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REVIEW ON PATHOGENESIS OF VARIOUS COMORBIDITIES IN COVID-19 AND HOMOEOPATHIC IMMUNOMODULATION

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ABSTRACT

Background: COVID -19 infection has already became pandemic with a heightened mortality. The emerging data suggest that there is an increased association of COVID-19 with comorbidities. The aim of this study was to understand the association between various comorbidities and COVID-19, probable pathophysiological mechanism leading to direct and indirect damage of the system and also to find whether Homoeopathy can offer anything at the pathogenetic level for controlling the infection.

Methods: A systematic search on all the available relevant articles and research publications in the English language was made on Pub Med database and Google Scholar using the Mesh key words 'COVID-19', 'comorbidities', 'diabetes ', 'hypertension', 'cardiovascular disease', 'kidney', 'pathogenesis' till June 7 2020.

Result: The probable pathophysiological mechanism of various comorbidities in COVID-19 were analysed. The expression of ACE2 in various locations can be considered as the main determinant of pathological damage in the system which results in the internalisation of organism triggering to inflammatory response such as a cytokine storm along with the rise of other inflammatory biomarkers can be a suggested mechanism in hypertension, diabetes, cardiovascular disease and acute kidney injury. The evidence obtained from the studies suggested that homoeopathic treatment has the potential for individual-specific immunomodulation and it is effective in upregulating T lymphocytes such as CD4, CD8 and CD4:CD8 ratio.

Conclusion: The increased level of cytokines (cytokine storm) as a result of release of inflammatory cells in addition to ACE2 activity can be a definite cause which can lead to the organ damage and multiorgan failure which favours the progression of disease in COVID 19. Since the immunomodulatory function of different homoeopathic drugs are already been identified and it can be utilised for the upregulation of the immunological activity in the system.

Keywords: comorbidities, ACE2, cytokine storm, immunomodulation

INTRODUCTION

COVID -19 is an on-going pandemic caused by the Severe Acute Respiratory Syndrome Corona Virus -2 (SARS– CoV 2) with more than 9 million infected cases around 216 countries with almost 4 lakh confirmed deaths. (1) In India, so far more than four lakh cases have been reported with around 13 thousand deaths till June 21,2020. (2)

The clinical spectrum of COVID-19 is heterogeneous ranging from mild symptoms like fever, dry cough, fatigue, sputum production, shortness of breath, sore throat, headache, myalgia, nausea or vomiting, diarrhoea to severe symptoms such as pneumonia, ARDS, dyspnoea and critical complications like septic shock and multi organ failure (3).

The higher prevalence of SARS-CoV-2 is seen among older people (4)and in those with pre-existing conditions such as hypertension, diabetes, cancer, heart failure and chronic obstructive pulmonary disease.(4,5)It is identified that SARS-CoV-2 can cause damage to the organs such as heart, liver and kidneys, organ systems such as blood and immune system other than lungs.(5)Most of the available studies have shown that patients associated with specific comorbidities have increased risk of infection and likely to have severe disease and worse outcomes leading to subsequent mortality. (6)

A review of available data was conducted as a trial to understand the association between various comorbidities and COVID -19 infection, so that the probable pathophysiological mechanism leading to direct and indirect damage of the system predisposing to increased morbidity and mortality can be recorded.

Homoeopathy through its holistic approach has stood the test of time over centuries and proved it worth as a prophylactic tool in controlling epidemics in the past, both in terms of morbidity as well as mortality. Along with the discussion of the possible pathophysiological mechanism related to COVID, it is also aimed to find whether Homoeopathy can offer anything at the pathogenetic level for controlling the infection.

METHODS

A systematic search on all the available relevant articles and research publications was made on Pub Med database and Google Scholar using the Mesh key words ‘COVID-19’, ‘comorbidities’, ‘diabetes ‘, ‘hypertension’, ‘cardiovascular disease’, ‘kidney’,

'pathogenesis 'till July,2020. Full texts of the retrieved articles that are published in English language were accessed.

