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A REVIEW ON SUSCEPTIBILITY OF HYPERTENSIVE PATIENTS TOWARDS COVID-19: LIFESTYLE MODIFICATION FOR BETTERMENT AND CONTROL

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ABSTRACT: Hypertension is a major global health challenge due to its prevalence and increased risk of cardiovascular disorder. Non-pharmacological intervention or lifestyle modification is a safer option to control blood pressure and shows effective results in regulating high blood pressure. In this review, we have described the pathophysiology of a hypertensive patient infected with severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) and functioning Angiotensin-converting enzyme 2 (ACE2) receptor during novel coronavirus disease 2019 (COVID-19). We summarized that article with the statement that hypertensive patients are more susceptible to SARS-CoV-2 not because they are taking ACE inhibitor drugs that regulate blood pressure and blocks angiotensin II-induced inflammation and tissue damage. Still, chronic drug intake makes their body weak to get infected with SARS-CoV-2 due to compromised immunity. Thus, lifestyle modification by taking healthy diet, regular, precise exercise, reducing stress, avoidance of salt intake, involvement of green leafy vegetables rich in potassium should be included in the meals, drinking of enough water (3-4 liters/day) daily, limitation in consumption of alcohol and caffeine make effectively control blood pressure with maintaining the required vigor of the body.

INTRODUCTION: Hypertension mortality and morbidity is now a global issue with an increase in associated disorder continuously and threatening conditions for other novel diseases [1, 2].

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Hypertension is an important modifiable risk factor for cardiovascular functional irregularities, including stroke [3, 4].

Many demographies were published for hypertension in 2020; it was expected to double in India from 2.3 million affected people in 1990 [5]. Additionally, it was also projected that hypertension would be a major risk factor for worldwide disability and death by 2020 [6]. As now we were in 2020, it is an established risk factor to be considered for cardiovascular patients [7].

Patients with risk of cardiovascular diseases particularly male, hypertensive, diabetics, obese and advanced age, have been identified as more vulnerable of these populations while infecting from novel coronavirus disease 2019 (COVID-19) [8].

Novel coronavirus disease 2019 (COVID-19) has emerged as one of the third highly pathogenic coronaviruses after Middle-East respiratory syndrome coronavirus (MERS-CoV) and Severe Acute respiratory syndrome coronavirus (SARS-CoV-1) infecting humans in past few decades [9-13].

It has announced a global pandemic by World Health Organization on 30 January 2020 [14-16]. Severe Acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a causative agent responsible for the deadly disease (COVID-19) that has become a major public health and economic concern worldwide [17-20]. COVID-19 has shown high-risk implications for cardiovascular patients [21] with life-long diseases such as hypertension, congenital heart disease, and acute coronary syndrome [22].

This primary phenomenon may extend further to the secondary stage, including disturbed lung function, increased cardiac workload, increased release of cytokines, and interleukins due to T cell activation. Ultimately, immune stimulation may lead to plaque instability and the development of acute coronary events [23].

In a recent study, a patient affected with COVID-19 has shown a medical history of hypertension and hyperlipidemia [24]. A study performed on COVID-19 affected patients revealed that these patients have comorbidities of hypertension and other cardiovascular-related diseases [25]. In a pooled analysis, it has been found that hypertensive patients are at 2.5-fold higher risk of COVID-19 [26].

Instead of several past researches of coronavirus, there is no approved vaccine or curative agent available to treat coronavirus infection [27]. However, these researches highlighted certain conditions and diseases that may cause complications to the infected persons in which cardiovascular disorders are one of them. Management of hypertension can be intervened by both pharmacological and non-pharmacological interventions [28]. The Pharma-cological interventions for cardiovascular patients include anti-hypertensive, anti-platelet, and antihyperlipidemic drugs [29]. The non-pharmacological intervention or medicine-free management is safer and shows effective results in regulating high blood pressure [30]. It prevents the progression of hypertension from the prehypertensive stage to a more chronic stage.

The problem of hypertension and prehypertension has been increasing due to frequent changes in lifestyle, eating habits, economic development, and acceleration of population age [31].

