Review of a Study on the Effect of Sars on Diabetes Mellitus Patients

Hatneiching Haokip[3], Prasurjya Saikia*[2] Rei Tabom[1],

1Scholar of Pharmaceutical Science, Himalayan University , Jollang, village, near central jail, Itanagar, Arunachal Pradesh 791111,India

*2Assistant Professor, Faculty of Pharmaceutical Science, Himalayan University , Jollang, village, near central jail, Itanagar, Arunachal Pradesh 791111,India

3Head of the department , Faculty of Pharmaceutical Science, Himalayan University, Jollang, village, near central jail, Itanagar, Arunachal Pradesh 791111,India

Corresponding Author details-

Prasurjya Saikia

Orcid ID- 0009-0004-3785-5894

Faculty of Pharmaceutical Science, Himalayan University, Jollang, village, near central jail, Itanagar, Arunachal Pradesh 791111, India

E-mail address: prasurjyasaikia17@gmail.com

Abstract

Diabetes mellitus (DM) is among the major global public health issues. According to recent projections, a continued rise in DM prevalence is expected in the following decades. The research has shown that DM is associated with poorer outcomes of coronavirus disease 2019 (COVID-19). However, there is growing evidence suggesting that COVID-19 is associated with new-onset DM type 1 and type 2.

This review aims to summarize the SARS effects the Diabetes Mellitus Patients. Increased risk of poorer COVID-19 outcomes (mechanical ventilation, death) was noted in persons with new-onset DM following SARS-CoV-2 infection. Studies investigating risk factors for SARS on Diabetes Mellitus in COVID-19 patients showed that severe disease, age, ethnicity, ventilation, and smoking habits were associated with DM occurrence. The information summarized in this review presents a valuable source of evidence for healthcare policymakers and healthcare workers in the effort of planning prevention measures for Diabetes Mellitus after SARS-CoV-2 infection and the timely identification and appropriate treatment of patients with Corona Virus who could be at greater risk for new-ones.

Background

The coronavirus disease 2019 (COVID-19) pandemic caused by the novel beta coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulted in large number of morbidity and mortality. The origin of the SARS-CoV-2 is still disputed. The severity of the disease depends on many factors including the viral strain, host immune genetics, environmental factors, host genetics, host nutritional status and presence of comorbidities like hypertension, diabetes, Chronic Obstructive Pulmonary Disease, cardiovascular disease, renal impairment.

Diabetes is a metabolic disorder mainly characterized by hyperglycemia. SARS-CoV-2 infection in patients with diabetes result in β-cell damage and cytokine storm. Damage to the cells impairs the equilibrium of glucose, leading to hyperglycemia. The ensuing cytokine storm causes insulin resistance, especially in the muscles and liver, which also causes a hyperglycemic state. All of these increase the severity of COVID-19.

Key points:-

1) Underlying diabetes mellitus and cardiovascular diseases are considered risk factors for increased coronavirus disease 2019 (COVID-19) disease severity and worse outcomes, including higher mortality.

2) Potential links between SARS and diabetes mellitus include effects on glucose homeostasis, inflammation, altered immune status and activation of the renin–angiotensin–aldosterone system (RAAS).

3) During the COVID-19 pandemic, control of glucose levels and prevention of diabetes complications might very crucial in patients with diabetes mellitus to keep liable and to prevent severe courses of COVID-19.

4) We found that Dipeptidyl peptidase 4 inhibitors and insulin can be used safely in patients with diabetes mellitus and COVID-19; sodium–glucose co transporter 2 inhibitors and metformin might need to be withdrawn in patients at high risk of severe disease.

5) Pharmacological agents of COVID-19 can affect glucose metabolism, particularly in patients with diabetes mellitus; therefore, frequent and personalized adjustment of medications and blood glucose monitoring are required.

Introduction

The Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus that causes coronavirus disease 2019 (COVID-19), was first reported in Wuhan, China, in December 2019 and has spread worldwide. As of 2020, more than millions of globally confirmed cases of COVID-19 have been reported on the World Health Organization COVID-19 dashboard, including millions of deaths. Seasonal influenza and Mortality from COVID-19 is not equivalent, as deaths associated with these diseases do not reflect frontline clinical conditions in the same way.

SARS-CoV-2 is a positive-stranded RNA virus that is enclosed by a protein-decorated lipid bilayer containing a single-stranded RNA genome. In human cells, the main entry receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2), which is highly expressed in cardiac myocytes, lung alveolar cells, vascular endothelium and various other cell types. In humans, the main route of SARS-CoV-2 transmission is through virus-bearing respiratory droplets. Generally, patients with COVID-19 develop symptoms at 5to 6 days after infection. Similar to SARS-CoV and the related Middle Eastern respiratory syndrome (MERS)-CoV, SARS-CoV-2 infection induces mild symptoms in the initial stage for 2 weeks on average but has the potential to develop into severe illness, including acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome, shock and multi-organ involvement. Patients at high risk of severe COVID-19 or death have several characteristics, including male sex and advanced age have underlying health issues, such as cardiovascular disease (CVD), Type 1 diabetes mellitus (T1DM) or Type 2 diabetes mellitus (T2DM).

A few early studies have shown that underlying diabetes mellitus and CVD are common among patients with COVID-19 admitted to ICUs. T2DM is typically a disease of advanced age, and, therefore, whether diabetes mellitus is a COVID-19 risk factor over and above advanced age is currently unknown.

The basic and clinical science of the potential inter-relationships between COVID-19 and Diabetes mellitus has been reviewed. However, knowledge in this field is emerging rapidly, with numerous publications appearing frequently. This Review summarizes the new advances in diabetes mellitus and COVID-19 and extends the focus towards clinical recommendations for patients with diabetes mellitus affected by COVID-19. Most available research does not distinguish between diabetes mellitus type and is mainly focused on T2DM. However, some limited research is available on how the SARS effects on Diabetes Mellitus Patients, which we highlight in this Review.

Prevalence of Diabetes and Its Clinical Severity in Patients With COVID-19

Emerging data suggest that COVID-19 is common in patients with , hypertension, diabetes and cardiovascular diseases (CVD), even if the prevalence rate changed in different studies and country-wise data. The rates of type 2 diabetes in subjects affected by SARS-CoV-2 vary, depending on the severity of illness, the location of the study population, the median age, and the method of testing.

A synthesis of various studies from an extensive search on bibliographic citation databases that explored the prevalence of diabetes according to the type of study, , sample size, population age, prevalence of diabetes, sex, hypertension, and obesity.

the prevalence of diabetes and sex differences increases according to the increase of median age. Current evidence indicates that fatality rates are higher in men than in women. A report on May 22, 2020, from the Italian National Institute of Health, shows that of 23.248 deaths from COVID-19 infection in Italy, approximately 75% were in men. This evidence might explain the higher prevalence of diabetes in elderly patients affected by COVID-19.

There are two other aspects to consider: how much does diabetes affect clinical severity? Since its relationship to, how does obesity? Some data might clarify these issues.

