University of Diyala

Collage of Medicine

Graduation project

Risk of covid 19 on diabetic patient

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هَذَا بَلَاغٌ لِلنَّاسِ وَلِيُنذَرُوا بِهِ وَلِيَعْلَمُوا أَنَّمَا هُوَ إِلَهٌ وَاحِدٌ وَلِيَذَّكَّرَ أُولُوا الْأَلْبَابِ

صدق الله العظيم

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Abstract

In light of the most challenging public health crisis of modern history, COVID-19 mortality continues to rise at an alarming rate. Patients with co-morbidities such as hypertension, cardiovascular disease, and diabetes mellitus (DM) seem to be more prone to severe symptoms and appear to have a higher mortality rate. In this review, we elucidate suggested mechanisms underlying the increased susceptibility of patients with diabetes to infection with SARS-CoV-2 with a more severe COVID-19 disease. The worsened prognosis of COVID-19 patients with DM can be attributed to a facilitated viral uptake assisted by the host's receptor angiotensin-converting enzyme 2 (ACE2). It can also be associated with a higher basal level of pro-inflammatory cytokines present in patients with diabetes, which enables a hyperinflammatory "cytokine storm" in response to the virus. This review also suggests a link between elevated levels of IL-6 and AMPK/mTOR signaling pathway and their role in exacerbating diabetes induced complications and insulin resistance. If further studied, these findings could help identify novel therapeutic intervention strategies for patients with diabetes comorbid with COVID-19.

Aims of the review

This review aims to collate currently available data about dia-

betes and COVID-19 infection. It specifically looks at the relation

between diabetes and COVID-19 in terms of epidemiology, patho-

physiology and therapeutics. and affected of anti diabatic drug on coronaviruses

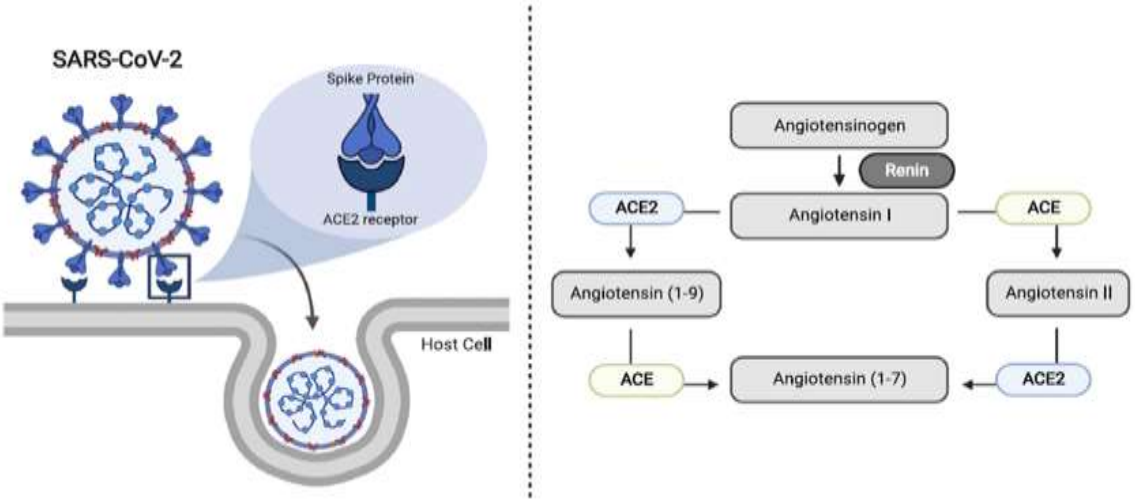
Introduction

Coronaviruses can affect a variety of animals, including cattle, pigs, goats, turkeys, cats, rodents, dogs, and people. In humans, these viruses cause serious diseases like extreme acute respiratory syndrome (SARS) and pneumonia, as well as more minor illnesses like the common cold and diseases of the stomach. The first coronavirus was isolated in 1937 from birds infected with the viral bronchitis virus, which has the potential to wipe out poultry flocks. Coronaviruses are responsible for 15–30% of the chronic colds. 1st Following the discovery in December 2019 of a cluster of patients in Wuhan with pneumonia of uncertain origin caused by a novel coronavirus, CoV-19 [1], The main clinical manifestations were pyrexia, myalgia, fatigue, coughs, dyspnea, and pneumonia, which were confirmed by radiographic examination of the chest[2].