RESULTS

SARS-CoV-2 is a beta corona virus like CoV-1 and it utilises zinc peptidase angiotensin-converting enzyme 2 (ACE 2) proteins for cell entry unlike Middle East Respiratory Syndrome (MERS) which utilises CD26. The cell entry is facilitated by the spike(S) protein. Therefore, the efficiency of interaction between S-protein and ACE-2 may be a key determinant which favours the transmissibility and replication of the virus and the severity of disease [7].

It is well known that ACE-2 is expressed in the Type I and Type II alveolar epithelial cells in the lungs and upper respiratory tract (considered as the predominant portal of entry) but it can be also expressed in other locations like heart, endothelium, renal tubular epithelium, intestinal epithelium and pancreas.[7,8]Eventually it may lead to the death of patient by multiple organ failure, ARDS, shock arrhythmias ,heart failure and renal failure. The expression of ACE2 on various organs could explain the multi organ dysfunction although the actual mechanism remains uncertain.[8]Those patients with comorbidities are at higher risk of tissue injury related enzymes release, excessive uncontrolled inflammation responses and hypercoagulable state favouring the progression and prognosis of COVID-19.Thus more attention should be paid to comorbidities in the management of COVID-19 which could improve patient outcomes.[9,10]

Evolving data suggests that the most common comorbidities associated with COVID-19 are diabetes, hypertension and cardiovascular disease although the prevalence rate are not consistent with different studies.[11] A hospital based case cohort study conducted in China comprising of 200 COVID-19 patients showed that comorbidities obviously elevated the death risk and also found that there was a trend for hypertension and diabetes to elevate the risk of death from COVID-19 pneumonia.[12]In a meta-analysis study conducted on 50,466 patients found that chronic obstructive pulmonary disease, cardiovascular disease and hypertension were the comorbidities significantly associated with severe morbidity and ICU admission.[13]

Special aspects of pathophysiology related with various comorbidities

Hypertension as a significant comorbidity with COVID-19

Studies showed that hypertensive patients are more likely to develop acute respiratory distress syndrome or progresses to death in COVID-19 pneumonia. This can be related to Angiotensin-converting enzyme 2(ACE2) activity as it may be the main determinant of lung injury caused by SARS CoV-2. ACE2 is required for viral entry of SARS-CoV-2.

The action of ACE2 on vascular bed is just opposite to that of ACE. ACE converts angiotensin I to angiotensin II which is a powerful vasoconstrictor while ACE2 degrades angiotensin II to angiotensin (1-7), which, after binding to the Mas receptor in the vascular bed, shifts the balance from vasoconstriction with angiotensin II to vasodilation. The circulating levels of soluble ACE2 are low and the functional role of ACE2 in the lungs appears to be relatively limited under the normal circumstances, but may be up-regulated with certain medications or clinical states. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are the two types of renin–angiotensin–aldosterone system (RAAS) inhibitors widely used for treating hypertension, heart and renal failure. It is shown from previous studies that the expression of ACE2 may be increased after treatment with an ACEI or ARB which could increase the patients' susceptibility to viral entry as well as propagation in the host cell. The data are still inconclusive whether this increased association of hypertension with COVID-19 and the increased risk of mortality can be directly correlated to hypertension or other associated comorbidities or to the treatment of hypertension. Therefore, evidence of the impact of these medications in patients with COVID-19 is urgently needed. [7]

Due to the uncertainty in the clinical data, there are still controversies toward the use of RAAS inhibitors during the COVID-19 pandemic. It has raised a theoretical concern that by increasing ACE2 expression with the use of ACEIs and ARBs it could increase the binding of SARS-CoV2 to the lung thereby leads to greater lung injury.

Chao Gao *et al* found that the results from laboratory studies reported that ACE2 abundance was down-regulated on cell surfaces after the initial engagement of SARS-CoV-1 spike protein. The down-regulation as well as the dysregulation of its activity in the lungs may facilitate the initial neutrophil infiltration in response to bacterial

endotoxin and may result in unopposed angiotensin II accumulation and local RAAS activation. An animal study done in mouse models has also shown that, exposure to SARS-CoV-1 spike protein induced acute lung injury, which is limited by RAAS blockade. Therefore, some researchers have hypothesized that high ACE2 expression could be deleterious during the contamination phase, whereas the high ACE2 expression could, in contrast, be beneficial during the inflammation phase and may possibly prevent organ injury in COVID-19[14].