In Italy, a diabetes prevalence of 19% was reported in patients admitted to intensive care units for severe COVID-19. Recent data confirmed the findings mentioned above, outlining a diabetes prevalence of 18.6% in English people with severe COVID- 19 requiring intensive care unit. Other study showed a significant prevalence of diabetes (31.25% vs 12.75%) in dead patients compared to survivors in ICU wards in Italy. Moreover.In summary, diabetes resulted associated with a dramatic increase in mortality and emerged as an independent risk factor even after correcting for sex, age, race, hypertension and obesity.

Obesity increases the risk of hypoventilation syndrome in I.C.U. patients and it can lead to respiratory failure when ARDS is present. The mechanisms that explain these effects are poorly understood, but inflammatory and mechanical factors might contribute. At the same time, we have found that obesity is associated with low levels of adiponectin, which could be the link to increased cardiovascular risk in patients who present with the association between obesity and COVID-19. Finally, according to the sources, 76% of diabetic patients were obese, which may have contributed further to the increased risk observed in this population.

Diabetes as a risk factor of worst outcomes

In general, people with diabetes are at higher risk of developing complications because of infection, particularly viral one. The differences in response are likely the result of the degree of host immune response, age of the patient, viral load, and presence of comorbidities. Type 2 diabetes is associated with low-graded chronic inflammation induced by the excessive visceral adipose tissue. This inflammatory condition affects the peripheral

insulin sensitivity and homeostatic glucose regulation. Chronic hyperglycemia and inflammation can determine an ineffective immune response and abnormal.

Diabetic patients with Corona virus are at higher risk of excessively hypercoagulable state and uncontrolled inflammation responses, which may contribute to a poorer outcomes.

The lower prevalence of diabetes might explain this finding, and the lower age of the populations studied. Another meta-analysis of studies from China (n=2036) found a significant association between diabetes and COVID-19 severity. The prevalence of non-survivors was also higher in diabetic subjects with COVID-19. Also, a summary report of 55,572 patients of COVID-19 from the Chinese Center for Disease Control and Prevention reported a case fatality rate (C.F.R.) of 3.2% (2203 deaths among 35,672 confirmed cases). In any case, the C.F.R. was as high as 8.3% in patients with 8.0% in hypertension and diabetes.

Proposal of Pathogenetic Mechanisms

There are several specific factors and mechanisms by which diabetes predisposes to infections in general and may increase liability or risk and severity of SARS-CoV-2 disease. Potential mechanisms that may enhance the liability for COVID-19 diabetics patients include the role of higher affinity cellular binding, efficient virus entry, hyperglycemia and diminished T cell function, decreased viral clearance, increased susceptibility to hyper-inflammation, presence of CVDand cytokine storm syndrome.

The Role of Hyperglycemia

The susceptibility to SARS appeared primarily dependent on the affinity of spike to bind host ACE2 receptors (ACE2r) in target tissues in the initial viral attachment step. ACE2 receptors has been confirmed recently as the SARS-CoV-2 receptor causing COVID- 19, in concert with the host's TMPRSS2 membrane protease that primes the spike protein of the virus to facilitate its cell entry.

A possible explanation for a link between hyperglycemia and ACE2r levels in the severity of COVID- 19 disease could be the potential changes in and glycosylation of the viral spike protein and glycosylation of the ACE2r.

Elevated glycemia levels can directly increase glucose concentrations in airway secretion. Potentially, in uncontrolled hyperglycemia, aberrantly glycosylated ACE2r and high in the lung, , tongue, oropharynx and nasal airways could also serve as increased SARS-CoV-2 viral binding site. This indicates the presence of stress hyperglycemia, which may have a worse outcome in acute illness, compared to a previously diagnosed diabetes. Stress hyperglycemia was one of the poor prognostic factors and had been associated with a significant increase in respiratory failure and death in subjects with SARS.

Glycemic control could reduce levels of glycosylated ACE2r target in the lung. The number of glycosylated viral binding sites decreases, possibly ameliorate inflammation and symptoms of COVID-19 disease. ACE2r is expressed not only in type 1 and 2 alveolar epithelial cells in the lungs and upper respiratory tract, but also in several other locations like the endothelium, renal, tubular epithelium, intestinal epithelium, heart and pancreas.

Within the pancreas, ACE2 expression has been described in acinar cells and within subsets of islet cells. In preclinical studies, gain and loss of ACE2 function reveal physiological and pharmacological roles for ACE2, both independent of Angiotensin and dependent which may antagonize the actions of angiotensin 2 in glucose control and cell function, blood pressure,renal physiology, atherosclerosis and amelioration of experimental diabetes.

Hyperglycemia may also affect pulmonary function, such that it is exacerbated by influenza virus-induced respiratory dysfunction in patients with diabetes.

Impaired T-Cell Function and Increased Susceptibility to Hyperinflammation

The activation of pro inflammatory cytokines or chemokines causes infected cells apoptosis or necrosis and triggers inflammatory responses, which leads to the recruitment of inflammatory cells. SARS-CoV-2 increases apoptosis of lymphocytes and infects circulating immune cells leading to lymphocytopenia.

Lower T cell function diminishes the inhibition of innate immune system resulting in the secretion of high amounts of inflammatory cytokines. Neutrophil chemotaxis, the intracellular killing of microbes, and phagocytosis were inhibited by diabetes. In the beginning, a delay in the activation of Th1 cell-mediated immunity and a late hyper-inflammatory response is often observed in diabetics.

Several cytokines are increased in COVID-19 infection. It is believed that SARS-CoV-2 infection may enhance the cytokine response of such patients, thereby exacerbating the cytokine storm that seems to cause multiple organ failure in COVID-19.

The baseline proinflammatory state found in diabetes and obesity may serve to exacerbate. Diabetes occurs in part because the increase of activated innate immune cells in metabolic tissues leads to the overproduction of inflammatory mediators, especially TNFα and IL-1β, which can promote systemic insulin resistance and beta cell damage.

Therapeutical Considerations

Metformin:-

Metformin exerts anti-inflammatory action and reduces circulating biomarkers of inflammation in people with T2D.Metformin should be taken with caution in unstable hospitalized patients and should be discontinued in people with concomitant sepsis or severe impairment of hepatic and renal function.

If vomiting or poor oral intake occurs, metformin may also be stopped. Due to the level of blood sugar, the dosage of sulfonylureas and insulin may have to be changed.

It is worth mentioning that better health outcomes have been reported in COVID-19 patients receiving Metformin. It is hypothesized that Metformin may inhibit virus entry into cells through adenosine monophosphate (AMP)-activated protein kinase activation and the B–mammalian target of rapamycin (m TOR) signalling pathway.

GLP-1R agonists

GLP-1R agonists exert broad anti-inflammatory actions in animals with experimental inflammation and reduce biomarkers of systemic inflammation in human subjects with T2D and people with obesity. It is well known that the most severe form of COVID-19 is the Acute Respiratory Distress Syndrome characterized by the highest levels of inflammatory cytokines known as Cytokine Storm which hurts alveolar epithelial cells in the lung, inactivates pulmonary surfactant resulting

Dipeptidyl Peptidase-4 (DPP4)

ACE-2 is the receptor for SARS CoV and SARS CoV2, DPP4 acts as the receptor for MERS-CoV. Whether the use of DPP4 inhibitors (DPP4i) can reduce MERS-CoV's viral entry has aroused great interest.

