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COVID-19 INFECTION AND ARTERIAL HYPERTENSION: LITERATURE REVIEW OF THE RELATIONSHIP BETWEEN THE TWO ENTITIES

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ABSTRACT

Background: *To breakdown the relationship and its nature between the two pathological entities Arterial hypertension (AHT) and SARS-COV-2 infection. Literature analysis of existing literature on both the topics have been utilized. Sources include journals, books, existing publications and online platforms like Google Academic, PubMed, HINARI were used as search engines. Additionally, guidelines and circulars from European Society of Cardiology, American Heart Association and other respective bodies were also referred. Data from large meta-analyses and clinical studies were included to bring out the relationship study. Pathophysiological breakdown of the two entities, contradicting proposals regarding treatment, new treatment modalities and de novo onset of AHT in post-covid infection were included to delineate the relationship between the two pathological entities.*

Conclusions: *Findings emphasize that the role of arterial hypertension in SARS-COV-2 infection is mediated through its effect on the regulation of RAAS, inflammation and immune responses. In contrast to the effect of arterial hypertension on patients with SARS-COV-2 infection, de-novo arterial hypertension was also reported in post SARS-COV-2 infection patients on follow up. Though some initial studies hypothesized that RAAS inhibitors may add to clinical adversities, most studies afterward disproved the same and in fact revealed a protective role of the same. Angiotensin Converting Enzyme 2 (ACE2) is proposed as a treatment option in SARS-COV-2 infection.*

KEYWORDS: *SARS-COV-2 infection, Arterial hypertension (AHT), RAAS, RAAS inhibitors*

INTRODUCTION

Arterial Hypertension (AHT) is one of the important and major established cardiovascular risk factors and has been an integral part of the cardiovascular risk stratification systems including the SCORE chart for quite long. The proportion of hypertension in the global burden of diseases has increased from about 4.5% (0.9 billion adults) in 2000, to 7% in 2010 and was projected to rise to 1.6 billion adults in 2025 [1,2]. With the emergence of the severe acute respiratory syndrome (SARS)- Coronavirus II infection, hypertension as an entity gained spotlight than ever before. The SARS-Covid 2 infection or simply referred to as 'COVID-19 infection' was first reported in Wuhan, Province of Hubei, China on 31 December 2019 which later evolved into a global pandemic affecting the entire healthcare system and raised an entire arsenal of questions including those directed to its spread, epidemiology, pathogenic mechanisms, prevention and above all treatment and prophylaxis [3]. AHT has been identified as the most prevalent cardiovascular comorbidity in patients with SARS-COV-2 infection that demonstrably increases the risk of hospital admissions and death. Worser outcomes like profuse lung injury, higher severity and mortality was associated mostly with AHT (30%) followed by diabetes (19%), and coronary heart disease (8%) [4]. The importance of the relationship study was further catalyzed by the pathogenic linkage between the two entities. *The aim* of the study was to delineate the relationship between covid-19 infection and AHT and to shine light on other important and relevant areas within the relationship spectrum itself such as antihypertensive therapy in SARS-COV 2 infection. *The purpose* is to study and refer the vast array of literature, and understand the intricacies of the relationship. The study has *the objective* of giving forth some clarity on the relationship between the two pathological entities and addressing some concerns linked to the same, such as antihypertensives. Analysis of this relationship is rendered complex by many factors. For instance, AHT is more common among the elderly. At the same time, the elderly was associated with a higher risk of protracting SARS-COV-2 infection and having a worser outcome in comparison to the general population. In addition, many elderlies have other systemic comorbidities like Type 2 Diabetes Mellitus (T2DM) and dyslipidemia. They also receive polychemotherapy which along with the above-mentioned comorbidities hinders in clearly delineating the relationship.