Diabetes as a significant comorbidity with COVID-19

Diabetes and associated complications can increase the rate of morbidity and mortality during acute infections due to suppressed innate and humoral immune responses. The data obtained from the recent studies also suggest that COVID-19 patients with diabetes are more often associated with severe or critical disease. According to Singh et al, the pathophysiology behind the relationship of diabetes and CoVID-19 is related with ACE-2 activity. The conformational change occurring as a result of binding of S-glycoprotein on the surface of SARS CoV-2 with ACE-2 allows proteolytic digestion and helps in the internalization of the virus in turn triggers inflammatory response with recruitment of T-helper cells which produce interferon. This results in the release of other inflammatory cells leading to a 'cytokine storm' which could lead to the organ damage and multi organ failure.

There are several factors responsible for increased risk and severity of infection in diabetes:

- The increased expression of ACE-2 has been found in renal cortex, liver and pancreas and this might predispose people with diabetes to infection with SARS CoV2
- Diabetes is associated with an increase in furin which is a type-1 membrane bound protease involved in the entry of coronaviruses in to the cell which might facilitate viral replication.
- The alterations in the CD4 lymphocytes and impaired T-cell function has been observed with COVID-19 patients and correlated with prognosis.

- Several cytokines are increased in COVID-19 infection out of which IL-6 is increased in diabetes and may play a more deleterious role in COVID-19 infection.
- It has been seen to cause hyperglycaemia in people without pre-existing diabetes and it may be linked with the expression of ACE-2 in pancreatic islets indicating a transient damage to beta cells. Thus, it is important to monitor the blood glucose levels in acute stage and follow up [11].

The association between diabetes and infection has been clinically recognised. SARS CoV-2 infection in diabetics triggers higher stress conditions, with increased release of hyperglycaemic hormones such as glucocorticoids and catecholamines resulting in increased blood glucose levels and abnormal glucose variability. Hyperglycaemia and insulin resistance promote the tissue inflammatory activity by increasing the production of glycosylation end products and pro-inflammatory cytokines, oxidative stress and also the synthesis of adhesion molecules that mediate tissue inflammation. In addition to the inflammatory activity, several defects in immunity has also been linked to hyperglycaemia such as reduced lymphocyte proliferative response to different kinds of stimuli as well as impaired activity of monocyte/macrophage and neutrophils in addition to abnormal delayed type hypersensitivity reaction and complement activation dysfunction. Besides the marked inflammatory process, there is an imbalance between coagulation and fibrinolysis takes place, with increased levels of clotting factors and relative inhibition of the fibrinolytic system. Both insulin resistance and T2DM can be related with endothelial dysfunction and enhanced platelet aggregation and activation which favours the development of a hypercoagulable pro-thrombotic state. Atherosclerosis, vascular inflammation and endothelial dysfunction can be a part of the pathogenesis of other chronic conditions like hypertension and CVDs. [15]

Based on the data obtained from a study conducted on 174 COVID-19 patients, Guo et al found out that diabetic patients were at higher risk of severe pneumonia, release of tissue injury related enzymes, excessive uncontrolled inflammation responses and hypercoagulable state associated with dysregulation of glucose metabolism. The serum levels of inflammatory biomarkers like IL-6, CRP, serum ferritin and coagulation index, D-dimer were significantly higher in diabetic patients which suggests that they are

more susceptible to an inflammatory storm which could lead to rapid deterioration of COVID-19 patients. It also suggests that the cytokine storms are also the main cause of eventual death for many patients [9]

DM is a condition characterised by an exaggerated pro-inflammatory cytokine response particularly IL-1, IL-6 and TNF-α in the absence of appropriate stimulation. But it can be exaggerated further in response to a stimulus as in seen with COVID -19 patients with complications like ARDS [16]