DPP4 seem to increase inflammation in type 2 diabetes via noncatalytic and catalytic mechanisms. It is crucial to outline that the enzymatic activity of DPP4 causes the cleavage and may affect the function of several cytokines, growth factors and chemokines.

DPP-4 may act as a receptor for some COVID 19, and hence, DPP-4 inhibitors might inhibit such binding and mitigate COVID-19 infection. However, this anticipated advantage has not been proven in clinical trials

Insulin

Insulin exerts anti-inflammatory actions in humans and reduces biomarkers of inflammations in hospitalized individuals with a critical illness. For the treatment of acute disease complicated by diabetes, insulin has been the most extensively used agent in human subjects with bacterial or viral infections and in hospitalized critically ill patients. Most hospitalized patients with COVID-19, especially those with respiratory distress, would require insulin.

Insulin therapy has an optimal glucose-lowering effect in patients affected by diabetes, it is suggested that insulin is the treatment of choice in hospitalized COVID-19 patients with diabetes.

SGLT2-Inhibitors

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are demonstrated to have cardiovascular and renal benefits in addition to its anti-diabetic effects. The combined use of SGLT2i and ACEI/ARB significantly increases intra renal ACE2 expression, which may be closely related to improving cardiac and renal function.

The increased ACE2 may be detrimental to patients infected with the coronavirus infection 2019 (COVID-19), which is found to invades cells via the entry receptor of ACE2. Besides, SGLT2i induced natriuretic effect may also increase the risk of acute kidney injury and affect hemodynamic stability during systemic infection.

SGLT2i have been reported to prevent the release of various proinflammatory cytokines such as IL 6. Besides, SGLT2i lead to an increase in the ACE-2 levels, which leads to greater production of the angiotensin 17, which is anti-oxidant, anti-fibrotic, and potent vasodilator which helps in the prevention of acute respiratory distress syndrome (ARDS) and alleviating cytokine storm.

A.C.E. Inhibitors/A.R.B.s

According to a recent study, the use of A.C.E. inhibitors in COVID-19 patients, was associated with lower mortality after hospital discharge (no association was found for the use of A.R.B.s). Whether there is an immunosuppressive state, the presence or absence of hyperlipidemia or diabetes mellitus and the race or ethnic group were not independent predictors of death in the hospital.

Statins

Statins exert pleiotropic effects on inflammation and oxidative stress, contributing to their beneficial impact on cardiovascular diseases. Statins modulate the immune response at different levels, including immune cell adhesion, antigen presentation and cytokine production.

Statins also interfere with ACE2 signalling. After initial entry through ACE2, SARS-CoV-2 down-regulates ACE2 expression, possibly facilitating the initial infiltration by innate immunity cells and causing an unopposed angiotensin 2 accumulation, leading to organ injury.

In COVID-19 infection, statins lipid-lowering action could treat the hyperlipidemia associated with the use of protease-inhibitor-based antiretroviral and immunosuppressive drugs. The hepatic isoenzyme CYP3A4 metabolizes simvastatin and, to a lesser extent, atorvastatin. Concomitant administration of CYP3A4 inhibitors such as cobicistat and ritonavir, currently used in COVID-19, could increase the risk of muscle and liver toxicity.

Clinical Consideration

Diabetes should be considered as a risk factor not only for increased susceptibility to infection but also for a rapid progression and bad prognosis of COVID-19. Therefore, According to pathophysiological consideration, people with diabetes should be paid more intensive attention to the importance of glycosylation of both the ACE2r and viral spike protein.

So, This consideration argues for better glycemic control in patients with hyperglycemia at hospital admission. It is found to be Pre-diabetes and diabetes are potential mechanisms to slow the spread of COVID-19 and reduce symptoms and improve outcome. In human blood glucose control is essential for patients with COVID-19.

Nevertheless, hyperglycemia is still a powerful predictor of the prognosis of hospitalized Covid-19 patients.Covid-19 patients with hyperglycemia, compared with subjects normoglycemia, showed a higher cumulative incidence of serious diseases. Optimal blood glucose control mediated by insulin infusion can improve the prognosis of hospitalized Covid-19 and hyperglycemic patients.

Patients with mild infections, and regular oral doses can continue routine hypoglycemic drugs. Due to the unpredictability and social nature of the disease, mental stress is also great. Do not move as well as social immobility.

All these factors may lead to uncontrolled glycemia or worsening status of comorbid diseases (e.g., hypertension) and predispose the patients to complications like other types of infections, hyperosmolar coma, ketoacidosis, and even acute cardiovascular or cerebrovascular events.

According to this review, it is possible to summarize measures for good health in patients with diabetes:-

- Diabetics need to maintain a regular diet.
- Exercises should be continued at home.
- Physical activitiy like aerobic exercise increases muscle glucose uptake up to fivefold through insulin-independent mechanisms improves blood glucose control in type 2 diabetes,
- Regular intake of ACE2-inhibitors and other anti-diabetic drugs and antihypertensive drugs(including GLP1-R agonists) and, insulin is important and should be emphasized for the best blood pressure glucose control.
- Telemedicine can be beneficial in these times. Patients can consult their physicians *via* telemedicine, who can give appropriate advice about treatment.

Co-infections in diabetic patients with COVID 19

Diabetes mellitus is an important prognostic factor, as studies have shown a higher risk of death in this patient population. In addition, a disturbing glucolipid metabolism undoubtedly leads to immunosuppression by decreasing the innate immune response, and COVID 19 itself leads to a weakening of the immune system by lowering the T-lymphocyte count.

Candida species (Albicans and non-Albicans) are among the co-infections observed in COVID-19 patients and presented as invasive candidiasis. It can also cause fungal pneumonia.

Another severe fungal superinfection is invasive pulmonary aspergillosis which is associated with high mortality rates.

Patients with diabetes mellitus, especially those with poorly blood glucose control, and COVID-19 were noticed to have an increased risk of coccidioidomycosis. Patients at risk lived in endemic areas (California, Arizona) and had occupational exposure.

Diabetes potentiated the likelihood of disseminated disease, relapsing coccidioidomycosis, and cavitary lung disease. Fungal infections can be missed, as many of them manifest similar to corona virus.

The Mucormycosis is an emerging fungal infection globally, with severe and often fatal disease symptoms and varied clinical manifestations. The outbreak of cases reported in the wake of the second wave of COVID-19 in India has brought unprecedented focus to this disease worldwide. A total of 79% of COVID-19 associated mucormycosis (CAM) cases are reported from India.

India has the highest burden of mucormycosis in the world and has the second-largest number of adults with diabetes. Innocuous organism in an immunocompetent host can become aggressive and highly destructive in patients with an impaired immune system, such as those with hematological malignancies, immunosuppression, poorly controlled diabetes, iron overload, and significant trauma. Diabetes Mellitus was present in 96% of CAM patients, that highlighting the significant role of diabetes in the development of such complications.