COVID-19 is a member of the coronavirus family, which consists of four genera: Alpha-, Beta-, Delta-, and Gammacoronavirus [3]. Coronaviruses of the genera Alpha and Betacoronavirus are mostly found in mammals, while viruses of the genera Gamma and Deltacoronavirus are mostly found in humans. [4].

SARS-CoV-1, the virus that caused the 2002 epidemic, and SARSCoV-2 are both members of the -genus [5]. Many of the signs associated with SARS-CoV-2, such as ARDS, are similar to those associated with SARS-CoV-1 [14The structural similarity between the two virus's envelope-anchored spike (S) protein, which mediates their entry into host cells, can be traced back to this. [15]. SARSCoV-1's cross-species and human-to-human transmissions are regulated by crucial interactions between its S protein receptor-binding domain (RBD) and its host receptor angiotensin-converting enzyme 2 (ACE2). [6]. The S proteins of SARS-CoV-1 and SARS-CoV-2 have a 76 percent to 78 percent sequence similarity for the entire protein and a 73 percent to 76 percent sequence similarity for the RBD, indicating that both viruses use the same entry door to host cells: Angiotensin-converting enzyme 2 is a protein that converts angiotensin II into angiotens (ACE2) [7] (Fig.1)

Fig. 1 Schematic diagram representing (a) SARS-CoV-2 entry into the host cell and (b) the role of ACE2 in the renin-angiotensin system



Furthermore, infection with SARS-CoV-2 causes a rise in the production of pro-inflammatory cytokines and chemokines such as interleukins IL-1, IL-4, and IL-10, monocyte chemoattractant protein 1 (MCP-1), interferon- (IFN), and interferon gamma-induced protein 10. (IP-10) [8]. Notably, ICU patients with severe disease had significantly elevated plasma levels of IL-2, IL-6, IL-7, IL-10, granulocytes colony stimulating factor (GCSF), IP-10, MCP-1, macrophage inflammatory protein-1A (MIP-1A), and tumor necrosis factor-α (TNF-α), suggesting a potential "cytokine storm" correlated with COVID-19 disease severity [9]. The release of pro-inflammatory cytokines and chemokines may potentially be attributed to massive epithelial and endothelial cell apoptosis and to vascular leakage resulting from rapid viral replication[10] . IL-1β was shown to be increased in the bronchoalveolar lavage fluid and in the plasma of patients with ARDS [11]. Similarly, IL-6 functions as a proinflammatory factor and was shown to play an important role in the progression of lung fibrosis[12]. IL-6 is an important pleiotropic cytokine that significantly contributes to acute inflammation. Elevated IL-6 levels were correlated with increased severity of COVID-19-associated pneumonia. In mild cases, systemic levels of IL-6 were less than 100 pg/mL. However, in critical cases, IL-6 levels were greater than 100 pg/mL, a concentration above which we usually witness the emergence of an "inflammatory storm" [13]. Consequently, it was reported that the inhibition of both IL-1β and IL-6 is beneficial in many viral infections [14]. A retrospective study observing the efficacy of tocilizumab (IL-6R antagonist) in treating COVID-19 suggested that tocilizumab might be an effective treatment in patients with the severe form of the disease [15].The pathophysiology of SARS-CoV-2 infection has not yet been

extensively investigated, but it is speculated that it can resemble that of SARS-CoV-1 overall. Infection with SARSCoV-1 results in an aggressive inflammatory response that begins with binding to the membrane-bound ACE2 receptor [16] followed by entry into the cell and subsequent viral replication [17]. Similarly, downregulation and shedding of ACE2, a terminal carboxypeptidase that degrades angiotensin II to angiotensin (1–7), may be a function of SARS-CoV-2-mediated inflammatory responses., As a result, it acts as a renin-angiotensin pathway negative regulator [18]. Although ACE causes lung edema and facilitates lung damage by converting angiotensin I to angiotensin II, ACE2 tends to shield the lungs from acute injury [19]. (Fig. 1). Loss of pulmonary ACE2 expression was linked to increased inflammation, increased vascular permeability, increased lung edema, and neutrophil aggregation in several trials, ultimately contributing to reduced lung function. [20].

