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Review: COVID-19 Outbreak and Diabetic Patient's Treatments Close Relationship

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Abstract: The severe acute respiratory syndrome (SARS-COV) are well known viruses from the family of Coronaviridae which in past caused outbreaks that led to various detrimental effect on world in many aspects. In the year 2019 when the new strain of coronavirus family (SARS-COV2) which is now known as COVID-19 (corona virus disease and 19 refer to the year it was first recognized) outbreak occurred in Wuhan affected the globe seriously. The health system got into a big challenge as this new strain of coronavirus spread much rapidly and caused much more mortality than the previous ones. The mortality was higher in those population which had comorbid conditions such as cardiovascular disease, lung disorders, chronic illnesses, diabetic patients and at the same time affected by COVID-19. Various regimes were selected but still proper and effective management is not available for such patients as these patients are already on multiple drugs. Among those chronic illnesses diabetic patients were found be highly susceptible to COVID-19. High disease mortality and worse outcomes in patients with diabetes urges that Diabetes appropriate management and better selection of drugs is crucial for the better outcomes in diabetic patients as most of the patients are treated for hypertension, hyperglycaemia and ongoing other chronic illnesses which could lead to worse case scenarios.

Keywords: COVID-19, Diabetes, ACEIs, Hyperglycemia

1. Introduction

Coronaviruses are from the family of the Coronaviridae which are the RNA viruses that affect multiple species. The two subfamilies of the family Coronaviridae contain Coronavirinae and Torovirinae. The members are further subdivided into Alphacoronavirus, Betacoronavirus, Gammacoronavirus, Torovirus, and Bafinivirus. The Coronaviridae members are from the family member who is enveloped and viruses are positive-stranded RNA of three classes of vertebrates, which include corona- and toroviruses for mammals, bafiniviruses for fishes and coronaviruses for birds [1].

Most human coronaviruses which are regarded as infecting humans mildly but in recent decade 2 outbreaks which led to an epidemic and panic situation worldwide. In zoonosis the coronaviruses (COV) jump from the animals to humans by adapting to the host environment, causing an abrupt increase in its pathogenicity and at the same time affecting a large proportion of the human population, which then confronts significant increase in the death rate. The major outbreaks which are instigated by the beta coronaviruses in the past two decades led to human suffering were Severe Acute Respiratory Syndrome coronavirus (SARS-COV) in 2002-2003 which happened in China [2] and Middle East respiratory syndrome coronavirus (MERS-COV) in 2012 in Saudi Arabia [3], which causes the respiratory viral illness resembling flu but one of the deadly sources of viral pneumonia raised the mortality rate up to 10% in SARS-COV and 36% for MERS-COV [4]. This group of coronavirus emerging as a new strain which is named by the WHO as "COVID-19" and meanwhile the international committee of the taxonomy named it Severe Acute Respiratory Disease-Coronavirus-2 (SARS-COV2). COVID-19 has come into notice in late December of 2019 in Wuhan, China with the cluster of atypical pneumonia and today it has led to a pandemic situation worldwide [5].

It is now been recognized that population who are more likely to have a greatest risk for complications and at the same time high fatality rate from COVID-19 are those with preexisting diabetes mellitus (DM), severe morbid obesity, and uncontrolled blood pressure, and other comorbid conditions which make them highly susceptible [6, 7]. Diabetes Mellitus plays an essential role by contributing in weakening the immunity and well identified as a key risk factor in contributing severe pneumonia and viral illness in around 20% of patients presenting with diabetes which require multiple hospitalizations throughout the year [8]. Diabetes was recognized as a key contributor among other related co-morbidities which ameliorated the disease severity in those patients infected with Middle East Respiratory Syndrome (MERS-CoV) [9]. The areas profoundly affected by COVID-19 which was evident from the investigations of the epidemiologist and reports disclose by the Centers for Disease Control and Prevention (CDC) medical centers around the country were the hospitals which exhibited that the diabetes mellitus patients compared to those patients without diabetes had a high risk of a serious outcome from COVID-19 related complications [10].

