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"A REVIEW ON DIABETES MELLITUS ENHANCES THE COMPLICATION OF PATIENTS WITH COVID -19".

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Abstract:

The RNA virus known as severe acute respiratory syndrome coronavirus-2 (SARS Cov-2) is the source of the current pandemic infection known as coronavirus disease 2019 (COVID-19). The organs primarily impacted by COVID-19 are the lungs, and the disease has killed patients from multi-organ failure, pneumonia, and severe acute respiratory syndrome. The mortality rate was higher in people with chronic illnesses, such as diabetes mellitus (DM). The COVID-19 pandemic is spreading quickly, thus it's critical to comprehend the molecular process by which diabetes mellitus heightens COVID-19 symptoms to develop more effective treatments. The purpose of this study was to re-analyze publically accessible data to determine the mechanisms by which diabetes mellitus (DM) enhances susceptibility to COVID-19 infection and/or increases the risk of SARS-Cov-2 infection complications. Angiotensin-converting enzyme-2 (ACE2), a membrane-bound enzyme, allows SARS-COV-2 to enter host cells. This results in an excess of activity in the vasodeletorious arms of the renin-angiotensin system (RAS) and an imbalance between the vasoprotective and vasodeletorious arms. Breathing becomes difficult and the alveoli become flooded as a result of this RAS imbalance. Due to DM's suppression of ACE2 and weakening of innate immunity, the risk of lung infection increased. Therefore, in addition to severe acute respiratory syndrome, diabetic COVID-19 patients also die from shock, heart failure, arrhythmias, multi-organ failure, and renal failure. Therefore, it may be said that DM exacerbates COVID-19 problems by promoting the development of RAS imbalance. From the perspective of public health, it is advised to prevent and lessen the acute effects of COVID-19 in diabetic patients by maintaining lung health, controlling blood glucose levels, and consuming foods high in antioxidants and anti-inflammatory compounds.

Keywords: *COVID-19, Antioxidant, Angiotensin converting enzyme, Diabetes mellitus, Renin-angiotensin system*

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INTRODUCTION:

Corona disease 2019 is a current corona virus infection caused by an RNS virus, severe acute respiratory syndrome corona virus 2 is the current corona virus pandemic infection. It was first detected in Wuhan ,China , in December 2019 and has since spread around the world .The WHO declared the 2019-2020 corona virus epidemic an international public health emergency on January 30 , 2020 and a pandemic on March 2020.[1,2] Currently more than 200 countries around the world are suffering from COVID -19.[3] As of April, more than 1.2 million people were infected with COVID 19 and more than 70,000 has died, mostly from viral pneumonia and multiple organ failure.[4,5]More than 2.5 million people have died from COVID -19 worldwide. Elderly patients with comorbidity such as diabetes and hypertension have a higher mortality rate. [6] Diabetes Mellitus is a global epidemic and the sixth most common cause of mortality .[7] Heart failure, cerebrovascular illness and coronary artery disease are all at risk due to diabetes mellitus. According to the WHO, the prevalence of DM in adults was estimated at 4% in 1995 and is projected to reach 5.4 % by 2025.[8] The international Diabetes Federation reports that the total number of Diabetes in the world will increase from 366 million in 2011 to 552 million by 2030 , or one in ten adults will suffer from DM. [9]The prevalence of DM in India is very high and India is considered to be the Diabetes capital of the world from 2025 onwards.[10] In addition to known complications and co-morbidities DM patients also suffer from impaired lung function and immune function.[11-13] People with diabetes are more likely to get infections and have a higher risk of complications after an infection.[14-15] Diabetic animals show impaired innate immunity and circulating polymorphonuclear leukocyte function at the site of infection . Pulmonary infections are a common and important risk for patients with DM .[16] According to a recent Chinese study, 22% of diabetic died, from COVID -19.[17] In another study 16.2 % confirmed that patients with COVID-19 were diabetes.[18] However, the article focuses on the pathophysiology of SARS COV 2 infection in diabetes patients.

REVIEW OF LITERATURE

CORONAVIRUS

Coronaviruses are not segmented positive sense RNA viruses that are enclosed. Both the family Coronaviridae and the order Nidovirales comprise them.[19] The severe acute respiratory syndrome coronavirus (SARS-Cov) is one of two types of coronaviruses.[20–21] Additionally, the Middle East respiratory syndrome coronavirus (MERS-Cov) is widespread.[22–23] The newly discovered severe acute respiratory syndrome coronavirus, SARS Cov-2, was initially identified in patients with acute respiratory illness-related pneumonia in Wuhan, China. The original SARS-Cov.[24] and SARS-Cov-2 are closely related. The primary means of transmission for this virus is close contact and the tiny droplets released when an infected person coughs, sneezes, talks, or exhales. Additionally, people can get infected by contacting a contaminated surface and then touching their face. Because COVID-19 enters host cells through the membrane-bound ACE2 enzyme in type II alveolar epithelial cells, the virus mostly affects the lungs.