The non-pharmacological intervention includes lifestyle modification such as avoiding alcohol and smoking, regular exercise, and low salt intake [32-34]. The dietary approaches may help in this regard to regulate hypertension. Dietary Approaches to Stop Hypertension (DASH) include green leafy vegetables, fruits, nutritious food, dairy products, food enriched with Mg^{2+}, Ca^{2+}, K^{+} and phosphorus may help in this regard [35].

It has been reported that following lifestyle modification for 6-12 months was found very helpful to stage-1 hypertensive patients without any complications to cardiovascular functioning [36].

Other lifestyle intervention including regular exercise that showed effective results in controlling hypertension. It has been reported that exercise suppresses voltage-gated Ca^{2+} conductance, thus restoring mesenteric arterial function and vasodilation in hypertension [37].

Fig. 1 represents primary and secondary stages for controlling cardiovascular diseases (CVD). The modifiable and non-modifiable factors create a primary stage if uncontrollable They introduce other disorders and risk factors such as hypertension, diabetes, obesity, dyslipidemia, and hyperuricemia that lead to the secondary stage of CVD.

The risk factors for hypertension that can be modified include obesity, excessive sodium consumption, physical inactivity, and over-consumption of alcohol, as shown in **Table 1** [38]. However, the non-modifiable risk factors contributing to hypertension are age, race and genetic factors. Lifestyle modification may help in this regard to normalizing the blood pressure [39].

TABLE 1: LIFESTYLE MODIFICATION HELPS IN REDUCTION OF SYSTOLIC BLOOD PRESSURE

Lifestyle modification	Recommendation	Reduction of SBP (Range)
Reduction of weight	Bodyweight should be in proportion to height and age	5–20 mm Hg per 10 kg reduction of body weight
Dietary approaches	A Diet plan must include green vegetables, fruits, dairy products with low saturated fat	8–14 mm Hg
Reduction in sodium intake	Reduction of sodium intake should not be more than 2.5-5 g per day	2-8 mm Hg
Exercise	Exercise daily, including aerobic at least 30 min per day	4-10 mm Hg
Alcohol consumption in limit	Alcohol consumption should not be more than 2 drinks	2-4 mm Hg
Dietary potassium	Diet plan must include Bananas, oranges, cantaloupe, Cooked spinach, cooked broccoli, potatoes, sweet potatoes, and mushrooms	4-5 mm Hg