2. Role of Hyperglycemia in COVID-19

As we know that patients having the diagnosis of diabetes are at greater risk of developing high glucose levels (hyperglycemia) in the blood due to several factors. Data from the COVID-19 affected patients indicates that the high serum glucose in the blood of diabetic patients, and people without the diabetes disorder, the former depicted the worsening of prognosis and raises the mortality rate [11, 12]. It is assumed that the bad prognostic factor at the time of

admission is the presence of high serum glucose level of the patient, chronic complications of diabetes and those factors could potentiate the SARS-COV2 infectious stage which could be few of the risk factors for worse prognosis outcome in such patients. Few of the reasons which can explain that patients presenting with a drastic increase in blood glucose level can have detrimental effects on SARS-COV2 infection is, Hyperglycemia can affect the immune cells by increased activation of inflammatory cells, which then initiate the inflammatory process and creating an abnormal inflammatory environment which could one of the factors for abnormal cytokine storm [13].

A process known as non-enzymatic glycosylation is carried out in diabetes in which the sugars are attached to the various proteins of the body in the presence of hyperglycemia [14]. The immune cells recognize these different structurally modified proteins as foreign receptors and initiate an attack over these modified proteins, which in turn leads to abnormal flare up of inflammation leading to damage of the cells [14]. It's also been suggested that patients with a high level of glucose could change the structure of the ACE-2 receptor by adding a carbohydrate chain to it and making it available for the SARS-COV2 to attach to the host receptor [15]. A study is being published depicting that the hyperglycemia leading to increased glycosylation could be the main culprit behind COVID-19 infectivity and also in displaying its severity in the patient with a high level of glycosylated ACE-2 receptors and the SARS-COV2 particles found in the lung epithelium [15]. Therefore, the hyperglycemia which is not managed correctly can cause increased glycosylation of the ACE2 receptors in the various tissues and leading to change of these ACE2 receptors, which is now well recognized for the SARS-COV2 entry point to invade inside the host cell and high likelihood of COVID-19 infection and severity [15]. It is highly likely that the ACE2 receptor which is not glycosylated in comparison with the one which is glycosylated in high amount might play a crucial role for the SARS-COV2 in binding with the host cell receptor [15]. Once these ACE-2 receptors which are present in the respiratory tract have been modified by hyperglycemia in the diabetic patients could serve the fusion point for the SARS-COV2 binding sites. So it is possible that if the high blood glucose is managed aggressively and correctly it not only will decrease the alteration of the ACE-2 receptors but also diminish the release of the inflammatory cytokines which plays a crucial role in the cytokine storm of the COVID-19 infection, this could help in the outcome of the disease [16].

3. Role of ACEIs & ARBs in COVID-19 Patient with Diabetes

The cornerstone for treating various cardiovascular diseases and diabetic nephropathy are the novel Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) which are among one of the widely used medicine for such patients with these conditions [17,

18]. Various other choices are present in managing the patients with hypertension but ACEIs and ARBs are the drug of choice when it comes in reducing the risk of sudden death due to the heart problems [19].

SARS-COV and SARS-COV2 are the human pathogenic coronaviruses which cause cytokine storm and causes acute inflammation in lungs leading to severe respiratory distress. The attachment site and the entry access for the SARS-COV2 is through its spike protein which tightly binds to the human angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed on the various epithelial cells of the body such as lung, intestine, kidney, and blood vessels [20, 21].

