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COVID-19 and Diabetes Mellitus: A Complex Interplay

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Abstract

COVID-19 pandemic, which caused by the newly emerged severe acute respiratory syndrome coronavirus-2 (SARS- CoV-2), puts the entire world in an unprecedented crisis, leaving behind huge human losses and serious socio-economical damages. The clinical spectrum of COVID-19 varies from asymptomatic to multi-organ manifestations. Diabetes mellitus (DM) is a chronic inflammatory condition, which associated with metabolic and vascular abnormalities, increases the risk for SARS-CoV-2 infection, severity and mortality. Due to global prevalence, DM effect on COVID-19 outcomes as well as the potential mechanisms by which DM modulates the host-viral interactions and host-immune responses are discussed in this review. This review also highlights the effects of anti-diabetic drugs on treatment of SARS-CoV-2 infection and vice versa.

Keywords: COVID-19, diabetes, risk factor, cytokines

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INTRODUCTION

Late 2019, a novel coronavirus (CoV), known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, previously 2019-nCoV), has emerged in Wuhan, Hubei province, China. This virus has spread rapidly within and between other countries, and causing coronavirus disease-2019 (COVID-19). On March 2020, World Health Organization (WHO) declared COVID-19 outbreak as a global pandemic. COVID-19 is associated with a wide spectrum of symptoms such cough, fever, headache, myalgia, loss of taste and smell, respiratory problems and in severe cases, it may cause respiratory failure and death[1-8].

In addition to older ages, certain chronic medical conditions such as hypertension, diabetes, and cardiovascular diseases increase the risk for severe SARS-CoV-2 infection[9,10]. It is unsurprising that diabetic patients are more likely to be infected and have a significantly high risk for hospitalization and mortality from COVID-19. Similar increased risk for other coronaviral infections such as severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012 has been reported in diabetic patients[11,12].

Considering global prevalence of diabetes mellitus (DM) (about 422 million worldwide, WHO) and high transmission rate of SARS-CoV-2, these two pandemics cause significant mortality and morbidity. So, it is not advised to underestimate COVID-19 infection in diabetic patients even if the initial symptoms are mild. In this review, medical data have been collected to better understand the relation between DM and COVID-19 infection and severity.

Coronaviruses

Coronaviruses (CoVs) are enveloped positive-sense, single-stranded RNA viruses belonging to *Coronaviridae* family[13-15]. Most known human CoVs are associated with self-limiting mild diseases. However, three beta-CoVs, such as SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV) and novel SARS-CoV-2, resulted in major outbreaks with life threatening effects[16,17]. Despite phylogenetic similarity (79.5%), SARS-CoV-2 has lower mortality rate but higher transmission rate than SARS-CoVs[18]. The genome of SARS-CoV-2 contains several open reading frames (ORFs)[19,20]. Structural proteins of CoVs are spike (S), envelope (E), membrane (M), and nucleocapsids (N) proteins (Fig. 1)[21-23]. S protein, which is expressed on virus surface, is responsible for recognition and binding to host cell receptors and it has two conserved domains S1 and S2 [15].

Genomic analysis revealed that sites of receptor binding domains (RBDs) of SARS-CoV-2 bind angiotensin-converting enzyme 2 (ACE2) receptor, which is the same human cell receptor
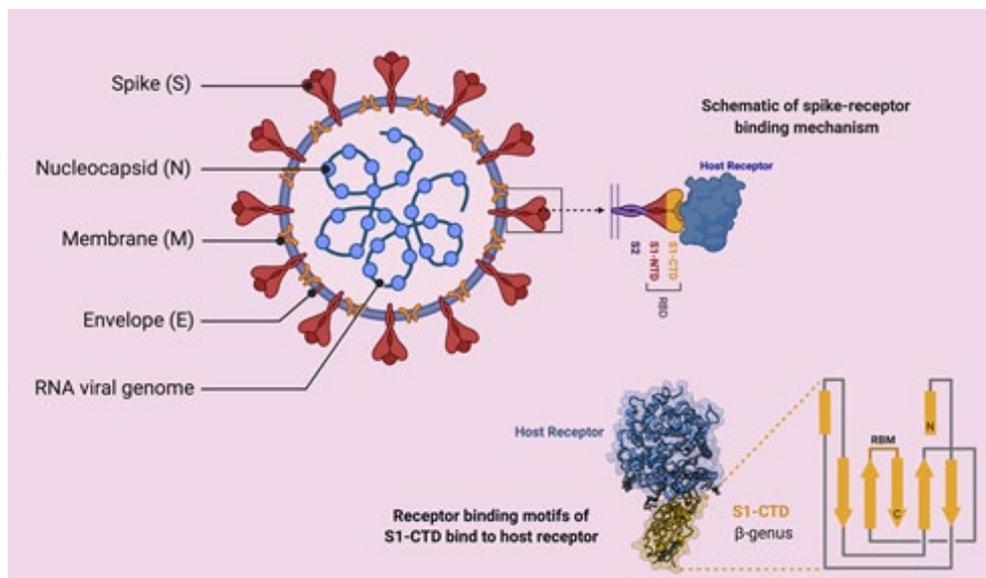