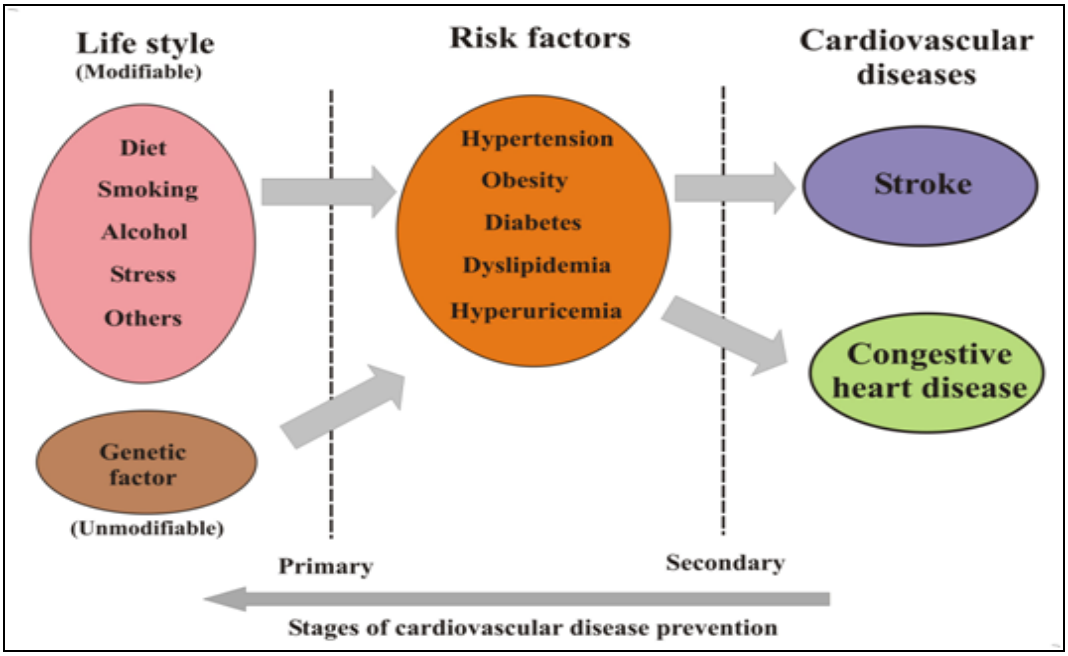

FIG. 1: DIAGRAMMATIC REPRESENTATION OF STAGES FOR PROGRESSION OF CARDIOVASCULAR DISEASES

1.1 Clinical Manifestations of Cardiovascular diseases and COVID-19: Several patients of corona positive have underlying cardiovascular problems or cardiac injuries during the course of illness. Thus, the understanding interplay between cardiovascular diseases and COVID-19 is very important for optimum management of these patients. The major manifestation of COVID-19 is a respiratory illness. However, the cardiac patients have undergone an acute cardiac injury due to increased cardiac troponins as a reported cardiac abnormality in COVID-19. The earlier two Coronavirus diseases (*i.e.* MERS-CoV and SARS-CoV-1) and were also associated with cardiovascular morbidities and other complications [40]. As of now, COVID-19 seems to have similar cardiovascular manifestations. The autopsies of infected patients have shown myocarditis and ischemia due to infiltration of inflammatory cells by the myocardium and increased cardiac biomarkers [41]. However, the elevated level of troponin T has been seen in cardiac patients infected with COVID-19 [42]. These patients have more comorbidities with specific disorders and diseases such as hypertension, coronary artery disease, diabetes, and arrhythmia [43]. Among 44672 confirmed cases in China affected with SARS-CoV-2, 12.8% of patients had hypertension, 4.2% had other cardiovascular diseases, and 5.3% had diabetes [44].

2. Pathophysiology of Hypertension in Aspect of Angiotensin-Converting Enzyme 2 (ACE2): There are probably several factors contributing to the pathophysiology of hypertension in patients. The main factors are salt intake, renin-angiotensin

system, insulin resistance, sympathetic nervous system, and obesity [45]. The renin-angiotensin system (RAS) is the most important system that plays a crucial role in regulating blood pressure in the body [46]. The release of renin from the kidney during reduced salt intake leads to the conversion of angiotensinogen (renin substrate) to angiotensin I. Angiotensin I is converted to angiotensin II in the presence of an angiotensin-converting enzyme (ACE). Angiotensin II causes vasoconstriction and stimulates the secretion of mineral corticoids from the adrenal gland, leading to a rise in blood pressure [47]. The pathophysiology of COVID-19 involves binding of SARS-CoV-2 with the host angiotensin-converting enzyme 2 (ACE2) to enter into the cells [48, 49]. ACE is an ectoenzyme present at the cell surface and hydrolyzes circulating peptides. It is abundantly found on the lungs' endothelial surfaces and existence in other endothelial cells like muscles cells, adipocytes, testis, and T lymphocytes [50]. Angiotensin-converting enzyme 2 (ACE2) is a homolog of ACE that counterbalances ACE activity in RAS [51]. ACE2 was first identified in 2000 as a monocarboxypeptidase enzyme composed of the transmembrane domain, metalloproteinase zinc-binding site, and signal peptide [52]. It has an immense role in the pathology of cardiovascular, respiratory, and renal systems. ACE2 forms Ang 1-9 by removing a single residue from Ang I and generating Ang 1-7 from Ang II [51]. Ang 1–7 shows anti-proliferative, vasodilatory, and anti-inflammatory activities by binding with Mas receptor **Fig. 2.**