PATHOPHYSIOLOGY

High levels of ACE2 are expressed by lung epithelial cells.[25, 26] ACE2 participation in SARS-Cov and SARS-Cov2 produced acute respiratory distress syndrome (ARDS) has been demonstrated in several animal models.[27] ACE2 knockout mice display severe ARDS pathogenesis.[28] Mice with ACE2 knockout treated with ART1 blocker are saved from ARDS. The glycoprotein spike on the surface of SARS-Cov and SARS-Cov-2 binds to the angiotensin-converting enzyme-2 (ACE2) on the target cell, allowing them to enter through endocytosis.[29, 30] The type-II alveolar epithelial cells in the lungs have a lot of ACE2. This demonstrates that the organ primarily impacted by COVID-19 is the lungs. Lung surfactant, which is secreted by type II alveolar epithelial cells, keeps the lungs clear and fluid. The maintenance of blood pressure homeostasis is facilitated by the vasoactive peptide cascade known as the renin-angiotensin system (RAS). The two main enzymes in this system are called ACE and ACE2. The decapeptide angiotensin I is cleaved by ACE into the octapeptide angiotensin II. A 42% homolog of ACE and captopril-insensitive carboxypeptidase is ACE-2 carboxypeptidase.[31, 32] It creates Ang-(1-9) and Ang-(1-7), which are the products of the cleavage of the carboxy-terminal peptide bond of angiotensin I and angiotensin II.32 When compared to Ang-I, ACE2's catalytic efficiency is noticeably higher.[33] Therefore, the primary enzyme in many tissues that generate Ang-(1–7) is ACE2.[34] Hence, the two angiotensin-converting enzymes (ACE and ACE2) and the two mediators (Ang-II and Ang-1-7) in the RAS work in tandem to produce either vasodilator/antiproliferative or vasoconstrictor/proliferative effects, depending on the balance of ACE and ACE2.[35, 36] This concept states that increased ACE activity is linked to decreased ACE2, increased Ang-II formation, increased Ang-(1–7) catabolism, and vasoconstriction; in contrast, vasodilation is associated with decreased ACE2, increased Ang-II, decreased ACE, and increased Ang-

(1–7). There are two types of G-protein coupling membrane-bound receptors for angiotensin peptides: type-1 (AT1) and type-2 (AT2). Whereas the AT2 receptor is linked to the opposite processes, the AT1 receptor is linked to growth, inflammation, and vasoconstriction.[37] Ang-II stimulates the production of reactive oxygen species and other proinflammatory reactions by acting as a cytokine via the AT1 receptor.[38]

Acute respiratory distress syndrome-related pulmonary edema is caused by either increased micro vascular permeability or increased hydrostatic pressure, which is brought on by pulmonary vasoconstriction.[39] One of the primary indicators of acute lung damage is increased pulmonary vascular permeability. Forty by stimulating the AT1 receptor, the loss of ACE2 expression after acute lung damage causes leaky pulmonary blood vessels.

Consequently, ACE-2 permits SARS-CoV-2 to enter the target cell and inhibits the virus's expression. This may indirectly cause organ damage in COVID-19 by increasing Agn-II activity.[41] There is a decrease in the quantity of membrane-bound ACE2 following SARS-CoV-2 contact with it. Neutrophil infiltration in response to bacterial endotoxin is facilitated by down regulating ACE2 activity in the lungs due to unopposed local RAS activation and Agn-II buildup.[42]In an investigation involving Agn-II was shown to be increased in COVID-19 patients, and this relates to both the overall viral load and the severity of lung injury. This catastrophic lung injury can be reversed by administering recombinant ACE2, which restores ACE2.[43, 44] ACE up regulates Ang-II in the pathophysiology of lung damage, which leads to severe lung failure via the AT1 receptor. However, ACE2 and the Mas receptor offer protection against lung damage. The ACE2 gene is found on the X chromosome.[45] As a result, females will express ACE2 more than males. This could be one of the causes of women's COVID-19 being less severe than that of men.[46] In older coronavirus patients, there was a correlation between the severity and increased mortality of ARDS and age-related decrease of ACE2 in the lungs.[47]

Based on the explanation above, it appears that acute lung injury results from an imbalance in the RAS and is linked to the following: i). a decrease in pulmonary ACE2 ii). Elevate Ang-II in the lungs (iii). Lung damage is improved by ACE2 supplementation or Ang-II inhibition. iv). Lung harm caused by viruses is aggravated by a reduction in or absence of pulmonary ACE2.