Telemedicine and diabetes during COVID-19 pandemic

Telemedicine delivers healthcare services from a distance by using information and communication technology to exchange valid information to manage the patients. It is a part of e-health, which also includes mobile health and electronic medical record. Phone calls, video conferences, and social media apps facilitate communication between healthcare providers and diabetic patient.

However, this approach faced several obstacles such as regulations, payment, privacy, confidentiality, and prescription. Several developed and developing countries started to create telemedicine laws and regulations during the COVID-19 pandemic.

Lockdown during the COVID-19 pandemic has a negative impact on blood glucose levels by changing food habits, decreasing physical activity, and running out of medications. Telemedicine could help mitigate the effects of lockdown by providing education, adjusting medications, decreasing visits to healthcare facilities, and reducing the risk of unnecessary direct exposure and disease transmission. Moreover, diabetic patients need regular foot check ups..

Sulfonylureas

Sulfonylureas may induce hypoglycemia, so in the patients with severe COVID-19 with inadequate oral intake, because it is safer to restrict their usage. Also, simultaneous use of hydroxychloroquine may increase the risk of hypoglycemia.

Glucagon-like peptide-1 receptor agonists (GLP-1 agonists)

The GLP-1 agonists may decrease water intake, and they may also cause nausea and vomiting in the patients. GLP-1 agonist therapy is associated with an increased risk of dehydration and aspiration pneumonia.

GLP-1 agonists should be restricted in patients with severe COVID-19. Because they should be closely monitored, and fluid intake should be adequate. GLP-1 agonists have an anti-inflammatory effect and attenuate pulmonary inflammation in rats with a respiratory syncytial virus (RSV) infection and experimental lung injury. GLP-1 agonists have an anti-inflammatory effect in patients with COVID-19 or not needs further evaluation and assessment.

Pioglitazone

Pioglitazone upregulates the Angiotensin converting-2 enzyme (ACE-2) in rat tissues, which leads to concerns that it may increase COVID-19 severity. Since ACE2 acts as a receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enter cells.

Pioglitazone may be a potent inhibitor of 3 chymotrypsin, which is necessary for RNA synthesis and replication of SARS CoV-2. It requires both in-vitro and in-vivo validation.

COVID-19 infected diabetic patients have a higher risk of developing a cytokine storm. Pioglitazone inhibits the secretion of proinflammatory cytokines, and so it may mitigate the cytokine storm.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors

SGLT2-inhibitors may have a potent antiviral effect by increasing lactate concentration and simultaneously decreasing the intracellular pH, which potentially lowering the viral load. An SGLT2-inhibitor and Canagliflozin therap, could induce a reduction in interleukin-6 levels, which plays an essential role in triggering the cytokine release syndrome (CRS) in COVID-19 patients.

SGLT2 inhibitors increase the excretion of sodium and glucose through urine, leading to osmotic diuresis and possibly dehydration. SGLT2 inhibitors can cause euglycemic ketosis.

SGLT2 inhibitors should not be given for critically ill patients with severe COVID-19. However, there is no reason to limit their use in patients with a mild form of the disease.

Possible Mechanisms that Predispose COVID-19 Patients with Diabetes and/or Obesity to Poor Outcomes

It Considering the high incidence of hypertension, obesity and CVD in patients with diabetes, it remains unclear whether diabetes is an independent contributor to the higher morbidity and mortality associated with COVID-19. Some resources have shown that patients with cardiometabolic multimorbidity, and not diabetes or CVD alone, experience worse COVID-19 outcomes. where, plasma glucose levels and diabetes are independent predictors of mortality and morbidity in patients with SARS.

Mechanisms that likely increase the vulnerability for COVID-19 in Diabetes Mellitus patients comprise increased binding affinity and efficient virus entry, increased susceptibility to cytokine storm disorder, reduced viral clearance, weakened T-cell role and the existence of CVD.

Lung cells, including pneumocytes, are the main cellular sites for coronavirus entrance and inflammation. They express key proteins that enable coronavirus entry into cells, such as ACE2, furin, dipeptidyl peptidase-4 (DPP4) and transmembrane protease serine 2 (TMPRSS2). ACE2 and DPP4 also have established multiple metabolic activities linked to the pharmacologic and physiologic control of cardiovascular and glucose homeostasis and DPP4 inhibitors are used extensively in diabetes therapy.

Increased ACE2 expression in pulmonary cells, pancreas , kidney, myocardium and may mediate increased cellular binding of SARS-CoV-2.Insulin administration downregulates ACE2 expression, other hypoglycemic agents such as glucagon-like GLP-1 agonists and thiazolidinediones, anti-hypertensive drugs such as statins, and ACE inhibitors increase ACE2 expression. Using a phenome-wide Mendelian randomization analyses, they identified the association between diabetes and higher lung ACE2 expression. Moreover, circulating levels of furin (cellular protease) were found to be higher in patients with type-II diabetes.

ACE2

ACE2 acts as the receptor for the binding of SARS-CoV-2 with the host cell. It is already known that the binding of the SARS coronavirus to its receptor damages islets and causes acute diabetes. Patients with mild and severe COVID-19, established the existence of mild pancreatitis. Diabetes and hypertension are often treated with ACE inhibitors and angiotensin II type-I receptor blockers.

Studies have reported that the expression of ACE2 is elevated in people with diabetes treated with these medications. The higher levels of ACE2 can facilitate critical illness in COVID-19 patients.

Furin

The SARS-CoV-2 S-protein S1/S2 cleavage site is the target for furin during infection. This cleavage is critical, it allows the fusion sequences on the COVID-19 spike protein to be exposed for the fusion of the virus with the host cell membranes. since furin has high level of ability to enhance the virus to enter the host cell.

It is known that individuals with high plasma furin concentrations have a pronounced dysmetabolic phenotype and elevated risk of diabetes and premature mortality. A point mutation at the furin cleavage site in the insulin pro-receptor was seen in an individual with extreme insulin-resistant diabetes. Furthermore, variations in the furin gene have been associated with decreased triglyceride and increased high-density lipoprotein cholesterol levels.

Furin has an impact on the pancreas, which demonstrated that furin controls the growth of pancreatic β-cells. It also plays a crucial role in granular acidification in the endocrine pancreas via impaired processing of AC45.

TMPRSS2

SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry, and the serine protease TMPRSS2 is required for S-protein priming, which entails S-protein cleavage at the S1/S2 and the S2′ site and allows fusion of viral and cellular membranes.

TMPRSS2 belongs to the family of serine proteases. It is known that ser/thr protein kinases contribute to the onset of insulin resistance via the introduction of phosphorylation-based negative feedback control mechanisms, which disengage the insulin receptor from its downstream effect.

Circulating levels of serine proteases, such as granzyme B, are elevated in diabetes patients. Hence, it can be assumed that the increased activity of TMPRSS2 can increase the viral entry in the host.