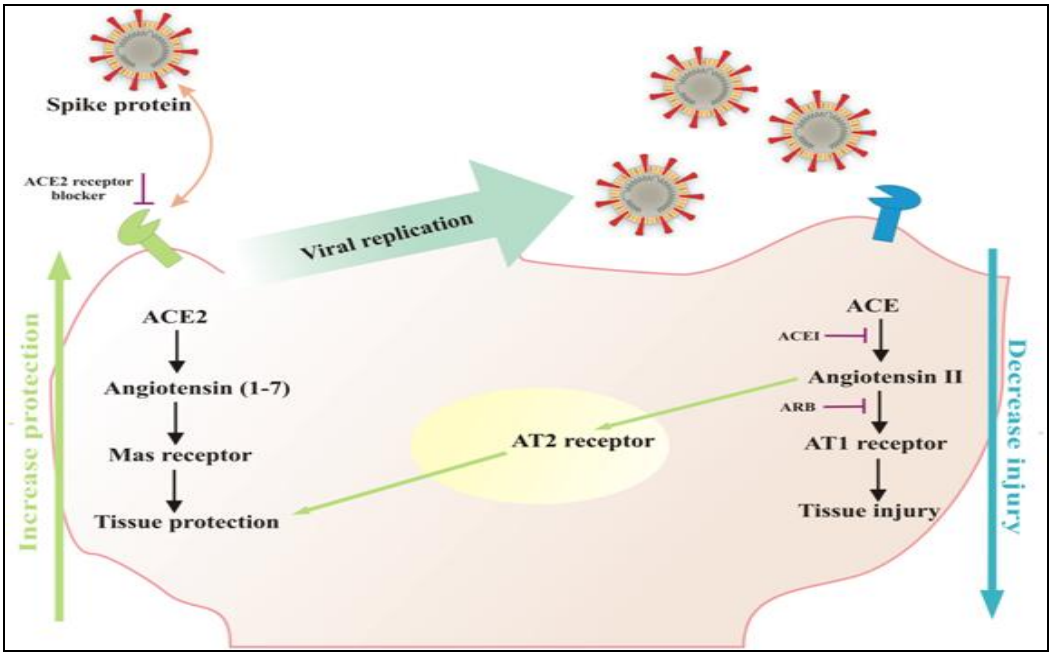

FIG. 2: ACE2 AS POTENTIAL THERAPEUTIC TARGET AGAINST SARS-COV-2 INFECTION

ACE2 plays the opposite role to ACE acts as a negative regulator of RAS. It has been found that high salt intake decreases the level of ACE2 in the body and increases the expression of ACE/ACE2 ratio, thus, causing hypertension [53]. It has been reported that ACE promotes lung injury; conversely, ACE2 protects from a lung injury at respiratory tract [54]. ACE2 was earlier identified as a potential receptor for severe acute respiratory syndrome coronavirus (SARS-CoV), and it has again been confirmed in COVID-19 pandemic [55]. It facilitates the entry of SARS-CoV-2 to the cells. ACE2 acts as a double-edged sword by protecting the body from pathological changes and opening the door for SARS-CoV-2[56]. The cells containing ACE2 receptors on their surface have a high affinity towards S1 domain of SARS-CoV-2 Spike glycoprotein. The research found that cell lines infected with SARS-CoV-2 showed reduced expression of ACE2 and significantly raised Ang II levels, causing serious lungs problem [55]. It has been seen that ACE inhibitors increase the availability of ACE2 on the cell surface for binding with SARS-CoV-2, thus, leads to respiratory syndrome and lung injury [57]. The infection of SARS-CoV-2disturbed the balance between angiotensin 1-7

(Ang 1-7) and angiotensin II (Ang II); however, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) protect heart from injury caused by RAS activation during infection. It has seen the RAS gets dysregulated during COVID-19 infection to hypertensive patients [58]. The figure represents the role of ACE2 during a COVID-19 attack in a hypertensive patient. **Fig. 2** shows the potential therapeutic target against SARS-CoV-2 infection. The virus binds with ACE2 receptor on cell surface through its spike protein and replicates abundantly to release more replications results in damage. ACE2 blocker drugs may potentially inhibit the binding of SARS-CoV-2. ACE inhibitor and ARB restore RAS dysfunction and tissue injury in hypertensive patients. However, these drugs are not devoid of toxic effects.

