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Impact of Diabetes Among People Infected with COVID-19

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Abstract

This is a brief review aimed to characterize the novel coronavirus (SARS-CoV-2) for a better understanding of the COVID-19 in people with diabetes, and its management. We searched for articles in PubMed and Google Scholar databases for articles related to this subject.

The clinical spectrum of COVID-19 is heterogeneous. Older age, diabetes, and other comorbidities are reported as significant predictors of morbidity and mortality. Chronic inflammation, increased coagulation activity, immune response impairment, and potential direct pancreatic damage by SARS-CoV-2 might be among the underlying mechanisms of the association between diabetes and COVID-19.

Human pathogenic coronaviruses (severe acute respiratory syndrome coronavirus (SARS-CoV and SARSCoV-2) were bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels. The expression of ACE2 is substantially increased in patients with type 1 or type 2 diabetes, who are treated with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs).

These data suggest that ACE2 expression is increased in diabetes with ACE inhibitors and ARBs increases ACE2 expression. Consequently, the increased expression of ACE2 would facilitate infection with COVID-19. We therefore hypothesize that diabetes treatment with ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19.

Caution should be taken to potential hypoglycemic events with the use of chloroquine in diabetic patients. In conclusion: It is difficult to extract specific conclusions based on currently limited evidence. Therefore, further researches are needed to identify the real relationship between diabetic patients and COVID-19.

Keywords: COVID-19, SARS-CoV-2, diabetes, diagnosis, treatment.

1. Introduction

The relationship between peoples with diabetes and coronavirus disease (COVID-19) caused by SARS-CoV-2 is still limited and unclear. Therefore, the understanding the nature of this relationship is very important to enabling patients and healthcare professionals to adopt the right choice about how to manage peoples with diabetes during the COVID-19 pandemic.

Diabetes as one of the most common comorbidities lead to higher mortality has been reported (Yang et al., 2020: 533).

COVID-19 is rapidly increasing globally.

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However, risk factors for the severity and prognosis of COVID-19 are poorly understood. Such information is critical to identify high risk patients and to facilitate planning (Matsushita et al., 2020: 4).

A meta-analysis study revealed that there are some risk factors associated with COVID-19 such as cardiovascular disease (CVD)(sever COVID-19 with patients with CVD compared without CVD: RR=3.58 [2.06-6.21]), age (Older age was consistently associated with severe COVID-19 with RR >~5 in >60-65 vs < 50 years), gender (severe COVID-19 in men than in women, with a pooled crude relative risk estimate of severe COVID-19 between men and women of 1.70 (95 % CI 1.52-1.89), current smoking (the association across categories of current smoking (odds ratio 2.84 [1.57-5.14]), hypertension (a positive association of hypertension with severe COVID-19, with the pooled relative risk estimate of 2.74 (95 % CI 2.12-3.54), and diabetes (a positive association between diabetes and severe COVID-19, with a pooled relative risk estimate of 2.81 (2.01-3.93) (Matsushita et al., 2020: 8).

However, results have been inconsistent. Few studies concerned for the confounding between age and sex when they evaluated other risk factors. For example, some studies reported that hypertension is a risk factor of severe COVID-19, but it is well known that hypertension is more common in older adults (Benjamin et al., 2020: 67).

This observation, together with the fact SARS-CoV-2 uses angiotensin-converting enzyme 2 as an entry to human body (Zhang et al., 2020: 588), has raised a concern about continued use of renin-angiotensin system increase among some clinicians and researchers (Esler, Esler, 2020: 782; Fang et al., 2020: 21).

Diabetes was seen as a risk factor for mortality in patients infected with Pandemic Influenza A 2009 (H1N1), Severe Acute Respiratory Syndrome (SARS) coronavirus and Middle East Respiratory Syndrome-related coronavirus (MERSCoV) (Yang et al., 2006: 625; Schoen et al., 2019: 964; Song et al., 2019: 11).