PULMONARY INFECTION AND DIABETES MELLITUS

It appears that having type-2 diabetes mellitus increases the chance of contracting a fresh coronavirus infection.[48] Patients with diabetes are often at risk for pulmonary infections. Tissue damage and compromised immune function raise the risk of serious complications in diabetes mellitus.[49] Pneumonia results from unchecked bacterial proliferation brought on by diminished innate immunity.[50] Diabetes mellitus has a strong correlation with nephropathy, retinopathy, hypertension, and cardiovascular disorders. There have been reports of localized RAS in the heart, blood arteries, kidney, and pancreas, among other organs.[51] RAS inhibitors lower the incidence of complications in DM patients' hearts and kidneys and also lower the development of new cases of DM in hypertensive individuals.[52] Via the proteolysis of Ang-II, ACE2 in the respiratory system generates Ang-(1–7). Via the AT1 receptor, an increase in the Ang-II level causes vasoconstriction and pro-inflammatory reactions when ACE activity is raised and ACE2 activity is lowered. Conversely, elevated ACE2 activity results in the production of Ang1-7, which, through the Mas receptor, generates anti-inflammatory and anti-fibrotic reactions beneficial to COVID-19 patients' recovery.[53]

A key function of RAS in the vascular system. Its two arms are known as the Vaso protective arm, which mediates vasodilation, anti-proliferation, and anti-inflammatory effects by activating the ACE2-Ang-(1-7)-mas receptor, and the Vaso deleterious arm, which employs the ACE-Ang-II-AT1 receptor to promote vasoconstriction, proliferation, fibrosis, and inflammation. The Vaso protective effect of Ang-(1–7) involves stimulating the generation of nitric oxide and reducing the formation of ROS by inhibiting NADPH oxidase via the mas receptor.[54] Through an Akt-dependent mechanism, Ang-(1–7) stimulates endothelial nitric oxide synthase (eNOS).[55] eNOS is a dimer consisting of two monomers with the same reductase and oxidase domains. The oxidase domain contains binding sites for tetrahydrobiopterin (BH4), zinc, and the heam group, while the reducase domain has binding sites for NADPH, FMN, and FAD.[56]In the presence of oxygen and NADPH, eNOS converts arginine to NO. Molecular oxygen attaches itself to the eNOS heam group.[53] For effective NO formation, BF4 is necessary. When BF4 is missing, dimeric eNOS turns monomeric, or uncoupled. Superoxide anion is produced by uncoupled eNOS. eNOS has a protective function in the vasculature by boosting synthesis of nitric oxide (NO). The soluble guanylate cyclase is activated by NO, which diffuses across the vascular

smooth muscle cell membrane and catalyzes the conversion of GTP to cyclic GMP. Cyclic GMP causes protein kinase-G (PKG) to become active. PKG then phosphorylates target proteins, lowering intracellular Ca2 and encouraging vascular relaxation.[58] NO directly inhibits the action of arginase and ornithine decarboxylase to reduce the creation of polyamides, which is necessary for DNA synthesis, or it indirectly inhibits Ca2 influx through cyclic GMP.[59] Because it increases the production of the enzyme super oxide dismutase, which catalyzes the conversion of super oxide to hydrogen peroxide, NO also has anti-oxidant qualities. This decreases super oxide anion.[60] The movement of progenitor cells from bone marrow to the site of arterial damage and re-endothelization depends critically on NO-dependent signaling.[61,62] In addition to the function, NO prevents leukocyte adherence on endothelial cell membranes.[63]

Nitric oxide bioavailability is reduced in diabetes due to either increased ROS generation through upregulated NADPH oxidase or decreased eNOS activity.[64] Under these circumstances, NO and superoxide anion combine to generate peroxynitrite. Peroxynitrite promotes the uncoupling of eNOS and oxidizes BF4 to BF3 and BF2. Instead of producing NO in this configuration, eNOS creates a superoxide anion. Thus, suppression of ACE2 may be the cause of vascular damage in DM.