3. Role of Angiotensin-Converting Enzyme 2 (ACE2) During COVID-19 in Hypertensive Patients: ACE2 is found on cell surfaces of major organs like heart, intestine, lung, and kidney [59]. SARS-CoV-2 using its spike protein bind with the ACE2 receptor and enter into the body [60]. ACE2 is a doorway receptor for coronavirus that causes COVID-19. ACE2 breaks Ang II and prevents Ang II-induced lung injury and inflammation [61]. However, during SARS-CoV-2 attack, this receptor is occupied by virus and reduced ACE2 unable to prevent pathological effects of Ang II. Higher Ang II is likely to contribute to injury during COVID-19. Although SARS-CoV-2 primarily attacks the lungs, the digestive tract, kidneys, liver, and blood vessels are also get injured [62]. The drugs that inhibit the action of ACE prevent the formation of Ang II and thus, inhibit Ang II-induced injury of lungs and inflammation to tissues. Hypertensive patients treated with ACE inhibitors prevent the formation of Ang II in the body, but it is not clear that ACE inhibitors increase the level of ACE2 on cell surface [63].

It has been hypothesized that hypertensive patients taking ACE inhibitors are at increased risk of fatal COVID-19 due increase in ACE2 receptor availability for binding with SARS-CoV-2[64]. However, this statement is conflicting that ACE2 reduces lung inflammation and is a potential source of treatment for lung disease, hypertension, and diabetes [65]. **Fig. 3** shows the ACE2 receptor on the surface of the cell and its binding with the spike protein of SARS-CoV-2. A: Binding of the spike protein of SARS-CoV-2 with ACE2 receptor on the cell surface. B: Inhibition of effect of ACE2 upon binding with spike protein of SARS-CoV-2, ACE inhibitors, and angiotensin receptor blocker (ARB) drugs prevent the formation of angiotensin II, thus, prevents harmful effect of angiotensin II.