COVID-19 and cardiovascular disease

There is a high prevalence of cardiovascular disease (CVD) in COVID-19 patients, increasing morbidity by provoking myocardial injury and dysfunction. Even though the exact mechanism of cardiac involvement remains unclear, it was noted that there is a rise in high sensitivity cardiac troponin I (hs-cTnl) in patients with CVD abnormality and can be correlated with cardiac injury. Along with the rise in hs-cTnl, other inflammatory biomarkers (D-dimer, ferritin, IL-6, lactate dehydrogenase) also found to be raised suggesting the possibility that this reflects cytokine storm or secondary hemophagocytic lymphohistiocytosis more than isolated myocardial injury. Thus, a cytokine storm mediated by an imbalanced response among subtypes of T helper cells, and hypoxia induced excessive intracellular calcium leading to cardiac myocyte apoptosis can be a suggested mechanism. Another mechanism which found to be potential is direct myocardial involvement mediated by ACE2. [17]

COVID-19 and acute kidney injury

Considering the possible pathogenic mechanisms of acute kidney injury (AKI), the cause can be found multifactorial such as related with sepsis and other unrelated pathways which reflects a significant effect of virus on the kidney tubules. SARS CoV 2 uses ACE2 as a receptor to facilitate viral entry into target cells and its strong expression is found along the apical membrane of proximal tubule cells. So, the infection may worsen the local inflammatory response and can cause direct injury to the tubular cells and consequently the incidence and duration of AKI episodes. The development of sepsis or septic shock could develop kidney injury as a consequence of their altered hemodynamic status including right heart failure, fluid overload and systemic congestion.

Several studies also pointed out the relevance of inflammatory or immune mediated reaction with the release of high levels of circulating harmful inflammatory mediators which can interact with kidney-resident cells and can cause endothelial dysfunction, microcirculatory derangement and tubular injury [18,19]

DISCUSSION

COVID-19 is a rapidly spreading pandemic and has already became a threat globally. The higher prevalence of this is seen among older people and those with pre-existing comorbidities (4,5). This review aimed to understand the association between various comorbidities and COVID-19 infection in order to analyse the probable pathophysiological mechanism leading to direct and indirect damage of the system. This review also analysed that the risk is higher in those patients with associated comorbidities like diabetes, hypertension, cardiovascular disease, kidney injury etc. The main findings of the present review include:

- ACE 2 activity is the main determinant of pathological damage in COVID-19 patients
- It is also found out that there is an increase in the level of cytokines (cytokine storm) as a result of release of inflammatory cells which could lead to the organ damage and multiorgan failure.

Accumulating data demonstrated that ACE2 may be the main determinant for the direct damage caused by SARS CoV 2[7,11,17,18,19]. Indeed, the present study showed that ACE 2 plays an important role in the pathological damage in the system associated with hypertension, diabetes, CVD and kidney injury.

There is a defect in immunity with alteration in the CD4 lymphocytes, impaired T-cell function, impaired activity of monocyte/macrophages and neutrophils has been noticed in the study. Some of the previous preclinical studies showed that homoeopathic drugs in different potencies produced modulation of immune function at multiple levels and thereby influencing macrophages, lymphocytes and polymorpho nuclear cells. The evidence obtained from the studies suggested that homoeopathic treatment has the potential for individual-specific immunomodulation [20] In a study on the effect of Arsenicum album 30C for upregulating the immunological markers conducted as a preliminary trial at Pathanamthitta district of Kerala state found out

that Arsenicum album 30C is effective in upregulating T lymphocytes such as CD4, CD8 and CD4:CD8 ratio [21]

The results obtained may change in the future as this are given on the basis of the conclusion obtained from the literature to the date. Further fundamental studies have to be done for better evaluation of the data.

CONCLUSION

The expression of ACE2 in various locations can be considered as the main determinant of pathological damage in the system which favours the progression of disease in COVID 19. In addition to that the increase in level of cytokines (cytokine storm) as a result of release of inflammatory cells can be a definite cause which can lead to the organ damage and multiorgan failure. Those patients with comorbidities are at a higher risk of tissue injury, uncontrolled inflammatory response and hyper coagulable states, thus more attention should be paid to comorbidities in the management of COVID-19. ACE2 activity and the resultant cytokine storm may be considered as the probable pathogenetic mechanism in COVID-19 infection.

Since the immunomodulatory function of different homoeopathic drugs are already been identified it can be utilised for the upregulation of the immunological activity in the current scenario as there are no specific vaccines or medicines are known to be available for the management of COVID-19.

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