Increased expression of ACE-2 receptors are found in the patients which are treated for various cardiovascular problems and diabetic patients ACE-2 receptor upregulation have been found in the patients who are treated with ACE inhibitors and angiotensin II Type-I receptor blockers (ARBs) for diabetic nephropathy and hypertension, the increased expression of such ACE-2 receptors could possibly explain that it could be one of the factor in contributing severity in such population [20]. Hypertension is one of the leading risk factor for many of the diseases, which is also widely managed by ACE inhibitors and ARBs, which results in an upregulation of ACE2 receptors [22]. A study conducted by Guan et al presented descriptive analysis of 1099 patients who were confirmed with COVID-19 infection, had more serious and fatal results with concomitant comorbid conditions such as chronic renal failure, hypertension, and diabetes. ACEi and ARBs were the drugs that were indicated in all of those patients who were positive for the COVID-19 infection [7]. The study concluded that patients with COVID-19 infection with concomitant chronic disorders, which were most likely treated with ACEIs or ARBs, suffered more severe disease outcome in compare to those without receiving these medications. The severity of the disease in patients was whether they have been admitted to the intensive care unit (ICU), needed the intubation for ventilation, mechanical ventilation was carried out and death. On the other flip side of the coin, a study showed that Renin-angiotensin system blockers ameliorated the clinical outcomes in those patients who were already being treated for hypertension and at the same time were positive for the COVID-19 infection [23]. It was suggested that the main factor which caused hypertension and lung failure was the unusual increase in the peptide hormone angiotensin II. Besides, RAS inhibitors are associated with reduced mortality in patients which are treated chronically for cardiovascular diseases and diabetic nephropathy [24]. Angiotensin II is a peptide hormone that exerts its effects mainly by binding to its (AGTR1) and (AGTR2) receptors and producing its desired effects [25]. Angiotensin II also plays a positive role in upregulating the response of inflammatory cytokines through its binding to the specific (AGTR1 receptor) in various tissues [26]. The ACEi/ARBs exerted their main effect by reducing the inflammatory response in tissues especially involving the inhibition of the interleukin-6 [27, 28].

4. Role of Antidiabetic Agents in COVID-19 Patient with Diabetes

Patients who are positive with COVID-19 and at the same time have a comorbid condition as diabetes are being treated with extreme caution that these patients don't progress to the severe form. As we know many treatments are available for managing the diabetics effectively but few of the managements have shown a positive effect while tackling the COVID-19 and diabetes simultaneously.

Sitagliptin an oral DPP-4 inhibitor has shown promising effect in reducing the severity in patients with type 2 diabetics admitted to the hospital for COVID-19. Sitagliptin was added in the regime in the hospitalized patients with reduce mortality and improved clinical outcomes. Insulin was the main choice due to its rapid effect on blood sugar levels and achieving the tight glycemic control which was found to be abnormal in most of the diagnosed patients. Sitagliptin was observed to reduce the pro-inflammatory cytokines in COVID-19 patients [29].

Glucagon like peptide 1 agonist (GLP-1) are also being implicated in diabetics treatment and at the same time has shown minimizing the cytokine storm [30] which is the basis in the severity of COVID-19. Despite the desired effect still GLP-1 treatment should be monitored closely to prevent any adverse effect. Sodium glucose co transporter-2 (SGLT-2) were not preferred while treating the diabetic patient with the risk of dehydration and urinary tract infection, which could have detrimental effects on the patient.

5. Conclusion

COVID-19 has emerged as one of humanity's most difficult tasks since World War II. It is critical to identify effective prevention and treatment techniques. Diabetes and associated comorbidities have been linked to a poorer outcome, albeit the pathophysiological and molecular processes behind this association are yet unknown. Researchers and authorities throughout the world should act quickly to address key problems about COVID-19 prevention and management, as well as the safety of diabetics. Different regimens have been shown to be affective but still further studies are needed to accurately select the most effective treatments for those diabetic patients which are diagnosed with COVID-19 and to possibly dampen the side effects caused by these agents used to treat such patients. The diabetic patient's appropriate treatment could lead to better outcome in COVID-19 patients.

To lower the risk of morbidity and death related to chronic illnesses such as diabetes, healthcare systems should implement techniques for case diagnosis and treatment while sustaining care and availability of critical drugs. The strategic use of human resources in healthcare services and the

protection of their health is an urgent requirement. The current health-care crisis should be viewed as an opportunity to enhance service delivery, learn from effective regional and global initiatives, and prepare for future difficulties of larger scope. The pandemic also emphasises the importance of coordinated public health interventions and policies that cover everyone.

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