Neutrophils play a vital part in the ARDS etiology. Neutrophils infiltrate when exposed to DM.[65] Tissue damage results from the release of dangerous mediators by activated neutrophils, such as ROS and matrix metalloproteinase.[66] Tumor necrosis factor, IL1, IL6, IL8, and other cytokines are proinflammatory and cause lung damage.[67] The development of neutrophil extracellular traps is induced by hyperglycaemia. Therefore, in the extracellular milieu of diabetic mice, ROS was elevated.[68] The intracellular compartments of diabetic rats treated with Ang-(1–7) showed an increase in ROS and other different cytokines (produced by neutrophils).[69] Therefore, higher tissue damage in diabetic patients is caused by increased extracellular ROS generation .[70]

With COVID-19, there is an imbalance between the vaso-protective arm, which mediates vasodilation, anti-proliferation, and anti-inflammation through activation of the ACE2-Ang-(1-7)-mas receptor, and the vaso-deleterious arm, which causes vasoconstriction, proliferation, fibrosis, and inflammation via the ACE-Ang-II-AT1 receptor. Reduced numbers of membrane-bound ACE-2 are the cause of the increase in activity in the Vaso deleterious arm of the RAS produced by SARS-Cov-2. Similar to SARS-Cov-2 in DM, the Vaso deleterious arm of the RAS is more active. When type 2 diabetes mellitus and coronavirus infection coexist, the immune system becomes dysregulated, exacerbating and prolonging lung disease.[72]RAS is the target of DM and SARS-Cov-2. These systems are found in the brain, pancreas, liver, kidney, heart, and lungs, among other tissues.[73] The primary cause of DM-induced myopathy, neuropathy, and nephropathy is an imbalance in RAS. A large number of COVID-19 elderly individuals have severe illness, including renal, liver, or cardiovascular disease.[74] In addition to causing pneumonia, COVID-19, especially in individuals with diabetes, can harm other organs including the heart, kidney, liver, pancreas, and immune system.[75,76] Since type-2 diabetes causes an imbalance in the receptor-amyloid system (RAS) in other tissues, such as the liver, heart, and lungs, it can exacerbate multiorgan failure in SARS-Cov infections.77 Deaths occur due to shock, cardiac failure, arrhythmias, multi-organ failure, and renal failure.[78] As a result, type-2 diabetes is now thought to be a risk factor for contracting fresh coronavirus infections.

DISCUSSION:

Hyperglycaemia and DM are independent predictors of mortality and morbidity in SARS patients .[71] In COVID 19, there is an imbalance between the vascular-damaging arm and the vascular-protective arm, which increases the activity of the vascular damaging arm. The increase in the activity of the vascular brands of the RAS caused by SARS-COV2 is due to a decrease in the amount of membrane-bound ACE-2. Similar to SARS COV2 DM, the activity of the vessel-damaging branch of the RAS is increased. The combination of corona virus infection and type 2 DM induces a dysregulated immune response leading to worsening and duration of lung pathology .[72]Both SARS COV2 and DM target the RAS. Such a system is distributed in several tissues, including the lungs, liver, kidneys, heart, blood vessels, pancreas, and brain. [73] Myopathy, neuropathy and nephropathy are caused by RAS imbalance. Many COVID 19 patients with heart, liver or kidney disease are critically ill. [74] Especially for people with diabetes, COVID 19 not only causes pneumonia but also damages other organs, such as the heart, kidneys, liver, pancreas, and immune system. [75,76] Type 2 DM causes RAS dysfunction in a variety of tissues including the lung, liver and heart. Thereby predisposing various organs to SARS COV infection. Patients suffer from multiple organ failure, shock, heart failure, arrhythmias, and kidney failure. [77]

Therefore, type 2DM has been considered a risk factor for novel corona virus infection .[78]

CONCLUSION:

Severe acute respiratory syndrome is the most common clinical symptom of COVID 19. This results from increased vascular permeability, alveolar flooding, damage of type 1 alveolar epithelial cells, death of type 2 epithelial cells, deterioration of surfactant synthesis, increase in alveolar epithelial surface and alveolar collapse. Pathological changes in the lungs are caused by inflammation and tissue damage due to increased production of inflammatory cytokines and reactive oxygen species. The pathology caused by COVID 19 is due to the imbalance of the RAS due to immune deficiency and excessive activity of the negative arm. DM affected by chronic disease and RAS, such as COVID 19, increase the risk of Corona Virus infection. Analysis of published data concluded that DM may increase susceptibility to COVID 19.

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