Fig. 1. Coronavirus structure and spike-receptor binding (Created by Biorender.com).

for SARS-CoV but with higher receptor binding affinity (10- to 20- fold)[24,25]. Unfortunately, ACE2 receptors are widely distributed on plasma membrane of host cells of many tissues such as lungs, heart, kidney and liver[18,26-30]. This explains the multi-organ dysfunction including acute respiratory distress syndrome (ARDS), acute myocardial and kidney injury[31,32]. It was found that injury of these organs was much more serious in diabetes compared to those without diabetes[33]. Furthermore, immunestaining of ACE2 revealed significant expression of ACE2 protein in pancreatic islets, which also explains that SARS-CoV-2 may result in diabetes via damaging the pancreatic islets[34,35]. Nucleocapsids protein (N) in SARS-CoV has the ability of neutralizing the host's immune system by acting as an antagonist to IFN-g. If this ability proved to be absent in SARS-CoV-2, it would present an explanation for the lower mortality rate of the novel CoV[36].

Clinical characteristics of COVID-19

The clinical spectrum of COVID-19 varies from asymptomatic to multi-organ manifestations. The symptoms start as mild flu-like symptoms, and may rapidly develop severe symptoms. The different symptoms reported with COVID-19 include cough, fever, headache, myalgia, loss of taste and smell, shortness of breath, sore throat, vomiting and diarrhea[37-39]. However, severe cases can develop signs and symptoms of acute respiratory distress syndrome (ARDS), respiratory failure and failure of other organs. Severe cases require supportive treatment and admission to intensive care unit[39-41].

Diabetes as a risk factor for COVID-19

Diabetes, which is a worldwide leading cause of morbidity and mortality, has a high potential risk for viral infections, mainly due to defects of innate and adaptive immunity (Fig. 2).

Some potential mechanisms, which increase diabetic patients' susceptibility to infection, are discussed in this review. ACE2, as the receptor responsible for SARS-CoV-2 binding and entry, has an increased expression level in DM (Fig. 3) [42]. Additionally, Fernandez et al.[43] found that a cellular protease (furin), which plays a role in virus entry through cleavage of S1 and S2, is high in DM. Viral clearance is based mainly on T-cell action, natural killer cell activity and complement action, which are disturbed in diabetes[44]. Several studies reported a significant relation between DM and infection severity of different CoVs such as SARS-CoVs, MERS-CoVs and SARS-CoV-2[45-50]. Diabetes, as a chronic inflammatory
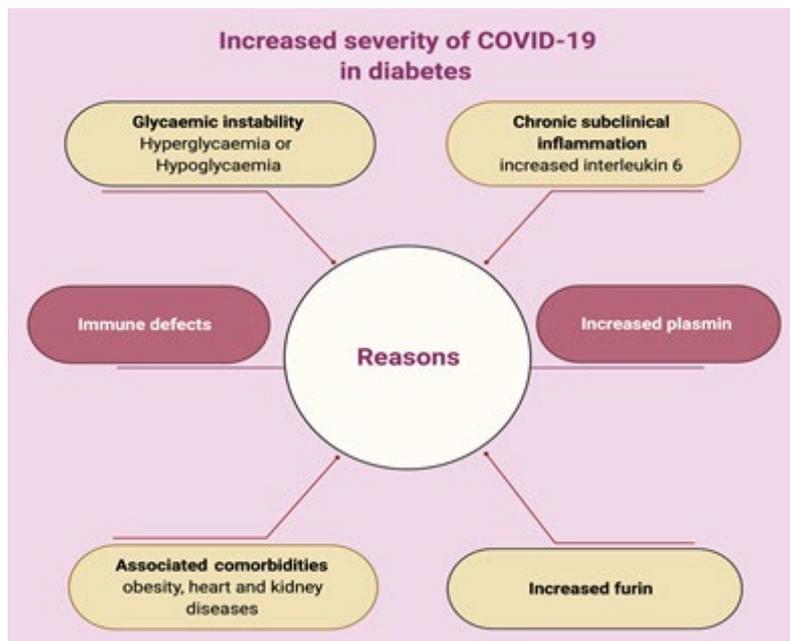