IFITM3

Interferon-Induced Transmembrane (IFITM) proteins are important effectors that inhibit viral infections. IFITM3 directly engages and shuttles the incoming virus particles to lysosomes. It is known that the MERS-CoV entry into host cells is sensitive to inhibition by IFITM proteins and that the cellular context and IFITM expression levels can affect the efficiency of inhibition.

IFITM3 is now indicated as a novel entry site in the SARS-CoV-2 domain as well. Inhibitors of the mammalian target of rapamycin (mTOR), such as downregulate endogenous, rapamycin IFITM3 through a lysosomal

degradation pathway in non-hematopoietic and hematopoietic cells. mTOR signalling has a role in pancreatic β cells and immune cells, and hence it is also involved in the pathogenesis and treatment of diabetes.

ADAM17

Metallopeptidase domain 17 (ADAM17) protein to release the extracellular domain of ACE2 into the extracellular space. This process promotes the uptake of SARS-CoV into cells. It is proposed that the inhibition of ADAM17 may exert a protective effect on COVID-19.

ADAM17 is a metalloprotease and disintegrin that lodges in the plasma membrane in several cell types and can cleave a wide variety of cell surface proteins. In this way, ADAM17 can influence several physiological and pathological processes.

In animal models of insulin-resistant diabetes, the intraperitoneal injection of ADAM-17 inhibitor, restored insulin sensitivity through the inhibition of TNF-α.

Other Players: GRP78 and CD147

Apart from the ACE2 receptor entry mode, SARS-CoV-2 may use the protease called TMPRSS2 to enter the cells; some researchers found that there can be at least 8 other different proteases. It is also proposed that other receptors such as glucose regulated protein 78 may provide binding to the SARS-CoV-2 spike proteins.

Protein–protein docking studies revealed that four regions of the spike protein can fit tightly in the GRP78 substrate binding domain β (SBDβ). GRP78 is critically important for β-cell maturation and survival, it is demonstrated that GRP78 heterozygosity attenuates diet-induced obesity and insulin resistance.

It is also possible that other receptors mediate the entry of SARS-CoV-2, such as CD147 into T cells. Also called Basigin or EMMPRIN, CD147 is a transmembrane glycoprotein that belongs to the immunoglobulin superfamily on the surface of T lymphocytes.

Use of Glucose-Lowering Therapies in COVID-19 Patients with Diabetes

Lack of specific and effective therapeutics is the major challenge in dealing with COVID-19 patients that are suffering from severe comorbidities such as diabetes. In the absence of specific medication for COVID-19 patients, it is essential to evaluate the applicability of drugs in practice for various comorbidities.

Diabetes is one of the major comorbidities of COVID-19 patients who developed ARDS. It was originally thought that some anti-diabetes treatment such as PPARs, DPP4 inhibitors, GLP-1R agonists, metformin,SGLT2 inhibitors and insulin therapy could influence the course of COVID-19.

GLP-1R Agonists

GLP-1-based drugs possess strong anti-inflammatory effects in lungs and could become possible repurposed drugs, useful to treat COVID-19 patients with ARDS. GLP-1R agonists target many anti-inflammatory pathways in animals and lessen systemic inflammation in individuals affected by diabetes and obesity.

These drugs decrease pulmonary type-2 immune cytokine reactions and the degree of lung injury in mice after respiratory viral infection. Thus, However, the beneficial effects of these drugs remain to be convincingly established in COVID-19.

SGLT2 Inhibitors

The organ-protective effects of SGLT-2 inhibitors, in addition to their glycemic benefits, these drugs were proposed to provide benefits in COVID-19 problems. however, these inhibitors were also known to lead to risk of dehydration and euglycemic Diabetic Ketoacidosis (DKA). Though SGLT2 inhibitors may be potentially beneficial as organ protective agents in COVID-19, there is no completed clinical trial to assess the risk balance of using these inhibitors in COVID-19 patients. There should be caution needs to be exercised when these inhibitors are used. It is advisable to re-evaluate or discontinue SGLT2 inhibitors upon hospital admission of unstable patients with severe SARS-CoV-2 infection.

ACE2 and DPP4

DPP4 is a transmembrane ectopeptidase, acts as a co-receptor for a subset of coronaviruses including MERS-CoV. Potentially modulate the levels and activity of many immunomodulatory cytokines and chemokines. Although ACE2 and DPP4 are crucial modulators of glucose homeostasis, Some groups have shown that patients with COVID-19 who were on Dipeptidyl peptidase 4 inhibitor (DPP-4is) had a similar disease outcome. ACE2 decoy receptors or antibodies targeting ACE2 can be promising tools to block the viral cell-entry. However, the impact of these drugs on metabolic parameters has not been sensibly investigated and requires further investigation.

Conclusion

In conclusion, the intersection of SARS and diabetes mellitus presents a complex clinical challenge, necessitating targeted strategies to manage and reduce adverse outcomes in this vulnerable population. Therefore, insulin is preferred to oral Hypoglycemic medications in the management of hospitalized Covid-19 infected diabetic patients.

References

1. Elamari S., et al. Characteristics and outcomes of diabetic patients infected by the SARS-CoV-

2. Ceriello A. Hyperglycemia and COVID-19: what was known and what is really new? *Diabetes Res Clin Pract.* 2020;167 108383-108383.

3. Nassar M., et al. *Diabetes & metabolic syndrome.* Clinical Research & Reviews; 2021. COVID-19 vaccine-induced myocarditis case report with literature review; p. 102205.

4. Sterne J.A.C., et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *Jama.* 2020;324(13):1330–1341.

5. Alessi J., et al. Dexamethasone in the era of COVID-19: friend or foe? An essay on the effects of dexamethasone and the potential risks of its inadvertent use in patients with diabetes. *Diabetol Metab Syndrome.* 2020;12:80.

6. Di Dalmazi G., et al. Comparison of the effects of lockdown due to COVID-19 on glucose patterns among children, adolescents, and adults with type 1 diabetes: CGM study. *BMJ open diabetes research & care.* 2020;8(2)

7. Biancalana E., et al. Short-term impact of COVID-19 lockdown on metabolic control of patients with well-controlled type 2 diabetes: a single-centre observational study. *Acta Diabetol.* 2020:1–6.

8. Lim S., et al. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat Rev Endocrinol.* 2021;17(1):11–30.

9. Ceriello A. Hyperglycemia and COVID-19: what was known and what is really new? *Diabetes Res Clin Pract.* 2020;167:108383.

10. Petrie J.R., Guzik T.J., Touyz R.M. Diabetes, hypertension, and cardiovascular disease: clinical insights and vascular mechanisms. *Can J Cardiol.* 2018;34(5):575–584.

11. Giacco F., Brownlee M. Oxidative stress and diabetic complications. *Circ Res.* 2010;107(9):1058–1070.

12. Berbudi A., et al. Type 2 diabetes and its impact on the immune system. *Curr Diabetes Rev.* 2020;16(5):442–449.

13. Šestan M., et al. Virus-induced interferon-γ causes insulin resistance in skeletal muscle and derails glycemic control in obesity. *Immunity.* 2018;49(1):164–177.e6.