MATERIALS AND METHODS

This research was conducted on the basis of vast literature on related topics and pathophysiological breakdown of both entities using journals, books, online platforms like 'Google Academic', 'PubMed', 'HINARI', respective guidelines and circulars from authorities like European Society of Cardiology (ESCAR) and American Heart Association (AHA). The literature also reviewed advancements over time and contrasting findings. An example of this would be the usage of antihypertensives. Contradicting hypotheses were put forth and an intense debate for discontinuation of certain medications were found to be present initially. The need for switching from

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Renin Angiotensin Aldosterone System Inhibitors (RAAS inhibitors) was also put forward. For debunking the very idea of an elderly hypertensive patient acquiring SARS-COV-2 infection being a mere coincidence, accumulating evidence of not only their prevalence but also worser outcome, severity and lethality can be pointed out by the study [5,6,7,8]. According to these, most elderly patients are at risk for both AHT and SARS-COV-2 infection. However, this does not mean that co-existence of both entities in an elderly patient is a mere co-incidence. AHT as a pathological entity itself has implications in SARS-COV-2 infection affecting disease course, morbidity, outcome etc. Age-related changes have effects on individual organs and organ systems that collectively increase the susceptibility to many pathologies. There may also be other risk factors that may be prevalent in adult and adult elderly populations which complicate their relationships.

RESULTS

The findings from a large meta-analysis that included 76,993 patients with SARS-COV-2 infection found that the pooled prevalence of AHT, cardiovascular disease, smoking history, and diabetes was 16.37%, 12.11%, 7.63%, and 7.87%, respectively [9]. It was also demonstrated that patients with severe SARS-COV-2 infection who required ICU-admission, mechanical ventilation and death attributed to the same were found to have a significantly higher percentage of AHT, diabetes, coronary artery disease, cerebro-vascular disease, COPD, chronic renal disease, and cancer [10]. These reveal that AHT independently contributes in disease protraction risk, severity and outcome. For a better understanding of their relationship, it is necessary to review the pathogenesis. The root of this pathogenetic linkage lies in the Renin Angiotensin Aldosterone System (RAAS) and its two main regulatory axes. Recent findings demonstrated that AHT plays significant and important role in the regulation of RAAS, inflammation, immune responses, and the gastrointestinal tract [11]. SARS-COV-2 infection itself is considered to have systemic implications on inflammatory and immune areas as well. SARS-COV-2 pathogen enters human cells by binding its spike protein to the membrane receptor angiotensin converting enzyme 2 (ACE2) and interacting with the transmembrane serine protease 2 (TMPRSS2, widely expressed in epithelial cells at the respiratory, gastrointestinal and urogenital levels), leading to unrestrained ACE2 downregulation [12,13]. While SARS COV-2 infection uses ACE2 and its axes to interact with RAAS system; AHT pathophysiology and treatment pharmacology is mostly linked to the ACE/Angiotensin II/Angiotensin II receptor type 1 axis; the other axes involved in RAAS. This axis is associated with positive regulation of RAAS and hence an increase in systemic arterial blood pressure, ACE and its products (e.g. -Ang II), aldosterone etc. will be result of its activation which translates to systemic vascular and cardiac remodeling effects. This is consistent with effects seen in long term hypertensive patients. This axis contributes to cardio-renal remodeling by inducing prooxidative, proinflammatory, and profibrotic changes [14,15,16]. Conversely, the other axis ACE2/Angiotensin (1-7), Angiotensin (1-9)/Angiotensin receptor type 2 is associated with vasodilation and decreasing blood pressure. Additionally, by MAS receptor and it plays protective roles in a variety of human target organs by reducing cardiac hypertrophy and pathological cardiac remodeling and preventing the occurrence of heart failure after myocardial infarction [17,18]. ACE axis activation or ACE2 axis downregulation hence results in target organ damage, as one works opposite to the effects of the other. Additionally, SARS-COV-2 infection was found to downregulate the ACE2 pathway [19]. This leads to an elevation or increase in angiotensin II through ACE pathway. This is brought upon by the decrease in ACE2 which implies a significant reduction in the conversion of angiotensin to angiotensin (1-7) [19,20,21]. The ACE 2 fall will also lead to decreased degradation of Ang I and Ang II leading to their increased levels in plasma, which brings along with it the prooxidative, pro-inflammatory and profibrotic changes associated with it [22,23,24,25,26]. This also means that there will be higher aldosterone production which will lead to K+ excretion via the urine, sodium (Na) retention and inflammation. Potassium (K+) excretion over time will lead to hypokalemia which was demonstrated to be biological marker or predictor of worsening outcome of the disease [27]. Hypokalemia a clinical marker of this complex interaction indicates sodium retention, raising ACE, both of which translates to prohypertensive, pro-inflammatory effect in SARS COV-2 infection and signifies its indulgence in AHT pathophysiology. In AHT the role of RAAS is mostly implicated, as it the major established regulator of blood pressure in the human body. Increased ACE and upregulated ACE/Ang-II/AT1R is mostly responsible for Hypertension. A genome wide association study of Korea and other countries inferred that ACE among the RAAS components has the strongest association with AHT after an adjustment for sex, age and weight [28]. Since the pathogenetic link between the two entities resides in RAAS, antihypertensive drugs became a hot topic. This was because a large proportion of patients used RAAS inhibitors for their treatment. Two of the most commonly employed groups of drugs are ACEIs which reduce the generation of Ang II by inhibiting ACE and ARBs which reduce blood pressure by blocking the binding of Ang II with AT1R. Both of them also increases the level of ACE2 and have been extensively used in patients with AHT and other cardiovascular diseases to maintain the stability of blood pressure and reduce the risk of adverse events in cardiocerebrovascular system and kidney [29,30]. The argument was that these drugs may contribute to higher disease protraction or worser outcome and extensive lung injury as more ACE2 meant more susceptible to pathogenic entry. The question arose to whether discontinuation of these drugs was necessary in SARS-COV-2 infection patients. Many early studies hypothesized that in-fact these drugs may bring potential harm. Later extensive studies showed a protective effective of these group of medications against lung injury. ACE2 independently demonstrated to reduce lung tissue damage, associated inflammation and severe acute lung failure [31]. To correlate this information, experimental studies were conducted which also revealed protective role of these drugs against lung injury [32]. An Intensive Care Unit team demonstrated and shown that an increase in angiotensin 1 to 10 and a decrease in angiotensin 1 to 9 (its ACE2 processing product) was correlated with a poor prognosis in ARDS [33]. In response to the proposed adverse effects of ARBs or ACE inhibitors in risk and poorer outcome, many studies were done which found no adverse role and even protective role of the