Fig. 2. Different reasons of increased severity of COVID-19 in diabetes (Created by Biorender.com).

condition associated with metabolic and vascular abnormalities, affects the body response to pathogens[51-54]. Accordingly, within hospitalized COVID-19 patients, diabetic patients are over-represented with higher mortality rate reaching 50% [41,47,55]. In diabetic patients, SARS-CoV-2 triggers higher stress conditions, inducing hyperglycemic hormones (glucocorticoids and catecholamines) and elevating blood sugar levels[46]. Uncontrolled diabetes is associated with inhibited lymphocyte proliferative response and impaired function of monocyte/macrophage and neutrophil (Fig. 3). A study on diabetic mice showed prolonged severe course of COVID-19 infection with delayed recovery and further histological study showed fewer levels of monocyte/macrophages and CD4+ T-cells, CD8+ T-cells, lower chemokine 10 expression, lower level of tumor necrosis factor alpha, IL-6 and IL-12b, but higher levels of IL-7a[55].

In DM, an inflammatory storm forms after SARS-CoV-2 infection due to the delay in initiation of adaptive immunity, resulting in respiratory failure and rapid deterioration of other organs (Fig. 3)[33]. Additionally, in diabetes there is a high level of plasminogen, which increases the virus virulence[56]. Further, the inflammation biomarkers (such as IL-6, serum ferritin and coagulation index, C-reactive protein and D-dimer) were significantly higher in DM[57-60]. Diabetes-associated comorbidities such as hypertension, kidney and heart diseases play a role in worsening the prognosis. Additionally, diabetes can result in structural lung changes, leading to impaired gas exchange and the pulmonary microvasculature may be well prepared to COVID-19 infection[48,61]. A study has been reported by Kohio et al.[62], showing that the high sugar level significantly increases viral replication.

The possible cause of severe hypoxemia in spite of well-preserved lung mechanics that occur with COVID-19 infection is the endothelial damage and pulmonary micro vascular thrombosis. DM affects innate immunity, leading to endothelial dysfunction and deregulation of V. D, fibrinolysis and anti-aggravations, this results in macrovascular diseases or even micro vascular diseases leading to pulmonary complications (diabetic lung)[63]. Glycemic instability either hyperglycemia or even hypoglycemia may increase the severity of COVID-19 [64]. Another link between COVID-19 and DM is down regulation of ACE2, leading to severe lung injury [65]. Severe cases and dead patients of COVID-19 show increase level of TYG (insulin resistance marker).

Interestingly, hospitalized COVID-19 patients with controlled levels of blood sugar showed lower mortality rates than those with poorly controlled blood sugar levels [47].

Type 1 DM (T1D) versus type 2 DM (T2D)

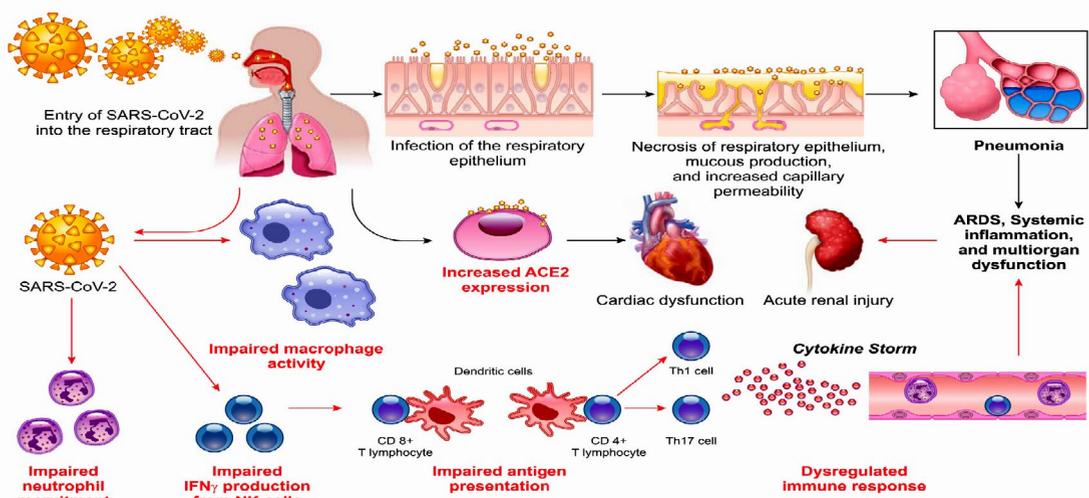Type 1 DM represents 10% of diabetic patients and it is mediated by autoimmune