Method of Transmission of Infection

Human coronaviruses are spread mostly through the air from an infectious person to a healthy person through sneezing and coughing. Close physical contact, such as rubbing or shaking hands and rubbing a virus-infected object or surface before brushing one's mouth, nose, or eyes before washing one's hands, seems to be spreading the virus. Fecal exposure is an unusual way for these viruses to spread. Human coronavirus infections are most common in the fall and winter, although the virus will infect people at any time of year, and the weather does not appear to affect transmission. Over his or her lifetime, someone may

become infected with one or more human coronaviruses. Infection is also a possibility extends to kids[1,4].

Diabetes and COVID-19

Diabetes mellitus is associated with poor prognosis in patients with COVID-19. On the other hand, COVID-19 contributes to worsening of dysglycemia in people with diabetes mellitus over and above that contributed by stress hyperglycemia[5], Multiple pathophysiological explanations can be put forward supporting the association between DM and COVID-19 severity. Innate immune system, the first line of defense against SARS-CoV-2, is compromised in patients with uncontrolled DM [21]. Moreover, DM is a pro-inflammatory state characterized by inappropriate and exaggerated cytokine response; this has been depicted in COVID-19 patients wherein serum levels of interleukin-6 (IL-6),C-reactive protein and ferritin were significantly higher in patients with DM than those without DM [22]. his suggests that people with diabetes are more susceptible to an inflammatory cytokine storm eventually leading to ARDS, shock and rapid deterioration of COVID-19. In addition, the aforementioned study also showed that COVID-19 patients with DM had higher D-dimer levels than those without DM [23]; perhaps signifying over-activation of the hemostatic system. Amid an already underlying pro-thrombotic hypercoagulable state predisposed by the mere presence of DM [24].

Due to COVID-19, patients with DM are more likely to suffer serious symptoms and complications than patients without DM, according to current evidence 6]. One theory is that hyperglycemia aids viral entry into cells because

both ACE2 and the virus need glucose to survive [25]. While further research is needed to fully understand the interactions between COVID-19 and DM, we have reviewed the possible molecular pathways involved from a cell biology standpoint. Higher-affinity cellular binding, effective viral entry, decreased viral clearance, reduced T cell activity, increased susceptibility to hyperinflammation and cytokine storm, and the involvement of cardiovascular disorders have all been proposed as explanations for the increased susceptibility of patients with DM to serious COVID-19 disease.. Phagocytosis

In patients with diabetes who also have malfunctions in neutrophil chemotaxis, bactericidal response, and innate cell-mediated immunity, neutrophils, monocytes, and macrophages were found to be deficient [58]. Even short-term hyperglycemia was discovered to suppress their innate immune responsePatients with diabetes have a faulty innate immune system as well as an ineffective adaptive immune response. [26].

Diabetes mellitus: A risk factor for the progression of COVID-19

Diabetes mellitus is one of the leading causes of morbidity worldwide, and it is projected to remain on the rise over the next few decades. A large body of evidence has highlighted an increased susceptibility of patients with diabetes to infectious diseases, which is possibly attributed to a defective immune system in diabetes. Given the decreased immunity in patients with diabetes, pneumonia has now become a considerable mortality factor in diabetes . In patients with SARS, diabetes, and plasma glucose levels were both shown to be independently

