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COVID-19 and Hypertension: A Mini-Review of Their Mutual Effect

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Cases of Coronavirus disease are rapidly increasing across the world. Hypertension is the commonest co-morbidity among COVID-19 infected patients and hypertension is one of the determinants of severity of COVID-19.COVID -19 virus uses ACE-2 as an entry receptor and ACE-2 plays a vital role in blood pressure control in an individual. Certain antihypertensive medications may affect ACE-2 level and hence COVID-19 pathogenesis. At present, while the worlds focus is on the COVID-19, there is a danger that management of other illnesses like hypertension might be overlooked. It is highly recommended to take antihypertensive medications as directed and following healthy lifestyle practices like regular exercise, consuming low salt heart-healthy diet, maintaining a healthy weight and reducing stress, and practicing mindfulness even during this pandemic.

Keywords: Hypertension; COVID-19; health control; ACE-2.

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1. INTRODUCTION

Cases of coronavirus disease-19 (COVID-19) are rapidly increasing across the world. According to the WHO, COVID-19 situation reported at 14 May 2021, more than 160 686 749 confirmed cases including 3,335,948 deaths have been reported via WHO. By 11 May 2021, around 1,264,164,553 vaccine doses have been administered globally [1]. The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2),the virus causing COVID-19, and the viruses that caused the past outbreaks of SARS and MERS are closely related. According to the published report cases, fatality rate of COVID-19 vary widely between countries. During the begging of 2021, a large number of cases were detected in Europe and United State and there was a significant decline of new cases towards March-April 2021 with the introduction of the COVID-19 vaccine. On the other hand, there is a significant surge of new cases in Asia including India towards April-May 2021[2,3]. According to the Bulletin released on 6th March 2020 by the American College of Cardiologists, the overall case-fatality rate for COVID-19 is 2.3% while the death rate shoots to 10.5% for people with cardiovascular diseases and 6.0% for people with hypertension [4]. Published data shows some specific comorbidities are associated with increased risk of infection and poor outcomes with increased severity of lung injury and mortality [5]. According to a retrospective cohort study done in China, the most common comorbidities reported were hypertension(30%),diabetes mellitus(19%), and coronary heart disease(8%) [6,7]. Another such study done in Wuhan, China, revealed that the most common comorbidities in individuals who developed acute respiratory distress syndrome were hypertension(27%),diabetes mellitus(19%), and cardiovascular disease(6%) [8,9]. As per Chinese National health Commission data, 35% of patients diagnosed with COVID-19 had hypertension [10,11]. A large study done in United State revealed an overall rate of hypertension was 56% among COVID-19 patients [12]. Accordingly, hypertension is a determinant of the severity of COVID-19 which needs further evaluation.

2. METHODOLOGY

Multiple search systems were utilized to recognise potentially relevant papers during the literature search. Searches were performed manually by the author and involved several sources, including high-impact journals, online databases (Medline, PubMed, ISI, IBSS,and Google Scholar), libraries (Elsevier ScienceDirect and Wiley). Reference lists of identified papers, relevant reviews, and meta-analyses were examined for additional articles. Studies published between 1990 to 2021 were included. The following Medical Subject Headings (MeSH) and keywords were used alone or in combination: hypertension, Coronavirus, Coronavirus infections, COVID-19, 2019-nCOV, ACE-2, andrenin-angiotensin-aldosterone system (RASS). Initial study selection was performed via title and abstract screening by the author with the full-text screening of shortlisted publications were undertaken later.Publications in languages other than English and letters, editorials, conference abstracts, and commentswere excluded. Then the selected articles were re-evaluated for relevance and duplication.The search strategy was conducted following previously published principles. Data abstraction was performed by the author after reading all selected articles. Detailed notes, impressions were written down and decided on which pieces of data possess values. Data weregrouped into relevant categories and subcategories. Relationshipsamong data sets were identified and analysed in detail and interpretations were made.

2.1 Main Text

Hypertension remains the leading cause of death worldwide, accounting for 10.4 million deaths annually [13]. In accordance with the Centre for Disease Control(CDC),almost 63% of adults over the age of 60 are hypertensive [14]. The estimated number of hypertensives showsa clear shift of numbers in high-income countries(HIC) (349 million) to low-middle income countries(LMIC) (1.04 billion) [13]. The large disparities in the regional burden of hypertension are accompanied by a low level of awareness, treatment, and control rates in LMIC when compare to HIC [13].

The regulation of blood pressure is complex and will be reviewed only briefly here.Neurogenic control, renin-angiotensin-aldosteronesystem (RASS), arterial natriuretic peptides, eicosanoids, kallikrein-kinin systems, endothelial mechanisms, adrenal steroids, renomedullaryvasodepression, and sodium and water metabolism are involved in the regulation of blood pressure [15].