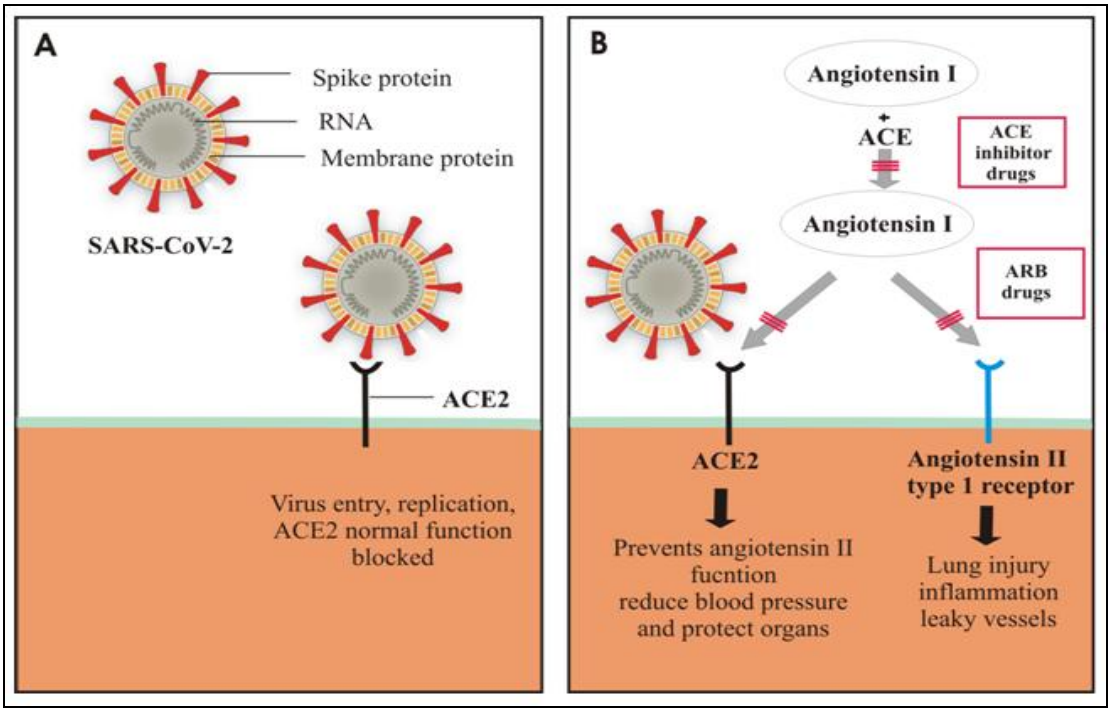

FIG. 3: ROLE OF ACE2 DURING COVID-19 IN HYPERTENSIVE PATIENTS

4. Lifestyle Modification to Control Hypertension during COVID-19 Pandemic: Hypertension is a very crucial risk factor for cardiovascular patients that may even cause death if uncontrollable [66-67]. The complications of hypertensive patients increase with age; thus, the lifetime risk of developing hypertension possesses significant importance [68-70]. It is very uncertain to predict who will develop hypertension because it can occur to anyone. However, few causative factors are known, including obesity, high salt intake, abrupt consumption of alcohol, and physical inactivity, leading to hypertension [71-72]. Starting with lifestyle modification is the best way to control high blood pressure. Long-established lifestyle modification may help to maintain body weight, electrolyte balance, good physical activity, and optimum alcohol intake [73-75]. This pattern of non-pharmacological approach is highly recommended for prehypertensive patients as initial therapy in stage 1 hypertension [76-77, 35]. However, for individuals taking anti-hypertensive drugs, lifestyle modification work as adjuvant therapy for them [78-79]. Lifestyle modification offers an alternative means to regulate high blood pressure effectively, economically, and with minimal toxicity [38]. **Fig. 4** shows the shielding effect of lifestyle modification against coronavirus infection. The long-term established lifestyle modification maintains optimum blood pressure and sufficient immune vigor that prepares the body to fight against infection.