associated with higher morbidity and mortality. In patients with SARS, diabetes and plasma glucose levels were both shown to be independently associated with higher morbidity and mortality [27. In Hong Kong, the first three deaths from SARSCoV-2 infection were patients with diabetes. In a study conducted on a group of 52 ICU patients infected with SARSCoV-2, the most common comorbidities between the 32 nonsurvivors of the group were diabetes (22%) and cerebrovascular disease (22%) . Recently, The Chinese Center for Disease Control and Prevention published the largest study relevant to patients with diabetes in Mainland China which involved 72,314 cases of COVID-19. While patients who reported no co-morbidities had a case fatality rate of 0.9%, patients with diabetes had a significantly higher case fatality rate (7.3%) . Furthermore, a meta-analysis of 76,993 patients infected with SARS-CoV-2 revealed that hypertension, cardiovascular disease, history of smoking, and diabetes were the most common underlying diseases with incidences of 16.37%, 12.11%, 7.63%, and 7.87%, respectively . In another study conducted on 1099 COVID-19-infected patients in China, 173 cases (16%) were classified as severe Out of these severe cases, 16.2% (28 individuals) had diabetes, while only 5.7% (81 individuals) of the non-severe cases had diabetes [28]. Furthermore, a retrospective study in Wuhan, China conducted on 174 patients with COVID-19 revealed a higher risk of severe pneumonia in patients with diabetes (n = 24) who did not suffer from any other complication .These patients also presented with a higher risk of tissue injury-related enzyme release and an overexpressed uncontrolled inflammation. Dysregulated glycemia also appeared to lead to a hypercoagulable state through the activation of plasmin, thrombin, and monocytes

macrophages and through the secretion of different tissue factors, a resultant of the inflammatory storm itself . According to the CDC, as of May 30, 2020, in a population of about 1.3 million individuals infected with SARS-CoV-2 in the USA, around 30% of those individuals who have underlying health conditions (86,737 individuals) have diabetes mellitus. The different studies presented suggest that patients with diabetes may not only be prone to a more severe COVID-19 disease, but also to an increased risk of infection with SARSCoV-2. However, several studies have shown that, despite these latter findings, no increased infectivity was observed in patients with COVID-19 comorbid with diabetes. In fact, the prevalence of diabetes in the patient population with COVID-19 is not so different from the prevalence of diabetes in the general population [29].

- ***Management of diabetes mellitus amid COVID-19 pandemic***

Given the severity of the pandemic and the lack of a conclusive COVID-19 treatment, people with diabetes should be extra vigilant and take all possible precautions [3,4]. Hand grooming and strict social distancing should be the rule. Glycemic regulation should be prioritized and it can aid in the enhancement of the innate immune system[30]. However, widespread national lockdowns would reduce their in-clinic appointments, restrict their physical exercise, change their eating patterns, and have a negative impact on their mental health, all of which would contribute to low glycemic control . Indeed, a recent Chinese study found that elderly people with type 2 diabetes had elevated fasting blood glucose levels during the COVID-19 pandemic . Teleconsultations with licensed medical professionals may help people with diabetes avoid many of the issues that

lockdowns cause . Although certain anti-diabetic drugs like pioglitazone and liraglutide have been shown to upregulate ACE2 in animal models, the current evidence does not support any change in the ongoing medications [31]. Similarly, international organizations recommend patients on ACEi/ARBs to carry on with their medications. Although used rarely, hydroxychloroquine can be good anti-diabetic medication in the present scenario as the drug has also been shown to inhibit SARS-CoV-2 infection in-vitro as well as reduce the viral load in COVID-19 patients. The drug has also been approved for prophylaxis against COVID-19 in many countries .Considering the low-cost, widespread availability, modest HbA1c reduction, once-daily dosing and relatively good tolerability, hydroxychloroquine may be a good add-on drug during this outbreak for patients with poor glucose control, provided contraindications like diabetic retinopathy and cardiomyopathy has been ruled out . Similarly, tocilizumab, a monoclonal antibody against IL-6, is being tried in patients with COVID-19. Tocilizumab is known to improve insulin resistance and reduce HbA1c in patients with rheumatoid arthritis and diabetes mellitus . In addition, camostat mesilate has been used as anti-viral drug against COVID-19; the drug was earlier pursued as an anti-diabetic drug as it was shown to lower blood glucose levels in insulin-treated patients with diabetes mellitus . In addition, remdesivir, an adenosine analogue that inhibits viral replication, does not affect blood glucose and lipids when compared to placebo . Convalescent plasma has been used in the management of COVID-19 and seems to be a safe alternative . The effect of drugs being tried in the management of COVID-19 on glucose and lipid profiles has been summarized in Table 1.