2.2 RASS and Hypertension

The RASS plays a critical role in regulating multiple tissue and organ functions including cardiovascular, renal, lungs, and liver, andspecifically involves in maintaining homeostasis of blood pressure, electrolytes balance, and inflammatory response [16,17,18]. Although RASS is considered as a systemic regulatory mechanism,over the past few decades findings have revealed that RASS plays a critical roleby acting locally in various organs and tissue [16].Deranged function of RASS leads to the pathogenesis of a number of diseases including hypertension, heart failure, myocardial infarction, diabetes, and inflammatory lung diseases [16].

In addition to the classical RASS pathway researchers have identified the counter-regulatory RASSpathway. The counter-regulatory RASS is made up of diverse peptides, receptors, and enzymes [19]. Angiotensin-converting enzyme 2(ACE2) is a novel member of counter-regulatory RASS and it has emerged as a potent negative regulator of the classical RASS [13]. The imbalanced activity of the angiotensin-converting enzyme(ACE) and ACE2 locally or systemically leads to many disease pathogenesis including lung disease [13,20].

ACE-2 is a type 1 transmembrane metallocarboxypeptidase with homology to ACE [21]. ACE2 neutralizes the inflammatory effects of angiotensin II,reduces the concentrations of proinflammatory cytokine interleukin-6,enhances the anti-inflammatory and antioxidant roles of angiotensin 1-7,increases the concentration of alveolar surfactant protein D, and triggers vasodilatation [22].

ACE-2 can negatively regulate classical RASS by degrading Angiotensin 11 to generate Angiotensin 1-7 and cleaving angiotensin 1 to generate angiotensin 1-9 [19]. ACE-2 has been shown to exhibit a protective function in the cardiovascular system and other organs [21]. Some preclinical studies have demonstrated that stimulating ACE2,can reduce blood pressure and lessen cardiovascular damage [19].

2.2.1 Role of ACE-2 in the pathogenesis of COVID 19

A number of recent research have shown that COVID-19 can infect various parts of the human body including the respiratory, cardiovascular, digestive, nervous, and urogenital system [9]. The life cycle of COVID-19 with the host consists of the following five steps: attachment, penetration, biosynthesis, maturation, and release [18]. COVID-19 utilizes ACE-2 as a cellular entry receptor [21,23]. ThoughACE2 is widely distributed in the human body its high expression is confined tothe endothelial cells of the arteries, arterioles, and venules of the heart and kidney [24]. Also ACE2 is present in many cell types and tissues including the lungs, heart, liver, and gastrointestinal tract [25,26]. In the lungs,ACE2 is highly abundant on type 2 pneomocytes [27]. As mentioned earlier, RASS is an important biochemical pathway in the body which is critical to regulate processes like blood pressure,inflammation, and wound healing.ACE2 is a vital component of the RASS pathway [27]. A protein called angiotensin II(ANG II) is a component of RASS.ANG II can increase blood pressure and augment inflammation.It also increases the damage to blood vessels linings and various types of tissue injury.ACE2 converts ANG II to other molecules that counteract the effects of ANG II [27]. When the COVID-19 virus binds to ACE2,a decrease in available ACE2 prevents ACE2 from performing its normal functions to regulate AGN II and more ANG II is available to injure tissues.This leads to injury,especially to the lungs and heart,in COVID-19 patients [27]. Though ACE2 is present in all people the quantity can vary among individuals and different tissues and cells.A study done in mice has found that lack of ACE2 is associated with severe injury in the heart,lungs, and other tissue types [27].

2.2.2 How does hypertension results in severe COVID-19 infection

According to the meta-analysis done byPranata et al, hypertension is linked to poor outcomes in COVID-19 patients including mortality, severe COVID-19, adult respiratory distress syndrome, need for ICU care, and disease progression [22]. The association between hypertension and severe COVID-19 infection is complex [28,29]. Some believe that poorly controlled blood pressure can leads to chronic inflammation throughout the body which can damage blood vessels leading to dysregulation of the immune system.Oliveira et al stated that reducing the amount of the pro-inflammatory cytokines,which leads to a weaker immune function in hypertensives may contribute to this [30]. This leads to difficulty in fighting the virus,or a dangerous overreaction of the immune system to COVID-19 [28]. Another factor that exacerbates

the effect of the COVID 19 virus is endothelial dysfunction which commonly occurs in hypertensives [31].

It was believed that hypertensive patients have raised ACE 2 expression due to associated genetic polymorphism and the use of antihypertensive drugs like angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB),which even though still controversial, may increase susceptibility and severity of COVID-19 [22]. But more recent data suggested that prescription and continuation of ACEIs/ARBs may in fact protect against SARS-CoV-2 infection and COVID-19 related deaths [29,32,33]. According to de Abajo, RASS inhibitors do not increase the severe COVID-19 risk and should not be discontinued to prevent a severe case of COVID-19 [34]. A meta-analysis done by Ssentongo revealed that prior use of RASS inhibitors was associated with lower risk mortality from COVID-19 in patients with hypertension. Further, they showed the protective effect of RASS inhibitors in hypertensive patients with COVID-19 [35]. Similarly meta-analysis done by Chan also concluded that treatment with RASS inhibitors was not associated with a higher possibility of a positive test for COVID-19 infection, disease severity, or mortality [36].