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same drugs. Other correlation studies also revealed no increase in risk or mortality [34,35,36]. The European Society of Cardiology (ESCAR) and other medical associations also advised it is advisable not to change the treatment regimen of ACEIs/ARBs for patients with hypertension during the COVID-19 pandemic, unless supported by definitive clinical evidence. For patients who are currently receiving RAAS antagonists for conditions for which they are known to be advantageous, such as hypertension, heart failure or ischemic heart disease, the ACC, HFSA and AHA advise continuing these medications. It was further stated that specific treatment decisions should be made based on each patient's hemodynamic situation and clinical presentation in the event that individuals with cardiovascular illness are identified with SARS-COV-2 infection. In fact, by preventing the pro-inflammatory effects of Ang II and by promoting the anti-inflammatory, anti-organ remodeling and tissue protective effects demonstrated in the lungs, these drugs can even have a protective role. Increased soluble ACE2 in the circulation could also serve as a binder of the SARS-CoV-2, thereby protecting other ACE2 bearing organs but most importantly the lungs itself. In this aspect recombinant ACE2 is also being extensively studied [37]. It was proposed that high-affinity variants of sACE2, can be engineered using mutagenesis, which may serve as decoy receptors for the pathogen. These variants by interacting with the spike proteins can serve as a competitor for native ACE2 in SARS-COV-2 infection. This can prevent the ACE2 downregulation as more native ACE2 will be available to convert angiotensin to Ang (1-7) and Ang (1-9) which can reduce inflammation potential [38,39,40]. In search of other treatment options in SARS-COV-2 infection, the medical research community focused on viral entry mechanism to find loop holes. In light of this direction, it was also demonstrated that pharmacological inhibition of proteases like TMPRSS2 or CatB/L reduced SARS-CoV-2 S-pseudo typed vesicular stomatitis virus or lentivirus entry [41,42,43]. Future treatment aspects also pose a need to further analyze host entry co-factors like Neuropilin-1, CD147, phosphatidylserine receptors, heparan sulfate proteoglycans, sialic acids, and C-type lectins. Another interesting but understudied area is the de novo onset of Hypertension after SARS-COV-2 infection. SARS-COV-2 infection can cause de-novo hypertension or worsen existing hypertension by its effect on RAAS or endothelium [44,45]. A retrospective study in a tertiary care center summarized that there is a real possibility that more than 10% of the general population is going to be affected by AHT post-SARS-COV-2 infection, many of them undetected, especially among patients with no prior conditions in their medical histories [46]. Among patients, 32 of them (16.08%) had either new onset arterial hypertension (15 patients) or a worsening of an existing hypertensive condition (17 patients) related to COVID-19. Another study found out new onset hypertension in 18 patients (12%), while diabetes mellitus, coronary artery disease, and COPD were not significantly different between admission and post-covid infection period [47].