Drug being used in the management of COVID-19	Mechanism of action in COVID-19	Effect on glucose profile	Effect on lipid profile
Corticosteroids	Anti-inflammatory, blocks cytokine Storm	Hyperglycemia	Dyslipidemia (increase in TC, LDL, TG)
Lopinavir/Ritonavir	Protease inhibitors, blocks viral cellular Entry	Lipodystrophy Hyperglycemia	Dyslipidemia (increase in TC, TG)
Darunavir/Cobicistat	Protease inhibitors, blocks viral cellular Entry	Lipodystrophy Hyperglycemia (less likely compared to lopinavir/ritonavir)	Dyslipidemia (increase in TC, TG) (less likely compared to lopinavir/ ritonavir)
Remdesivir	Adenosine analogue, inhibits viral Replication	Increased blood glucose seen in 7% of patients in remdesivir vs. 8% in placebo group	Increased blood lipids seen in 6% of patients in remdesivir vs. 10% in placebo group
Interferon-ß1 (and other Type 1 interferons)	Cytokine, stimulate innate antiviral Immunity	Can lead to autoimmune b-cell damage, thereby, precipitating or worsening diabetes mellitus	Dyslipidemia (increase in TG mainly)
Chloroquine/ Hydroxychloroquine	Increases host cell endosomal pH, prevents viral entry and immunomodulator	Improves glucose profile and HbA1c in people with T2DM	Improves lipid profile in people with T2DM (reduced TC, LDL, TG, variable effect on HDL)
Azithromycin	Macrolide antibiotic used with hydroxychloroquine, known to have invitro activity against Zika and Ebola virus, prevents severe respiratory tract infection in patients suffering from viral Diseuse	Risk of dysglycemia in people with diabetes mellitus	No robust data Being an enzyme inhibitor, may prolong half-life of statins
Camostat mesilate	Protease inhibitors, blocks viral maturation and entry into cells	Found to lower blood glucose levels in insulin-treated patients with diabetes mellitus	Not known
Tocilizumab	Monoclonal antibody against IL-6, blocks cytokine storm	Improves glucose profile and reduces HbA1c in people with rheumatoid arthritis and diabetes mellitus	Alters lipid profile in people with rheumatoid arthritis (increase in TC, HDL, TG, no change in LDL)
Convalescent plasma	Provides anti-SARS-CoV-2 antibodies	Not known (probably no effects)]	Not known (probably no effects)

Table 1summarizing the potential effects of drugs/treatment options being used in the management of COVID-19 on glucose and lipid profiles.

Act now People with diabetes are dying with COVID-19. It is highly likely that risk factor control by good diabetes care could reduce the impact of COVID-19 in diabetes. Share Diabetes UK's advice with people with Diabetes .9,10 Handwashing Repeated, regular, 20-second handwashing is vital. Remind every patient (and yourself) every time. A cleaning company observed the washroom habits of 100,000 people in Europe in 2015. 'Anonymous monitoring of 100,000 people reveals that only 38% of men and 60% of women wash their hands after going to the toilet.'11 Hyperglycaemia and weight Help people to control their blood glucose to within their safe limits. Try to help people with morbid obesity lose weight and address comorbidities.Renal impairment Prevent renal impairment with good blood pressure and glucose control. People with eGFR <15 and diabetes are highly vulnerable. Check Kidney Care UK's detailed advice about self-isolating (shielding) for each patient.12 Men, older people, BAME ethnicity, socio-economic deprivation Regularly remind these people about self-protection.Seek and treat additional risk factors.

