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Diabetes mellitus and COVID-19: Review article

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## Diabetes Mellitus and COVID-19: Review Article

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## Diabetes Mellitus and COVID-19: Review Article

### Abstract:

**Background and Aims:** We aim to cover most of the current evidence on the effect of both diabetes & COVID-19 infection on each other and the management of diabetic patients with COVID-19 infection.

**Methods:** We utilized databases to review the current evidence related to diabetes mellitus and COVID-19.

**Results:** We discussed the most recent evidence of diabetes mellitus and COVID-19 regarding risk factors, management, complications, and telemedicine.

**Conclusions:** Diabetes mellitus carry a significant risk of complications, more extended hospital stays, and mortality in COVID-19 infected patients.

**Keywords:** Diabetes Mellitus, COVID-19, management,

### Highlights:

- Hyperglycemia was observed as a risk factor for COVID-19-related complications.
- Insulin is preferred in the management of hospitalized COVID-19 infected diabetic subjects.
- Steroids cause worsening hyperglycemia, new-onset diabetes, and hyperglycemic complications.
- E-health should be part of the standard of care during and after the pandemic.

## Diabetes Mellitus and COVID-19: Review Article

### Introduction:

Diabetes mellitus is a well-known risk factor for worse clinical outcomes in patients with Coronavirus Disease 2019 (COVID-19). However, the relationship between these two entities seems to be bidirectional [1]. The ongoing pandemic of COVID-19 has significantly affected blood glucose control in patients with diabetes mellitus. The results of this can be classified into direct effects (those directly related to the viral infection) and indirect effects (those related to the impact of the pandemic on the management of blood glucose or the use of proposed treatments for the infection that also affect glucose homeostasis).

As a direct effect, the COVID-19 infection has resulted in significant changes in patients' metabolism with significant elevations in blood glucose described as a consequence of the increased release of cytokines and inflammatory mediators, which lead to increased insulin resistance and associated hyperglycemia[2]. In addition, it has been suggested that COVID-19 might be involved in developing acute diabetes mellitus in certain patients by targeting ACE2 receptors located in pancreatic islets resulting in pancreatic injury [3].

Many therapies have been repurposed for the management of COVID-19. For instance, glucocorticoids have a remarkable impact on blood glucose. The use of this class of drugs has been associated with a decreased mortality in critically ill patients infected with COVID-19 [4]. It is well known that glucocorticoid use results in significant glucose homeostasis change due to increased gluconeogenesis and increased insulin resistance in various tissues [5].

Several studies have also described the indirect effects of the COVID-19 pandemic in diverse populations while undergoing lockdown. Some studies indicated that there

is an improvement in glyceic control, while others state there is no significant change[6] or that there even is worsening of glyceic control in this population [7]. Herein we will review available literature related to COVID-19 and Diabetes Mellitus.