Cao et al found differences in the allele of the ACE2 gene and states such alleles differences may lead to a different response to COVID 19 among different populations [24,37]. Accordingly overexpression of ACE2 is considered as the main reason for hypertensive patients to get more severe COVID-19 illness [22].

According to Pranata et al,meta-regression analysis confirmed that the association between hypertension and increased composite poor outcome was influenced by gender(p=0.013),but not by age(p=0.233,diabetes(p=0.882) or cardiovascular diseases(p=464) [22]. More expression and activation of Angiotensin II type 1 receptors in hypertensive males may lead to vasoconstriction,pro-inflammatory response, increasing oxidative stress, leading to adult respiratory distress syndrome(ARDS) in severe COVID-19 compared to female [22,38]. Another postulation is oestrogen predispose towards good RAS in female causing less severe disease [22].

Possible thrombo-embolic complications and procoaguable state of COVID-19 are also mounting concern [39,40]. Various hypercoaguable states like inflammation, hypoxia, dehydration, immobilization, and diffuse intravascular coagulation have been described in COVID-19 [31]. Hypertension is also known to be associated with hypercoaguable state and it might lead to a worsening thrombotic milieu [31,41].

2.2.3 Management of hypertension during COVID-19 pandemic

At present, while the worlds focus is on the COVID-19,there is a danger that other illnesses might be overlooked. The public is urged not to attend emergency departments and clinics. It is also likely that patients are concerned about contracting the virus while attending the hospital and are staying away. As a result, there are reports of delayed presentation of acute medical emergencies and also the management of stable chronic illnesses like hypertension and diabetes are affected [31]. It is noted many hospitals worldwide have cancelled all in-patient care,including routine outpatients clinics,and moved towards telemedicine as part of social distancing measures [31]. But even in these circumstances,it is particularly important that blood pressure and blood sugar levels are monitored regularly as patients with diabetes and hypertension are at higher risk for complications of COVID-19 [31]. As mentioned previously hypertension is the most prevalent co-morbidity among patients admitted with COVID-19.Also hypertensive patients who develop COVID-19 are more likely to be admitted to hospitals than normotensives and carry poorer outcomes from COVID-19 [31].

One of the major problems during a pandemic is early conflicting data that can cause uncertainty and confusion in the management. At the start of this pandemic, concerns were raised regarding the safe use of ACEIs/ARBs. Discontinuation of these medications can precipitate uncontrolled blood pressure or heart failure which could contribute to morbidity and mortality in the infected patients [31]. Vaduganathan et al disagree with the discontinuation of ACEIs in stable COVID patients or people who susceptible to COVID-19.Cardiopulmonary protective effects of ACEI/ARBs are beneficial and both drugs group should be continued in COVID-19 patients [24,42]. Guo et al also concluded that ACEIs/ARBs should not discontinue for patients who have been on those medications for a long time in the context of COVID 19.They also stated that the use of ACEIs/ARBs might be a double-

edged sword in COVID-19 [7]. The use of ACEIs/ARBs can upregulate the expression and activity of ACE2 in the lungs, they play a dual role in COVID-19 [30]. On the one hand, a higher level of ACE2 might increase the susceptibility of cells to the virus.On the other hand, the activation of ACE2 might ameliorate the acute lung injury induced by the COVID-19 virus [7]. They further claimed that it would be unwise to discontinue these medications abruptly as the protective role of ACE2 in the respiratory system is supported by ample evidence, whereas the increased risk of infection is still a hypothesis [7]. A recent retrospective study from China which compares outcomes on hospitalized patients with COVID-19 with and without ACEI or ARBs for hypertension has suggested that in the former all-cause mortality was lower [31]. Considering these facts now guidance was issued advising that ACEIs/ARBs not to be discontinued in COVID-19 patients [43,44,45].

Even during the COVID-19 pandemic, it is paramount important to continue the guideline-based management of hypertension. Healthcare providers need to ensure that patients are appropriately advised and have access to their drugs.Patients should be made aware that despite the lockdown,hospitals and pharmacies are still open and Family physicians and General practitioners are still available for consultations, even if it is over the telephone [31].

2.2.4 How can people with hypertension reduce the risk of COVID-19

Meticulous blood pressure control and following appropriate safety measures like universal mask-wearing, regular use of hand sanitizer, and social distancing may help preventing severe COVID-19 [28].It is highly recommended to take antihypertensive medications as directed and following healthy lifestyle practices like regular exercise, consuming a low salt heart-healthy diet, maintaining a healthy weight and reducing stress, and practicing mindfulness [28].

3. CONCLUSIONS

Currently, we all are in the process of learning about this novel virus, and information continues to mount. This pandemic has brought about a profound change in the social and economic lives of many. Further, it has changed the way health care is being delivered and prioritized. The current pandemic taught us how the management of chronic diseases and illnesses like hypertension should go back to the community and the patient.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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