Fig. 3. Potential mechanisms that increase susceptibility of diabetic patients for COVID-19 infection (Adapted from Muniyappa R and Gubbi S [12]).

reaction to proteins of pancreatic beta cells. T2D is due to combination of some genetic and environmental factors[66-69]. Both Type 1 and 2 increase the risk for SARS-CoV-2 infection and related complications. Human immunity against CoVs depends mainly on the balance between T helper 1 (Th1) and T helper 2 (Th2) immunity. Th1 immunity, which acts mainly against intracellular pathogens such as SARS-CoV-2, mediated by T lymphocyte and modulated by IL-6 and interferon gamma. T1D shows imbalance between Th1 and Th2 immunity in favor of Th1, which may make type1 diabetic patients at a lower risk for COVID -19 infections [70].

COVID-19 patients and microangiopathy in hyperglycemia

Main reason of morbidity and mortality in diabetes is the vascular complications, which occur due to systemic metabolic disorders (hyperglycemia and dyslipidemia) and tissue reactions to toxic metabolites.[71] Control of blood sugar can delay onset of diabetic microvascular complications and slows down progression[72]. High blood sugar level starts its injurious effects by raising the amount of its metabolites in vascular cells; this can lead to certain changes in its functions. Additionally, high glucose metabolism can generate specific toxic products, which can mediate the specific toxic actions of high blood sugar level and lead to microvascular injuries. The specific pathologic outcomes are modulated by the needs of various tissues, significance of the various functions that are changed by high blood glucose level, and the protective reactions made by each tissue. The main microvascular injuries include retinopathy, nephropathy, and neuropathy. Also, brain, skin, cardiac muscle and other tissues are involved[72].

COVID-19 and pulmonary microangiopathy

COVID-19 caused pulmonary complications, which is characterized by dissociation between severity of hypoxemia and maintenance of good respiratory mechanics[73]. Coagulation dysfunction is common in intense COVID-19 and thrombogenic microvascular injury appeared in fatal cases[63,74]. Endothelial damage and pulmonary microvascular thrombosis currently indicate clinical severity of COVID-19 [73,74]. SARS-CoV-2 enters into endothelial cells through binding of viral entry protein (S protein)
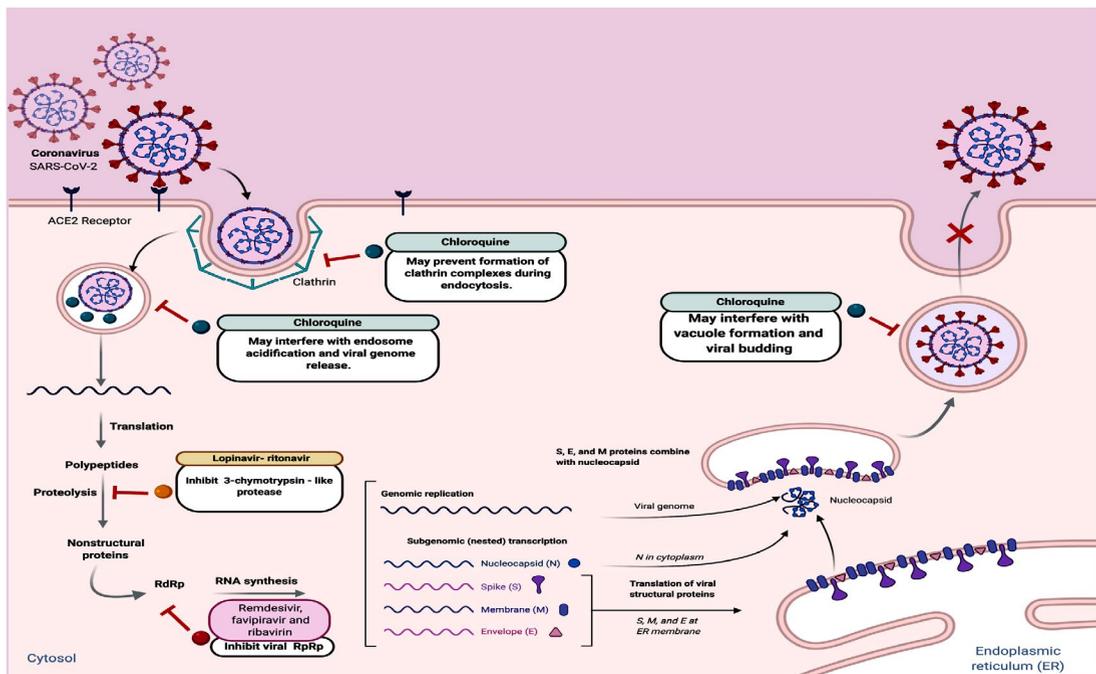