2. Results and discussion

Diagnosis

Diagnostics can play an important role in the containment of COVID-19, enabling the rapid implementation of control measures that limit the spread through case identification, isolation, and contact tracing (Udugama et al., 2020: 3830).

The symptoms expressed by COVID-19 patients are nonspecific and cannot be used for an accurate diagnosis because of Many of these symptoms could be associated with other respiratory infections (Udugama et al., 2020: 3830). There are several markers have been used for detection such as IgG, IgM, levels of C-reactive protein and D-dimer as well as levels of lymphocytes, leukocytes, and blood platelets (Guan et al., 2020a). The using of these biomarkers could lead to inaccurate diagnosis because of they are also abnormal in other illnesses (Udugama et al., 2020: 3830). However, the real-time fluorescence (RT-PCR) remains till now the standard method for diagnosis of COVID-19. Long et al. (2020) reported that RT-PCR may produce initial false negative results therefore they suggest that negative RT-PCR results should be isolated, and RT-PCR should be repeated to avoid misdiagnosis. Due to the shortage of kits and false negative rate of RT-PCR, the Hubei Province, China temporarily used CT scans as a clinical diagnosis for COVID-19 (Yang, Yang, 2020).

In recent years, smartphone components (e.g., camera, flashlight, and audio jack) have been used for the readout of diagnostic assays in place of conventional laboratory equipment (Malekjahani et al., 2019).

Treatments patients with COVID-19

Development of therapeutics and vaccines is underway, but there is no approved therapeutics or vaccines for the treatment of COVID-19 (Udugama et al., 2020).

The treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock (Cascella et al., 2020).

Although no antiviral treatments have been approved, several approaches have been proposed such as lopinavir/ritonavir (400/100 mg every 12 hours), chloroquine (500 mg every

12 hours), and hydroxychloroquine (200 mg every 12 hours). Alpha-interferon (e.g., 5 million units by aerosol inhalation twice per day) is also used.

The drug Chloroquine is approved to treat malaria and rheumatoid arthritis. It has been tested in vitro against a number of viruses, including SARS, and found to inhibit growth (Touret, de Lamballerie, 2020). This drug has been tested against SARS-CoV-2 – the cause of COVID-19 and found "highly effective," although the evidence is still limited and need larger controlled trials to determine accurately the effectiveness of chloroquine as a treatment for COVID-19 (Gao et al., 2020; Wang et al., 2020).

Reported that there are three effects could help to stimulate the body's ability to fight off covid-19: firstly: the virus is initially taken up into an intracellular 'compartment' which is typically acidic but Chloroquine could alter the acidity of this compartment, which can interfere with the ability of viruses to escape into the host cell and start replicating. Another possibility is that chloroquine may alter the ability of the virus to bind to outside of a host cell, and lastly, chloroquine has subtle effects on a wide variety of immune cells as this drug is used sometimes in autoimmune conditions (Mahase, 2020).

Kaletra drug which is a combination of two antiviral drugs—lopinavir and ritonavir—normally used to treat HIV. It was suggested for treatment patients with COVID-19 but the results from China depend on a randomized controlled trial obtained the non-benefit of its using (Cao et al., 2020). Also, there are other drugs have been used and need to test for patients with COVID-19 using a clinical trial such as: Interferon β 1a (SNG001), Remdesivir, Tocilizumab (Actemra), and Favipiravir (Avigan) (Chen et al., 2020; Financial Times, 2020; USFDA, 2020).