14. Chen J., et al. The impact of COVID-19 on blood glucose: a systematic review and meta-analysis. *Front Endocrinol.* 2020;11(732)

15. Chatterjee S., et al. COVID-19: the endocrine opportunity in a pandemic. *Minerva Endocrinol.* 2020;45(3):204–227.

16. Lippi G., Sanchis-Gomar F., Henry B.M. Response to: is newly diagnosed diabetes a stronger risk factor than pre-existing diabetes for COVID-19 severity? *J Diabetes.* 2021;13(2):179–180.

17. Scheen A.J., Marre M., Thivolet C. Prognostic factors in patients with diabetes hospitalized for COVID-19: findings from the CORONADO study and other recent reports. *Diabetes Metab.* 2020;46(4):265–271.

18. Wang X., et al. Impacts of type 2 diabetes on disease severity, therapeutic effect, and mortality of patients with COVID-19. *J Clin Endocrinol Metab.* 2020;105(12)

19. Moon S.J., et al. Independent impact of diabetes on the severity of coronavirus disease 2019 in 5,307 patients in South Korea: a nationwide cohort study. *Diabetes & metabolism journal.* 2020;44(5):737–746.

20. Alvarado-Vasquez N. Could a family history of type 2 diabetes be a risk factor to the endothelial damage in the patient with COVID-19? *Med Hypotheses.* 2020;146 110378-110378.

21. Nassar M., et al. The association between COVID-19 and type 1 diabetes mellitus: a systematic review. *Diabetes Metab Syndr.* 2021;15(1)

22. Ebekozien O.A., et al. Type 1 diabetes and COVID-19: preliminary findings from a multicenter surveillance study in the U.S. *Diabetes Care.* 2020;43(8):e83–e85.

23. Barron E., et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol.* 2020;8(10):813–822

24. Holman N., et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *The Lancet Diabetes & Endocrinology.* 2020;8(10):823–833.

25. Rabbone I., et al. Has COVID-19 delayed the diagnosis and worsened the presentation of type 1 diabetes in children? *Diabetes Care.* 2020;43(11):2870–2872.

26. Singh A.K., et al. Non-insulin anti-diabetic agents in patients with type 2 diabetes and COVID-19: a Critical Appraisal of Literature. *Diabetes Metab Syndr.* 2021;15(1):159–167.

27. DeFronzo R., et al. Metformin-associated lactic acidosis: current perspectives on causes and risk. *Metabolism.* 2016;65(2):20–29.

28. Bornstein S.R., et al. Practical recommendations for the management of diabetes in patients with COVID-19. *The Lancet Diabetes & Endocrinology.* 2020;8(6):546–550.

29. Chen Y., et al. Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. *Diabetes Care.* 2020;43(7):1399–1407.

30. Sharma S., Ray A., Sadasivam B. Metformin in COVID-19: a possible role beyond diabetes. *Diabetes Res Clin Pract.* 2020;164 108183-108183

31. Apicella M., et al. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *The Lancet Diabetes & Endocrinology.* 2020;8(9):782–792.]

32. Iacobellis G. COVID-19 and diabetes: can DPP4 inhibition play a role? *Diabetes Res Clin Pract.* 2020;162

33. Bettge K., et al. Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: a systematic analysis of published clinical trials. *Diabetes Obes Metabol.* 2017;19(3):336–347.

34. Bloodworth M.H., et al. Glucagon-like peptide 1 receptor signaling attenuates respiratory syncytial virus-induced type 2 responses and immunopathology. *J Allergy Clin Immunol.* 2018;142(2):683–687. e12

35. Viby N.E., et al. Glucagon-like peptide-1 (GLP-1) reduces mortality and improves lung function in a model of experimental obstructive lung disease in female mice. *Endocrinology.* 2013;154(12):4503–451

36. Zhang W., et al. Pioglitazone upregulates angiotensin converting enzyme 2 expression in insulin-sensitive tissues in rats with high-fat diet-induced nonalcoholic steatohepatitis. *ScientificWorldJournal.* 2014 2014.

37. Ni W., et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit Care.* 2020;24(1):422.

38. Zhang W.Y., et al. Pioglitazone inhibits the expression of inflammatory cytokines from both monocytes and lymphocytes in patients with impaired glucose tolerance. *Arterioscler Thromb Vasc Biol.* 2008;28(12):2312–2318.

39. Mukherjee J.J., Gangopadhyay K.K., Ray S. Management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol.* 2020;8(8):666.

40. Garvey W.T., et al. Effects of canagliflozin versus glimepiride on adipokines and inflammatory biomarkers in type 2 diabetes. *Metabolism.* 2018;85:32–37.

41. Kosiborod M., et al. Effects of dapagliflozin on prevention of major clinical events and recovery in patients with respiratory failure because of COVID-19: design and rationale for the DARE-19 study. *Diabetes Obes Metabol.* 2021;23(4):886–896.

42. Dharam J., Kumbhani M., SM, FACC *Dapagliflozin in respiratory Failure in patients with COVID-19 - DARE-19*. 2021 05/16/2021. https://www.acc.org/latest-in-cited 2021 July 22th]; Available from:

43. Lim S., et al. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat Rev Endocrinol.* 2021;17(1):11–30.

44. Hansen T.K., et al. Intensive insulin therapy exerts antiinflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. *J Clin Endocrinol Metab.* 2003;88(3):1082–1088.

45. Longo M., et al. Treating type 2 diabetes in COVID-19 patients: the potential benefits of injective therapies. *Cardiovasc Diabetol.* 2020;19(1):115

46. Organization, W.H. World Health Organization. WHO coronavirus disease (COVID-19) dashboard. https://covid19.who.int/. 2020 [cited 2020 12/12]; Available from: https://covid19.who.int/.

47. Bode B., et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. *J Diabetes Sci Technol.* 2020;14(4):813–821

48. Wang S., et al. Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-centre retrospective study. *Diabetologia.* 2020;63(10):2102–2111.

49. Zhu L., et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metabol.* 2020;31(6):1068–1077.e3.

50. Wang D., et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in wuhan, China. *J Am Med Assoc.* 2020;323(11):1061–1069.

51. Lee M.H., et al. Effects of hyperglycaemia on complications of COVID-19: a meta-analysis of observational studies. *Diabetes Obes Metabol.* 2021;23(1):287–289.

52. Palermo N.E., Sadhu A.R., McDonnell M.E. Diabetic ketoacidosis in COVID-19: unique concerns and considerations. *J Clin Endocrinol Metab.* 2020;105(8)

53. Yang J.K., et al. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol.* 2010;47(3):193–199.

54. Li J., et al. COVID-19 infection may cause ketosis and ketoacidosis. *Diabetes Obes Metabol.* 2020;22(10):1935–1941.

55. Oriot P., Hermans M.P. Euglycemic diabetic ketoacidosis in a patient with type 1 diabetes and SARS-CoV-2 pneumonia: case report and review of the literature. *Acta Clin Belg.* 2020:1–5.