Fig. 4. Potential repositioned drug candidates for COVID-19 (Created by Biorender.com)

to ACE2 receptor and then virus replication occurs. Replication of the virus results in cellular injury and release of proinflammatory signals. Additionally, virus binding to ACE2 results in increase in the level of local angiotensin-II, which results in vasoconstriction, endothelial activation, and proinflammatory cytokine release, causing damage for alveolar epithelial and vascular endothelial cells. Endothelial cell involvement may then spread across the vascularity of different organs[63].

COVID-19 and diabetic nephropathy

Nearly 25% of patients with T2D are affected by diabetic nephropathy, which is considered as main cause of end-stage renal disease. Additionally, diabetic nephropathy is associated with elevated cardiovascular risk[75]. Despite acute respiratory failure being main feature of COVID-19; it was found out that other organs affection might occur. Following SARS-CoV-2 infection of lungs, the virus may reach the circulation and then the kidney, causing renal cells injury. In a Chinese study, around 7% of patients infected with SARS-CoV suffered from acute kidney injury[75]. For this reason, knowing how the kidney is affected by SARS-CoV-2 is urgently needed. More than 40% of hospitalized COVID-19 patients developed kidney disease, which was linked with greater hospital mortality. Some patients with COVID-19 had a pre-existing chronic kidney disease, which makes it a possible justification of the high pervasiveness of kidney involvement at hospital admission. Such patients have a proinflammatory state with functional defects in immune cell and may develop upper respiratory tract infection and pneumonia more favorably[76].

Impact of both anti-diabetic treatments on COVID-19 outcomes, as well as therapeutic approaches for COVID-19 on management of diabetes requires further study.

Management of COVID-19 in diabetic patients

Diabetic patients have more risk for CoVs infection and mortality, this may be due to the poor glycemic control, which increases risk for secondary infection[77]. Combined with the latest guidelines of washing hands, social distancing and lockdown, good glycemic control help in reducing the risk for infection and even severity of the disease[78,79]. No specific treatment is approved for COVID-19 and only symptomatic and supportive

treatment are applied[17,80]. Therefore, development of effective vaccine and specific antiviral treatment is the ultimate aim to fight CoVs[81-89].

Nowadays, medical institutions and companies are recruited to design and produce effective vaccines for COVID-19 using whole virus (attenuated or inactivated)[90-92], plasmid encoding viral antigens[93,94] or viral proteins[95-99]. On 2020, several promising vaccine candidates have entered clinical phase such as Ad5-nCoV from CanSino Biologics (NCT04313127)[28], INO-4800 from Inovio (NCT04336410)[100], PiCoVacc from Sinovac Biotech, mRNA-1273 from Moderna (NCT04299724)[101], LV-SMENP-DC (NCT04299724) and pathogen-specific aAPC (NCT04276896) from Shenzhen Medical Institute.

Moreover, repositioning of drugs is fast option to find clinically effective agents against COVID-19. Several approved antiviral drugs (Fig. 4) were re-tested against COVID-19 such as remdesivir, favipiravir, ribavirin[81-88], lopinavir-ritonavir and chloroquine[81,89,102-107]. Despite their potential ability to inhibit viral replication, these repositioned drugs might show adverse effects with diabetic patients and overall outcomes have not yet been fully evaluated.

The low-cost proven antimalarial drugs, chloroquine and its derivative hydroxychloroquine, are tested clinically against COVID-19 and showed promising efficacy and safety[81,89,102-108]. Chloroquine acts via several mechanisms such as preventing endosomal acidification, inhibiting virus-host cells fusion/replication, interfering glycosylation of cellular receptors and inhibition of MAP-kinase altering virus assembly and budding[81,89,109-110]. Chloroquine has hypoglycemic effects and has been approved for diabetes since 2014[65,111]. This hypoglycemic effect could be attributed to improvement of insulin sensitivity, increase of insulin secretion, reduction of hepatic insulin clearance and reduction of systemic inflammation[112]. Therefore, diabetic patients infected with SARS-CoV-2 should be monitored for hypoglycaemia during and even after the use of chloroquine with other anti-hyperglycaemic drugs[111,113].