SARS CoV 2 infection associated with diabetes can trigger stress conditions with higher secretion of hyperglycemic hormones (glucocorticoid and catecholamines) that can result in insulin resistance, hyperglycemia, and other complications [11 12]. Pancreatic β cells, which are the only insulin producing cells in the body, could be also a target for infection and subsequent destruction as elaborated below, thus worsening the glucose homeostasis.

Role of antidiabetic drugs in current context

There is no data on the differential effects of oral antidiabetic drugs on the disease course in COVID-19. Metformin has anti-proliferative and immunomodulatory effects by virtue of inhibition of AMP activated protein kinase and has shown protective role in pneumonia in mouse models . In one study in patients with tuberculosis, patients treated with metformin had better survival than those who did not receive metformin . In a median 6.2 years of follow up of 5266 patients with diabetes, Mendy et al . showed that metformin was significantly associated with a decreased risk of mortality in patients with chronic lower respiratory diseases (HR: 0.30, 95% CI, 0.10 to 0.93), even after the adjustment for multiple confounding factors. In a study of 4321 patients with a follow up of 2-year period, Ho et al. showed metformin users had a significantly lower risk of death (HR, 0.46; 95% CI, 0.23 to 0.92), compared with non-metformin users, in patients with coexistent chronic obstructive pulmonary disease and diabetes. Thiazolidinediones (TZD) seen to increase the risk of pneumonia in a study when compared to sulfonylureas.
Experimental studies suggest that pioglitazone reduces steatohepatitis by increasing the ACE-2 expression in liver tissues [32], This purported increase in ACE-2 expression and its relation to COVID-19 has led some researchers to propose avoiding TZD in patients with diabetes and COVID-19. Experimental studies also suggest thatliraglutide, a GLP-1 receptor agonist increases the ACE-2 expression in lungs in type 1 diabetic rat and improves right ventricular hypertrophy .Implications of these findings in the current context

of COVID-19 and its relation to anti-diabetic drugs is not yet fully clear.

Discussion

People with diabetes with COVID-19 are at a greater risk

of worse prognosis and mortality. Given the high worldwide prevalence of diabetes, these individuals represent a large vulnerable segment of the COVID-19 population. The poorer prognosis of people with diabetes is the likely consequence of the syndromic nature of the disease. hyperglycaemia, older age, comorbidities, and in particular hypertension, obesity, and cardiovascular disease all contribute to increase the risk in these individuals. The picture, however, is more complicated as it requires factoring in societal factors such as deprivation and ethnicity as well as factors that become relevant at the time that a patient with severe COVID-19 needs to be managed. Here, a physician has to account for not only the health status of the person with diabetes but also who dealing with drugs of anti diabatic carefully.

Once again, diabetes management in patients with COVID-19 poses a great clinical challenge, one that requires a much-integrated team approach, as this is an indispensable strategy to reduce the risk of medical complications and death as much as possible. Careful assessment of the many components that contribute to poor prognosis with COVID-19 in patients with diabetes might represent the best, if not the only way to overcome

the current situation and enable our health systems to be ready to face any future challenges in a prompt and effective mannerFinally, the inter-relationship between diabetes and COVID-19 should trigger more research to understand the extent to which specific mechanisms of the virus (eg, its tropism for the pancreatic β-cell) might contribute to worsening of glycaemic control and, in some cases, to the striking development of diabetic ketoacidosis or hyperglycaemic hyperosmolar syndrome, and possibly the development of new-onset diabetes.

Conclusion

It has now been recognized that host cell condition has a significant role in the infectivity and determines pathogenicity of viruses such as SARS-CoV2. We have reviewed the potential molecular mechanisms on why patients with DM are at a higher risk of severe COVID-19 than infected individuals without DM . We suggest that preexisting pathophysiological pathways in patients with poorly controlled DM directly or indirectly increases the pathogenicity of SARS-CoV2. Although we currently have only limited experimental and clinical evidence, further studies on these pathways could potentially help finding more effective pharmacological agents against COVID-19 for patients with diabetes.

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