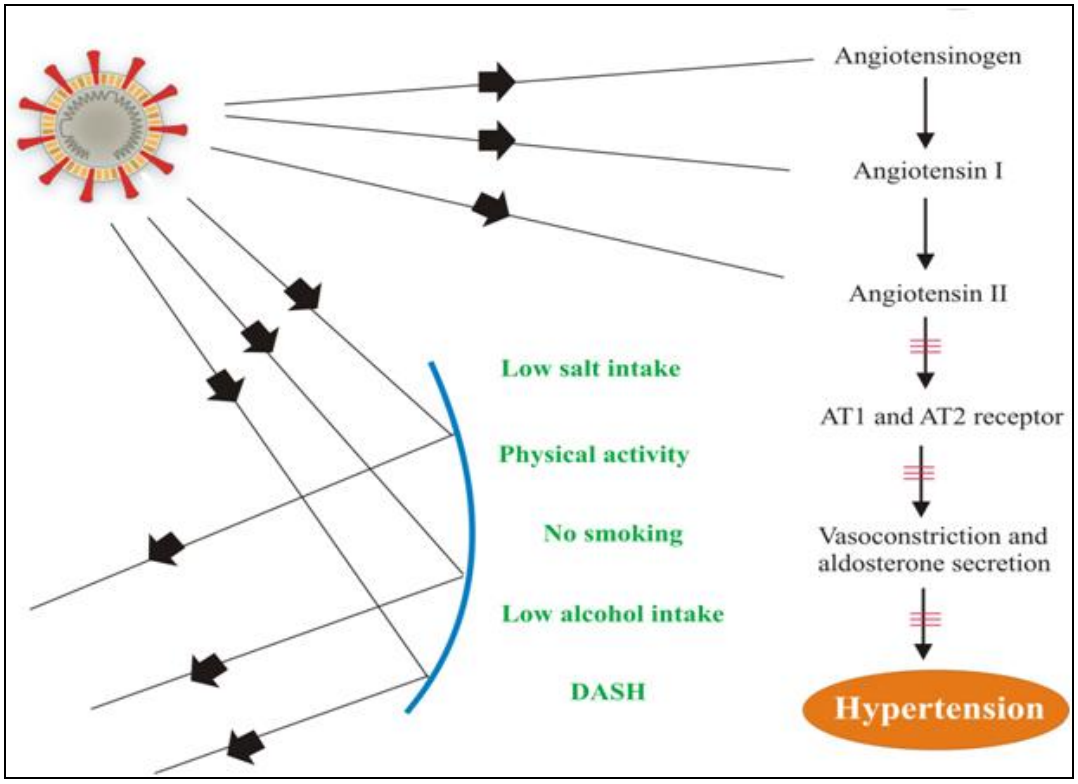

FIG. 4: SCHEMATIC REPRESENTATION OF PROTECTIVE EFFECT OF LIFESTYLE MODIFICATION TO REGULATE BLOOD PRESSURE AND PREVENT CORONAVIRUS INFECTION. SARS-COV-2, SEVERE ACUTE RESPIRATORY SYNDROME-CORONAVIRUS-2; DASH, DIETARY APPROACHES TO PREVENT HYPERTENSION; ACE, ANGIOTENSIN-CONVERTING ENZYME; AT1, ANGIOTENSIN RECEPTOR 1; AT2, ANGIOTENSIN RECEPTOR 2

5. Expert Opinion: The coronavirus outbreak in the present world is affecting everyone differently; in this period, hypertensive patients should be kept informed and stay safe as infection may be more severe to them. Hypertension does not increase the susceptibility of patients towards SARS-CoV-2. However, it has been seen that one-fourth or half of the COVID-19 patients admitted to the hospital have high blood pressure, including other ailments. The hypertensive patients exposed to the virus are likely to be admitted to the hospital or even ventilation compared to non-hypertensive infected patients. Other comorbidities with hypertension, including cardiovascular diseases, diabetes, and obesity, may contribute to the severity of the infection due to a weak immune system.

The person on anti-hypertensive medication is already at higher risk for infection due to compromised immunity. Physical inactivity or a sedentary lifestyle is often associated with weak immunity and an increased risk for infectious diseases. Stress is increasing with the current pandemic of COVID-19 and reducing an individual's immune response. However, exercising releases a few chemicals (endorphins and serotonin) in the body that regulate mood, cognition, depression, and the onset of dementia. A majority of the population in India and other developing countries suffers from stress and poor food habits; these tendencies lead to hypertension. The blood pressure can be controlled by adopting a good lifestyle taking a healthy diet, and regular, precise exercise, managing stress, avoidance of salt intake, involvement of green leafy vegetables rich in potassium should be included in the meals, drinking enough water (3-4 liters/day) daily, limitation in consumption of alcohol and caffeine, regular monitoring of blood pressure, etc. The eating plan of the hypertensive patient must include a DASH diet. It is suggested by the physicians and experts that hypertensive patients do not stop taking their medicines. It is required to maintain normal blood pressure and reduce cardiac stroke, heart attack and other heart diseases. Hypertension can be managed traditionally by improving awareness, controlling blood pressure, and normal treatments.

Hypertension is the key point to check future cardiovascular-related complications. It can be controlled by strict adherence to the prescribed therapy and changes in lifestyle as recommended. The DASH diet helps in the reduction of sodium in the diet and promotes to eat varieties of food containing nutrients such as magnesium, calcium and potassium that help in lowering blood pressure without taking drugs. DASH offers several health benefits to help reduce blood pressure and help prevent heart disease, cancer, osteoporosis, diabetes, and stroke. As we all know, the epidemics of COVID-19 will not be there forever. Special attention must be given to hypertensive and cardiovascular patients; empowering them to promote better lifestyle management, regular exercise, healthy diet, social distancing, and psychological fit. It is imprecated that patients with hypertension and other cardiovascular disorders possess higher levels of ACE2 receptors. Patients must reevaluate the use of medications (ACE inhibitors and ARB drugs) if infected by SARS-CoV-2.

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