However, some studies revealed that clinical trials of hydroxychloroquine did not show significant improvement in hospitalized COVID-19 patients compared to standard approaches[114,115].

Additionally, several adverse effects were reported with high doses of chloroquine with severe COVID-19 cases as well as life-threatening arrhythmias was reported when chloroquine is coadministered with azithromycin[116]. World Health Organization (WHO) has recently declared an official statement to prevent further clinical trial testing chloroquine and hydroxychloroquine on COVID-19 patients.

Corticosteroids could be used in COVID-19 for management of ARDS and sepsis, but they would negatively affect the glycemic levels.

Effect of diabetes treatment on COVID-19

The effect of oral anti-hyperglycemic drugs on the severity of COVID-19 is not fully studied. However, metformin and sodium glucose cotransporter (SGLT) inhibitors increase risk of lactic acidosis and should be stopped in sever ill patient with hemodynamic instability. Additionally, SGLT inhibitors (such as gliflozins) might result in over expression of ACE2 receptors, increasing risk of diabetic patients to have more complications if infected with SARS-CoV-2 (111). Therefore, SGLT2 inhibitors, which are used in management of T2D, may exacerbate the clinical outcomes of COVID-19. Sulfonylureas are effective in diabetes treatment but there is an increased risk of hypoglycemia in patients with irregular food intake[64]. Thiazolidinediones and glucagon-like peptide-1 agonists increase levels of ACE2 proteins[117,118]. Increasing ACE2 expression may not increase the entry of SARS-CoV-2 into host cells and this is because virus binding is also dependent on availability of transmembrane protease serine 2 (TMPRRS2)[119]. Thiazolidinediones is not recommended with COVID-19 patients due to risk of fluid retention and heart failure.

Although, insulin increases the expression of ACE2 protein via attenuation of disintegrin and metalloprotease effect, it is still the first choice to adjust blood sugar in hospitalized COVID-19 patients, especially patients in the intensive care units [120]. Patients with mild COVID-19 can normally use their anti-hyperglycaemic drugs as long as they have mild infection and with normal oral intake [77]. On other hand, dipeptidyl peptidase 4 (DPP4) inhibitors, which are used for oral management of T2D, may have advantages in treatment of COVID-19[121]. DPP4 is a serine exopeptidase receptor expressed ubiquitously in many organs and tissues such as lung, liver and kidney and has increased activity in T2D. DPP4 is the main entry receptor for MERS-CoVs and some studies described DPP4 as a co-receptor for SARS-CoV-2 entry[121,122]. DPP4 inactivates glucagon like peptide1 (GLP-1) and gastric inhibitory polypeptide (GIP), which are responsible for stimulation of insulin release and inhibition of glucagon release so lowering blood glucose[123]. If DPP4 enhances entry of SARS-CoV-2, DPP4 inhibitors (such as teneligliptin, vildagliptin and saxagliptin) could be repurposed for treatment of COVID-19 patients with diabetes.

Vaccines against COVID-19

Several vaccines have been developed against CoVs either via exposing the human body to viral antigens or to neutralizing antibodies. There are now several vaccines that are in use. The first mass vaccination programme started in early December 2020 and as of and as of 15 February 2021, 175.3 million vaccine doses have been administered. At least 7 different vaccines (3 platforms) have been administered. WHO issued an Emergency Use Listing (EULs) for the Pfizer COVID-19 vaccine (BNT162b2) on 31 December 2020. On 15 February 2021, WHO issued EULs for two versions of the AstraZeneca/Oxford COVID-19 vaccine, manufactured by the Serum Institute of India and SKBio. WHO is on track to EUL other vaccine products through June[124,125].

CONCLUSIONS

Tremendous international efforts are carried out to contain COVID-19 pandemic, which caused by the newly emerged SARS-CoV-2. Since DM is associated with high risk for SARS-CoV-2 infection and mortality, special attention should be given for diabetic patients. Potential mechanisms, which increase susceptibility of diabetic patients to viral infection, include defects of innate and adaptive immunity, efficient virus entry, delayed viral clearance, decreased T cell function and cytokine storm syndrome. Drugs of DM affect on the control of COVID-19 and vice versa, so, screening for (pre) diabetes in COVID-19 patients is critical as well as blood glucose monitoring and management during treatment of the infection.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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None.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

Not applicable.

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