DISCUSSION

Rodriguez et.al earlier pointed out that SARS-COV-2 is oftentimes underestimated as an infectious disease and gave insight to its effect on immune dysregulation caused by it [48]. The same inference can be obtained while analyzing the entity for connecting the dots between AHT and SARS-COV-2 infection. Immune and inflammatory dysregulations are caused by both AHT and SARS-COV-2 infection. It is fascinating to observe that both these entities are interspersed within RAAS. AHT acts through ACE axis while SARS-COV-2 infection uses ACE2 to interact with RAAS. Both these axis function opposite to each other and ACE2 downregulation induced by SARS-COV-2 infection can work parallel with AHT to promote proinflammatory, pro-oxidative and organ damage inducing activities. The immune deregulatory activities and proinflammatory activities also bridge these entities. Due to the complex nature of interaction of SARS-COV-2 infection with the RAAS, patients who recover from the infection should be encouraged to do mandatory follow ups as de novo onset of AHT or worsening of existing AHT has been found in many patients. This can also be considered as a marker of damage induced on the vessel structures by SARS-COV-2 infection by ACE2 downregulation. The potential of ACE2 as a decoy receptor also signifies the importance of their common pathophysiological roots. However, this also signifies the need to study host- factors and role of other proteases so that the combined knowledge can be laid down as a foundation into practical treatment options.

CONCLUSION

In simple terms it can be said that SARS-COV-2 infection and AHT are 2 entities acting on two regulatory axes of RAAS. Broadly speaking these two axes act opposite to each other, with areas of cross interactions and intricacies with their end effects culminating in the RAAS. Regarding treatment RAAS inhibitors were not proved to have a detrimental effect on disease protraction or severity as of now. Additionally, by raising ACE2, inflammation and organ injury can be reduced as well. By realizing the effects of ACE2 in organ protection and inflammation and owing to it serving as a covid entry receptor, engineered ACE2 is studied as a potential therapeutic agent. However, other host factors and their interactions need to be further broken down. The pathogenic linkage between SARS-COV-2 infection and AHT is complex. In a susceptible hypertensive patient SARS-COV-2 infection can contribute to various immune dysregulations and can give rise to vicious cycles which once started can be difficult to break. The advantage of therapy focusing on pathogenic entry is that if properly intervened, added benefit of preventing appearances of such vicious cycles and immune-inflammatory cycles can be prevented. The de-novo onset of AHT in patients post SARS-COV-2 infection may reveal the existence of a bidirectional relationship as opposed to a simple cause- effect relationship between the two entities.

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