The reliable results about COVID-19 in patients with diabetes are limited at present. The results also are inconsistent. Peng (2020) reported that Diabetes was present in 42.3 % of 26 death cases due to COVID-19 in Wuhan, China. Another study in 140 patients with COVID-19 in Wuhan, China, results showed that the diabetes was not a risk factor for severe disease course (Zhang et al., 2020). Whereas, another study in 150 patients (68 deaths and 82 recovered patients) in Wuhan showed that a total of 63 % (43/68) of death cases had underlying diseases (Ruan et al., 2020). Analysis of 11 studies out of 217 articles regarding laboratory abnormalities in patients with COVID-19 did not clearly describe the rate of patients with laboratories abnormalities, the results, including increased values of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH) and D-dimer. They did not mention raised blood glucose or diabetes as predictor of severe disease (Lippi, Plebani, 2020). On the other hand, a report published by Chinese Centre for Disease Control and Prevention showed that the overall case-fatality rate (CFR) was 2.3 % (1023 deaths among 44 672 confirmed cases) whereas, the CFR was elevated among those with diabetes (7.3 %) (Wu, McGoogan, 2020).

A meta-analysis study including 1527 patients in China showed that the most prevalent comorbidities with COVID-19 were hypertension (17.1 %, 95 % CI 9.9 – 24.4 %) and cardio-cerebrovascular disease (16.4 %, 95 % CI 6.6 – 26.1 %), followed by diabetes (9.7 %, 95 % CI 6.9 – 12.5 %). In this study, patients with diabetes or hypertension had a 2-fold at risk of severe COVID-19 disease (Li et al., 2020)

Limited data were existed regarding the glucose metabolism and development of acute complications of diabetes (e.g., ketoacidosis) in patients with COVID-19.

Infection of SARS-CoV-2 in those with diabetes possibly caused higher stress conditions, lead to greater release of hyperglycemic hormones, e.g., glucocorticoids and catecholamines, and then resulted to increased blood glucose levels (Wang et al., 2020).

Diabetes is a chronic inflammatory condition characterized by multiple metabolic and vascular abnormalities that can affect response to pathogens (Knapp, 2013). Hyperglycemia and insulin resistance promote increased synthesis of glycosylation end products (AGEs) and pro-inflammatory cytokines, oxidative stress, in addition to stimulating the production of adhesion molecules that mediate tissue inflammation (Knapp, 2013; Petrie et al., 2018). This inflammatory process may compose the underlying mechanism that leads to a higher propensity to infections, with worse outcomes thereof in patients with diabetes (Knapp, 2013).

The results of the *In vitro* studies showed that pulmonary epithelial cells exposure to high glucose concentrations significantly increases influenza virus infection and replication, thus, the hyperglycemia may enhance viral replication *in vivo* (Kohio, Adamson, 2013).

Animal studies involving SARSCoV reported that older age was related to defects in T-cell and B-cell function and excess inflammation markers. Thus, T2DM alone or in association with older age, hypertension and/or CVDs might contribute to a deficient control of SARS-CoV-2 replication and more prolonged proinflammatory response, potentially leading to poor outcomes (Zhou et al., 2020).

The fundamental component of cross-species transmission is viral entry into the host cells, particularly for the coronaviruses (CoVs). After exposure of the host to the virus, all CoVs, bind to cells by express specific receptors through a Spike protein. After that the host-cell protease cleaves the spike to be able to enter the cell and replicate (Letko et al., 2020). The angiotensin-converting enzyme 2 (ACE2) has been identified as one of the main receptors for both SARS-CoV (51) and SARS-CoV-2 (Letko et al., 2020). ACE2 is widely expressed on the respiratory tract, heart, kidneys, intestines, cerebral neurons, endothelium of arteries and veins, immune cells and pancreas (Song et al., 2019). A Chinese study compared 39 SARS-CoV patients without previous diabetes, who did not receive steroid treatment, with 39 matched healthy siblings and showed that 20 of the 39 SARS-CoV patients developed diabetes during hospitalization. Since immunostaining for ACE2 was strong in the pancreatic islets, it was suggested that SARS-CoV might have damaged islets and caused acute insulin dependent diabetes mellitus (Yang et al., 2010). Although further evidence is needed to confirm that pancreatic damage may also be present in COVID-19 patients, possibly contributing to worse outcomes in subjects with diabetes (Hussain et al., 2020).