### Pathophysiology of Diabetes Mellitus and COVID-19

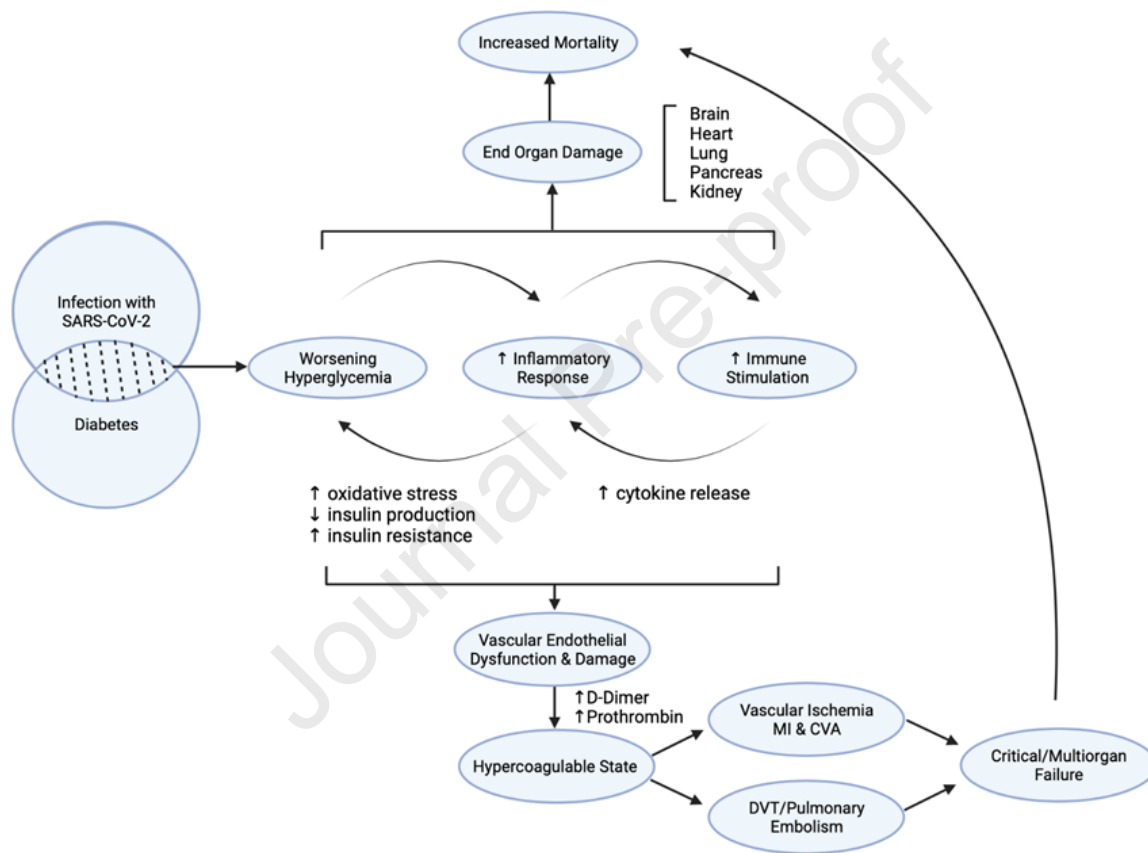


Figure No. 1: Pathophysiology of diabetes mellitus and COVID-19

Infection with SARS-CoV-2 in the setting of Diabetes mellitus (DM) initiates a flywheel of cascading effects that result in increased mortality. Infection with COVID-19 predisposes infected individuals to hyperglycemia, leading to hyperglycosylation of ACE2 and increased viral proliferation (figure No. 1) [8].

Worsening hyperglycemia induces inflammation, endothelial dysfunction, and thrombosis via the generation of oxidative stress driving further dysregulation of glucose metabolism and hypercoagulability [9]. Severe infection in individuals predisposed to vasculopathy and impaired immunity may accentuate thrombotic and ischemic complications associated with multiorgan failure and increased mortality rates.

All forms of DM can be characterized by abnormal signaling along pathways involved in glucose metabolism. DM is considered a vasculopathy equivalent as a progression of the disease is associated with both macrovascular and microvascular damage. Chronic hyperglycemia and insulin resistance contribute to vasculopathy through various mechanisms. These mechanisms include abnormal signaling along the AGE-RAGE and oxidative damage. Increased formation of advanced glycation end products (AGEs) and activation of the receptor for advanced glycation end products (RAGE) in the AGE-RAGE axis can accelerate vascular damage [10]. In addition, metabolic abnormalities associated with oxidative damage cause changes in mitochondrial expression of superoxide in endothelial cells of both large and small vessels. Over time, increased superoxide production mediates a cascade of epigenetic alterations that result in persistent expression of proinflammatory pathways even after normalization of blood glucose levels [11].

Alterations in innate and adaptive immunity, including abnormal cytokine responses, inhibition of leukocyte recruitment, and neutrophil dysfunction, are also driven by states of chronic hyperglycemia [12]. The complications of chronic hyperglycemia are compounded during acute viral infections as activated immune responses can promote systemic insulin resistance and worsening hyperglycemia [13]. In fact, severe COVID-19 progression is significantly associated with increased blood glucose level [14]. In the setting of concomitant SARS-CoV-2 infection and DM, monitoring blood glucose levels to track worsening hyperglycemia has more

prognostic value than hemoglobin A1c (HgbA1c) in these patients. These findings suggest that worsening hyperglycemia occurs acutely and may drive rapid clinical deterioration in patients with pre-existing vasculopathy and endothelial dysfunction.

While the relationship between Diabetes mellitus and COVID-19 remains complex, worsening glycemic control and aberrant immune responses may contribute to poor disease progression by accelerating thrombotic and ischemic complications associated with multiorgan failure and increased mortality rates.

### **Type 2 diabetes mellitus as a risk factor for COVID**

Type 2 Diabetes Mellitus (T2DM) is considered a risk factor for a worse prognosis in COVID-19 [1]. Many mechanisms have been described to explain the poorer prognosis of COVID-19 in diabetics, but these remain hypothetical at the time of this article. Some of these mechanisms include impaired neutrophil degranulation and complement activation, increased glucose concentration in airway secretion, which significantly increases viral replication, exaggerated proinflammatory cytokine response in diabetes, decreased viral clearance, and a more significant presence associated comorbidities [15].