56. Alfishawy M., et al. New-onset type 1 diabetes mellitus with diabetic ketoacidosis and pancreatitis in a patient with COVID-19. *Sci Afr.* 2021;13

57. Charles B.L. Telemedicine can lower costs and improve access. *Healthc Financ Manag.* 2000;54(4):66–69.

58. Tchero H., et al. Clinical effectiveness of telemedicine in diabetes mellitus: a meta-analysis of 42 randomized controlled trials. *Telemed J e Health.* 2019;25(7):569–583.

59. Association AD. Diagnosis and classification of diabetes mellitus *Diabetes Care*. 2014;37(Supplement 1):S81–S90

60. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the international diabetes federation diabetes atlas *Diabetes Res Clin Pract*. 2019;157:107843

61. Fowler MJ. Microvascular and macrovascular complications of diabetes *Clin Diabetes*. 2011;29(3):116–122

62. Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, et al Diabetes in older adults *Diabetes Care*. 2012;35(12):2650–266463. Xiu F, Stanojcic M, Diao L, Jeschke MG. Stress hyperglycemia, insulin treatment, and innate immune cells *Int J Endocrinol*. 2014;2014:486403

63. Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: A review of pathogenesis *Indian J Endocrinol Metab*. 2012;16(Suppl1):S27–36

64. Klekotka RB, Mizgala E, Król W. The etiology of lower respiratory tract infections in people with diabetes *Pneumonol Alergol Pol*. 2015;83(5):401–408

65. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Resp Med*. 2020;8(4):e21

66. Ashour HM, Elkhatib WF, Rahman M, Elshabrawy HA. Insights into the recent 2019 novel Coronavirus (SARS-COV-2) in light of past human coronavirus outbreaks *Pathogens*. 2020;9(3):186

67. Fung SY, Yuen KS, Ye ZW, Chan CP, Jin DY. A tug-of-war between severe acute respiratory syndrome coronavirus 2 and host antiviral defence: lessons from other pathogenic viruses *Emerg Microbes Infect*. 2020;9(1):558–570

68. Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome *Lancet*. 2015;386(9997):995–1007

69. Ghinai I, McPherson TD, Hunter JC, Kirking HL, Christiansen D, Joshi K, et al First known person-to-person transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the USA *Lancet*. 2020;395(10230):1137–1144

70. Hemida MG. Middle East respiratory syndrome coronavirus and the one health concept *PeerJ*. 2019;7:e7556

71. Cheng VC, Lau SK, Woo PC, Yuen KY. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection *Clin Microbiol Rev*. 2007;20(4):660–694

72. Sanami S, Zandi M, Pourhossein B, Mobini GR, Safaei M, Abed A, et al Design of a multi-epitope vaccine against SARS-CoV-2 using immunoinformatics approach *Int J Biol Macromol*. 2020;164:871–883

73. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic *Acta Biomed*. 2020;91(1):157–160

74. Ye ZW, Yuan S, Yuen KS, Fung SY, Chan CP, Jin DY. Zoonotic origins of human coronaviruses *Int J Biol Sci*. 2020;16(10):1686–1697

75. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, evaluation and treatment Coronavirus (COVID-19)Accessed on 01 March 2020 [Online] Available from.

76. Wang T, Du Z, Zhu F, Cao Z, An Y, Gao Y, et al Comorbidities and multi-organ injuries in the treatment of COVID-19 *Lancet*. 2020;395(10228):e52

77. Peiris JS, Yuen KY, Osterhaus AD, Stöhr K. The severe acute respiratory syndrome *New Engl J Med*. 2003;349(25):2431–2441

78. Fani M, Teimoori A, Ghafari S. Comparison of the COVID-2019 (SARS-CoV-2) pathogenesis with SARS-CoV and MERS-CoV infections *Future Virol*. 2020 10.2217/fvl-2020-0050

79. Wang H, Yang P, Liu K, Guo F, Zhang Y, Zhang G, et al SARS coronavirus entry into host cells through a novel clathrin-and caveolae-independent endocytic pathway *Cell Res*. 2008;18(2):290–301

80. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes *Acta Diabetolog*. 2010;47(3):193–199

81. Lecube A, Pachón G, Petriz J, Hernández C, Simó R. Phagocytic activity is impaired in type 2 diabetes mellitus and increases after metabolic improvement *PloS One*. 2011;6(8):e23366

82. Liao Z, Yao B, Guan K, Deng W, Hu G, Weng J. The clinical features of SARS patients with diabetes or secondary hyperglycemiaAccessed on 17 April 2020 [Online] Available from: https://professional.diabetes.org/abstract/clinical-features-sars.

83. Banik G, Khandaker G, Rashid H. Middle East respiratory syndrome coronavirus "MERS-CoV": current knowledge gaps *Paediatr Respir Rev*. 2015;16(3):197–202

84. Mardani M. Resurgence of Middle East Respiratory Syndrome Coronavirus outbreak in Saudi Arabia *Arch Clin Infect Dis*. 2015;10(3):e31466

85. Yeo C, Kaushal S, Yeo D. Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-CoV-2 possible? *Lancet Gastroenterol Hepatol*. 2020;5(4):335–337

86. Silva Júnior WS, Godoy-Matos AF, Kraemer-Aguiar LG. Dipeptidyl peptidase 4: a new link between diabetes mellitus and atherosclerosis? *BioMed Res Int*. 2015;2015:816164

87. Iacobellis G. COVID-19 and diabetes: Can DPP4 inhibition play a role? *Diabetes Res Clin Pract*. 2020;162:108125

88. Males VK. Letter to the editor in response to the article "COVID-19 and diabetes: Can DPP4 inhibition play a role?" *Diabetes Res Clin Pract*. 2020;163:108163

89. Raj VS, Mou H, Smits SL, Dekkers DH, Müller MA, Dijkman R, et al Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC *Nature*. 2013;495(7440):251–254

90. Du L, Yang Y, Zhou Y, Lu L, Li F, Jiang S. MERS-CoV spike protein: a key target for antivirals *Expert Opin Ther Targets*. 2017;21(2):131–143

91. Kulcsar KA, Coleman CM, Beck SE, Frieman MB. Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection *JCI Insight*. 2019;4(20):e131774

92. Xia C, Rao X, Zhong J. Role of T lymphocytes in type 2 diabetes and diabetes-associated inflammation *J Diabetes Res*. 2017;2017:6494795

93. Poortahmasebi V, Zandi M, Soltani S, Jazayeri SM. Clinical performance of RT-PCR and chest CT scan for COVID-19 diagnosis; a systematic review *Advanced J Emerg Med*. 2020;4(2s):e57

94. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al A novel coronavirus from patients with pneumonia in China, 2019 *New Engl J Med*. 2020;382(8):727–733

95. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China *Lancet*. 2020;395(10223):497–506

96. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D.. Structure function, and antigenicity of the SARS-CoV-2 spike glycoprotein *Cell*. 2020;181(2):281–292

97. Chen Y, Guo Y, Pan Y, Zhao ZJ. Structure analysis of the receptor binding of 2019-nCoV *Biochem Biophysical Res Commun*. 2020;525(1):135–140

98. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges *Int J Antimicrob Agents*. 2020;55(3):105924

99. World Health Organization. . Coronavirus disease 2019 (COVID-19): situation report, 46 2020Accessed on 01 March 2020 [Online] Available from.

100. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al Diabetes is a risk factor for the progression and prognosis of COVID-19 *Diabetes Metab Res Rev*. 2020:e3319 doi.org/10.1002/dmrr.3319

101. Pal R, Bhansali A.. COVID-19 diabetes mellitus and ACE2: The conundrum *Diabetes Res Clin Pract*. 2020;162:108132

102. Batlle D, Soler MJ, Ye M. ACE2 and diabetes: ACE of ACEs? *Diabetes*. 2010;59(12):2994–2996

103. Patel VB, Parajuli N, Oudit GY. Role of angiotensin-converting enzyme 2 (ACE2) in diabetic cardiovascular complications *Clin Sci*. 2014;126(7):471–482

104. Marhl M, Grubelnik V, Magdi M, Markovi R. Diabetes and metabolic syndrome as risk factors for COVID-19 *Diabetes Metab Syndr*. 2020;14(4):671–677

105. Yang J, Feng Y, Yuan M, Yuan S, Fu H, Wu B, et al Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS *Diabet Med*. 2006;23(6):623–628

106. Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis *Int J Infect Dis*. 2016;49:129–133

107. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb Res.* 2020;191:148–150.

108. Hadid T, Kafri Z, Al-Katib A. Coagulation and anticoagulation in COVID-19. *Blood Rev.* 2021;47:100761.

109. Lazzaroni MG, Piantoni S, Masneri S, Garrafa E, Martini G, Tincani A, Andreoli L, Franceschini F. Coagulation dysfunction in COVID-19: The interplay between inflammation, viral infection and the coagulation system. *Blood Rev.* 2021;46:100745.

110. Inspiration Investigators, Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, Farrokhpour M, Sezavar SH, Payandemehr P, Dabbagh A, Moghadam KG, Jamalkhani S, Khalili H, Yadollahzadeh M, Riahi T, Rezaeifar P, Tahamtan O, Matin S, Abedini A, Lookzadeh S, Rahmani H, Zoghi E, Mohammadi K, Abri H, Tabrizi S, Mousavian SM, Shahmirzaei S, Bakhshandeh H, Amin A, Rafiee F, Baghizadeh E, Mohebbi B, Parhizgar SE, Aliannejad R, Eslami V, Kashefizadeh A, Kakavand H, Hosseini SH, Shafaghi S, Ghazi SF, Najafi A, Jimenez D, Gupta A, Madhavan MV, Sethi SS, Parikh SA, Monreal M, Hadavand N, Hajighasemi A, Maleki M, Sadeghian S, Piazza G, Kirtane AJ, Van Tassell BW, Dobesh PP, Stone GW, Lip GYH, Krumholz HM, Goldhaber SZ, Bikdeli B. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. *JAMA.* 2021;325:1620–1630.

111. Paranjpe I, Fuster V, Lala A, Russak AJ, Glicksberg BS, Levin MA, Charney AW, Narula J, Fayad ZA, Bagiella E, Zhao S, Nadkarni GN. Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. *J Am Coll Cardiol.* 2020;76:122–124.

112. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, Goodarzi K, Bendapudi PK, Bornikova L, Gupta S, Leaf DE, Kuter DJ, Rosovsky RP. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood.* 2020;136:4

113. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, Kang L, Guo L, Liu M, Zhou X, Luo J, Huang Z, Tu S, Zhao Y, Chen L, Xu D, Li Y, Li C, Peng L, Xie W, Cui D, Shang L, Fan G, Xu J, Wang G, Zhong J, Wang C, Wang J, Zhang D, Cao B. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet.* 2021;397:220–232.

114. Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, Localio AR, Demissie E, Hopkins RO, Angus DC. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med.* 2012;185:1307–1315.

115. Sachdeva M, Gianotti R, Shah M, Bradanini L, Tosi D, Veraldi S, Ziv M, Leshem E, Dodiuk-Gad RP. Cutaneous manifestations of COVID-19: Report of three cases and a review of literature. *J Dermatol Sci.* 2020;98:75–81.

116. Mirza FN, Malik AA, Omer SB, Sethi A. Dermatologic manifestations of COVID-19: a comprehensive systematic review. *Int J Dermatol.* 2021;60:418–45

117. Killion L, Beatty PE, Salim A. Rare cutaneous manifestation of COVID-19. *BMJ Case Rep.* 2021;14

118. Daneshgaran G, Dubin DP, Gould DJ. Cutaneous Manifestations of COVID-19: An Evidence-Based Review. *Am J Clin Dermatol.* 2020;21:627–639.

119. Nikolopoulou GB, Maltezou HC. COVID-19 in Children: Where do we Stand? *Arch Med Res.* 2022;53:1–8.

120. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, Roguski K, Wallace B, Prezzato E, Koumans EH, Lee EH, Geevarughese A, Lash MK, Reilly KH, Pulver WP, Thomas D, Feder KA, Hsu KK, Plipat N, Richardson G, Reid H, Lim S, Schmitz A, Pierce T, Hrapcak S, Datta D, Morris SB, Clarke K, Belay E California MIS-C Response Team. COVID-19-Associated Multisystem Inflammatory Syndrome in Children - United States, March-July 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69:1074–1080.

121. Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H, Soma VL, Maddux AB, Mourani PM, Bowens C, Maamari M, Hall MW, Riggs BJ, Giuliano JS Jr, Singh AR, Li S, Kong M, Schuster JE, McLaughlin GE, Schwartz SP, Walker TC, Loftis LL, Hobbs CV, Halasa NB, Doymaz S, Babbitt CJ, Hume JR, Gertz SJ, Irby K, Clouser KN, Cvijanovich NZ, Bradford TT, Smith LS, Heidemann SM, Zackai SP, Wellnitz K, Nofziger RA, Horwitz SM, Carroll RW, Rowan CM, Tarquinio KM, Mack EH, Fitzgerald JC, Coates BM, Jackson AM, Young CC, Son MBF, Patel MM, Newburger JW, Randolph AG Overcoming COVID-19 Investigators. Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19. *JAMA.* 2021;325:1074–1087.

122. Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. *Eur J Pediatr.* 2021;180:2019–2034.

123. Payne AB, Gilani Z, Godfred-Cato S, Belay ED, Feldstein LR, Patel MM, Randolph AG, Newhams M, Thomas D, Magleby R, Hsu K, Burns M, Dufort E, Maxted A, Pietrowski M, Longenberger A, Bidol S, Henderson J, Sosa L, Edmundson A, Tobin-D'Angelo M, Edison L, Heidemann S, Singh AR, Giuliano JS Jr, Kleinman LC, Tarquinio KM, Walsh RF, Fitzgerald JC, Clouser