The data from 1590 laboratory-confirmed hospitalized patients across mainland China between December 11th, 2019 and January 31st, 2020 showed that the most prevalent comorbidity was hypertension (16.9 %), followed by diabetes (8.2 %). After adjusting for age and smoking status the hazards ratio (HR) of diabetes was 1.59, (95 % CI 1.03–2.45) and patients with two or more comorbidities were more commonly seen in severe cases than in non-severe cases (40.0 % *versus* 29.4 %) (Guan et al., 2020b).

Some studies reported that the prevalence of diabetes in people infected with the virus area slightly lower (Fadini et al., 2020; Li et al., 2020).

A meta-analysis (12 studies) from 2,108 Chinese patients with COVID-19 reported a diabetes prevalence of 10.3 % (Fadini et al., 2020) was similar to the national prevalence of 10.9 % reported by Wang et al. (2013). An equivalent prevalence was reported in Italy among 146 patients with confirmed SARS-CoV-2 infection at the University Hospital of Padova. The prevalence of diabetes in these patients was 8.9 % (mean age 65.3 year) and 11.0 % (mean age 65) for the same location in 2018 (Longato et al., 2020).

Treatment of patients with diabetic infected by COVID-19

The patients with diabetes infected by COVID-19 could be treated with chloroquine which was reported as a potential broad-spectrum antiviral drug (Hussain et al., 2020). Although the efficacy and safety of chloroquine for COVID-19 treatment still unclear, a recent study confirmed that the drug was highly effective in controlling SARS-CoV-2 infection *in vitro* (Wang et al., 2020).

The results of more than 100 patients included in a Chinese clinical trial showed that chloroquine was superior to the control group and revealed improvement without severe side effects (Gao et al., 2020).

Although, some studies reported that hydroxychloroquine improves glycemic control in patients with diabetes (Gerstein et al., 2002; Rekedal et al., 2010). The underlying mechanism of hydroxychloroquine's hypoglycemic effect is unclear (Rekedal et al., 2010).

However, a study contributed that the chloroquine will increase the C peptide response and lead to improve the pancreatic β-cell function (Rekedal et al., 2010). The increasing in the insulin accumulation has also been reported as possible effects of hydroxychloroquine in animals' models (Emami et al., 1999).

A Chinese Centre for Disease Control and Prevention report reported that from 72,314 cases, the overall case – fatality rate (CFR) was 2.3 % (1023 deaths among 44,672 confirmed cases) whereas the CFR was 7.3 % for diabetes.

In another study included of 191 patients from Wuhan Pulmonary Hospital I China showed that a total of 137 were discharged and 54 died. The patients who had a comorbidity was 91 (48 %), with hypertension being the most common (58 [30 %] patients), followed by diabetes (36 [19 %] patients and coronary heart disease (15 [8 %] patients and found that diabetes was associated with significantly higher odds of death (OR 2.85, 95 % CI 1.35 to 6.05) (Zhou et al., 2020).

In a retrospective case study included of 1,590 laboratory-confirmed hospitalized patients in China found that after adjusting for age and smoking status, diabetes significantly increased risk (hazard ratio 1.59, 95 % CI 1.03–2.45). 34.6 % of severe cases were in patient with diabetes compared to 14.3 % in non-severe cases (Guan et al., 2020).

3. Conclusion

COVID-19 is spread rapidly, therefor, the early diagnosis, and management represent the better control ways of the disease. Diabetes is significant predictors of morbidity and mortality in patients with COVID-19. Future research is urgently needed to provide a better understanding regarding potential differences in genetic predispositions across populations, underlying pathophysiological mechanisms of the association between COVID-19 and diabetes, and its clinical management. At the moment, the therapeutic strategies to deal with the infection are only supportive, and prevention in order to reducing the transmission in the community is our best weapon (Cascella et al., 2020).

Declaration of competing interest

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