of ACE 2 receptors in the heart and brain after the treatment with ARBs and ACEI [26] (Figure1).

HYPERTENSION - MAJOR RISK FACTOR IN COVID - 19 DISEASE

Hypertension is considered as the prognostic indicator in COVID -19. Many studies have reported that association of hypertension found to be high comorbidity with a viral infection. A study has also stated there is no sound evidence that hypertension would be a major risk factor in COVID -19 as ACEIs and ARBs also lower the incidence and improves the outcome of patients with lower respiratory tract infections. ARBs, ACEI, are found to directly inhibit ACE 2 receptors in the lungs increasing patient susceptibility to viral host cell entry and propagation. A cohort study done among 576 hypertensive adults found that there is an increased risk of pneumonia with the use of angiotensin-converting enzyme inhibitors [27]. The possible pathogenic link between hypertension and COVID-19 is also associated with the inflammatory dysregulation of IL -6. The hyper inflammation of interleukin IL-6 resulted in severe respiratory infection with pneumonia as , it has been produced by the lung epithelial cells. A previous study has reported , the effect of cytokine storm in an inflamed individual , leads to an increased ACE2 expression in lungs [28]. Another study also shows that if there is a high immunosenescence profile in CD8 cells , it leads to the production of cytokines which resulted in less efficiency in the antiviral defence mechanism [29,30].

The prevalence rate of hypertension has now been increased worldwide. It is usually observed as a frequent comorbidities in elderly aged people , who are more prone to COVID - 19 infection [31,32]. A population based study reported by Fang et al in China, found that 23% of hypertension patients have been affected by COVID-19. A similar data based study done among 20,982 covid affected patients, showed that about 12.6 % of them were self reported hypertensive patients. A clinical study reported that antihypertensive drugs, such as ARB blockers typically increase ACE2 expression with two-fold to five-fold in hypertensive patients [33]. A recent meta-analysis study among the Chinese population reported that about 15 percent of COVID-19 people are affected by hypertension [34]. Furthermore , about 30 percent of people who were tested as covid positive were frequently treated with angiotensin converting enzyme inhibitors and angiotensin receptor blockers. European countries are mostly affected by COVID - 19 with an increased mortality rate. The severity rate of hypertension ranges from 20 % to 35%, which is mainly related to age, ethnicity of the people affected with cardiovascular diseases [35] . Few studies have been reported that there is an independent association between COVID-19 infection and hypertension [36].

UPREGULATION OF ACE EXPRESSION:

Hypertensive patients have increased risk of COVID -19 progression due to the upregulation of ACE2 receptors present in the lungs which leads to severe respiratory infection. Previous clinical studies have reported that hypertension as a major risk factor with an increased mortality rate in the patients who are suffering from SARS and MERS. It has been hypothesized that excessive activation of the RAS system might also contribute to the progression of COVID-19 with severe lung injury [37,38]. Few studies have discussed that ACE expression is not associated with hypertension, but experimental studies have concluded that there is an increased ACE 2 expression when ACE inhibitors are infused into mice. This leads to severe lung injury and organ damage due to high viral load into the tissues. The viral load of SARS nCov mainly present in oropharyngeal saliva used for monitoring Covid infection. Several studies have also reported that there is an upregulation of ACE 2, during the treatment with ACEI. The type and dosage of RABs play a pivotal role in the ACE expression. A clinical study done on the effect of RAS blockade, shows that there is a significant increase in the urinary excretion in hypertensive patients when treated with ARBs for more than one year [39,40]. Impact use of angiotensin receptor blockers in hypertension and cardiovascular diseased patients are more likely prone to renal and lung injury. Thus hypertension, also found to be a significant factor among the people with cardiovascular problems and

other risk factors such as diabetes, kidney and liver damage. A recent study has proved that the inhibition of RAS mechanisms will lead to the high virulence of SARS-CoV-2 within the lung and heart tissues, which increases the severity of covid infection. As there is no specific treatment or vaccines of COVID -19 infection, the incidence rate and severity of this infectious disease have increased worldwide. Many clinical studies are ongoing to find out the effective treatment for this pandemic disease. But the definite association of hypertension with covid infection is likely to be less, though it is found to be confounded with age and comorbidities of patients [41,42].

CONCLUSION

COVID -19 being an infectious disease increases the mortality and morbidity of patients with hypertension. With many studies documenting the role of ACE receptors in CoV entry and fusion there is no clear evidence that impacts the use of ACEI or ARB's could increase the severity of COVID-19 infection in hypertensive patients. Few studies have also reported that there is no significant association of ACE expression with COVID-19. Thus, the future scope urges further experimental validation to acquire a clear pathogenesis of ACE expression associated with hypertension and other related diseases. In this context, this review had provided an overview on the association of ACE expression among hypertensive patients in COVID -19 pandemic.

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Author contribution:

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1. Execution of the work
2. Data collection
3. Drafting of manuscript

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1. Concept and design of the study
2. Validation of the data collection
3. Revision and proof- reading of the review

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Legend for figures:

Figure 1: ACE expression resulting in COVID - 19 progression in hypertension patients.

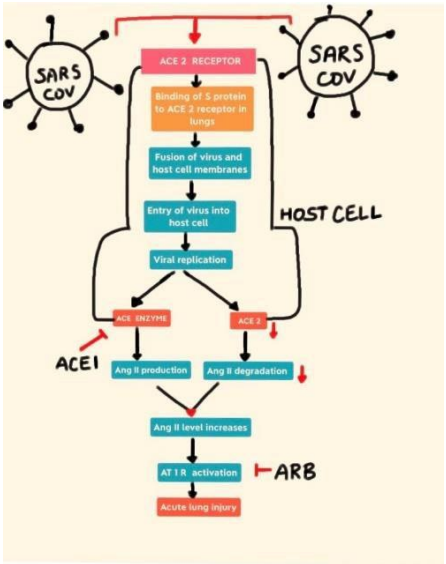

Figure 1: ACE expression resulting in COVID - 19 progression in hypertension patients. SARS COV - Severe Acute Respiratory Syndrome (Coronavirus); ACE - Angiotensin Converting Enzyme ; Ang II - Angiotensin; ACEI - Angiotensin Converting Enzyme Inhibitors; ARB - Angiotensin Receptor Blockers; ACE 2 - receptor in lungs.