An essential aspect of the relationship between COVID-19 and T2DM is that hyperglycemia at hospital admission is more relevant for prognostic purposes than the hemoglobin A1C. It is thought that COVID-19 predisposes infected individuals to hyperglycemia, leading to hyperglycosylation of the angiotensin-converting enzyme 2 (ACE2), the natural viral receptor at the host cell surface [16]. The acute hyperglycemia in these patients induces inflammation, endothelial dysfunction, and thrombosis via the generation of oxidative stress [2]. This may also enhance tissue tropism and viral penetration within the cells leading to increased virulence, pathogenicity, and susceptibility to more clinically severe infections. It has been hypothesized that the COVID-19 might affect pancreatic B-cells insulin production, which would worsen underlying glycemic control in the setting of T2DM [17].



Regardless of the mechanisms, when comparing covid-19 patients with and without T2DM, the patients with T2DM tend to develop more severe forms of the disease and tend to have a more significant increase in inflammatory markers compared to non-diabetics (i.e., higher levels of C-reactive protein, procalcitonin, ferritin, lactic dehydrogenase, and d-dimer) [18]. Furthermore, the prevalence of diabetes patients hospitalized in intensive care units for COVID-19 is two- to threefold higher, and the mortality rate at least doubles than that of non-diabetes patients [17]. There is limited evidence suggesting that newly diagnosed diabetes might be associated with a higher admission rate to ICU, invasive mechanical ventilation, and mortality risk than pre-existing diabetes [19].

Studies have also shown that a family history of T2DM might also represent a significant risk factor for this infection. Healthy individuals with a family history of T2DM tend to develop early endothelial dysfunction. Endothelial dysfunction has been reported to be a critical event in the pathophysiology of COVID-19, which has been associated with pulmonary microvascular thrombosis. Hyperinsulinemia and hyperglycemia seen in this population could favor the expression of ACE2 in various tissues, including microvascular endothelial cells known to act as a receptor for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) [20].

Based on these findings, T2DM affects the disease severity and is one of the independent risk factors for inadequate therapeutic response in patients with COVID-19 [18]. Understanding the interactions between these two diseases is crucial in developing appropriate therapeutic approaches. Further studies are warranted to elucidate the mechanisms by which diabetes affects these patients' prognosis and how these pathways can be modified to generate better outcomes in this population.

## **COVID-19 and Type 1 Diabetes Mellitus**

The prevalence of type 1 diabetes mellitus (T1DM) in COVID-19 patients range from 0.15% to 28.98% [21]. Hyperglycemia has been seen to be a risk factor for COVID-19-related complications. According to preliminary findings from a multicenter surveillance study in the United States that assessed clinical outcomes of COVID-19 in patients with T1DM, 48.5% of patients had high blood glucose levels; 45.5%, elevated temperature; 39.4%, dry cough; 33.3%, excess fatigue, and vomiting; 30.3%, shortness of breath; 27.3%, nausea; and 21.2%, body/headaches[22]. Additionally, abdominal and chest pain, chills, loose stools, and loss of taste and smell were reported by <15% of patients [22]. In these patients with COVID-19 and T1DM, obesity (39.4%) and hypertension or cardiovascular disease (12.1%) were the most prevalent comorbidities, while diabetic ketoacidosis was the most prevalent adverse outcome[22].

In a whole-population study that assessed the independent effects of diabetes status and type on in-hospital death in English patients with COVID-19, 1.5% of in-hospital COVID-19-related deaths were seen to occur in patients with T1DM versus 31.4% in those with type 2 diabetes.[23] Over the study's 72-day period, unadjusted mortality rates per 100,000 individuals were 138 for those with T1DM versus 27 for those without diabetes. Interestingly, when adjusted for age, sex, deprivation, ethnicity, and geographical region, the odds ratio (OR) for in-hospital COVID-19-related death was 3.51 (95% CI 3.16–3.90) in patients with T1DM[23].

A population-based cohort study assessed the associations between risk factors and mortality due to COVID-19 in patients with T1DM.[24] Older age and male sex were seen to be associated with increased COVID-19-related mortality.[24] COVID-19-related mortality was also significantly increased in those with black and Asian ethnicities.[24] Additionally, mortality was significantly higher among the most socioeconomically deprived individuals (Hazard ratio [HR] 1.93 [95% CI 1.36–

2.72],  $P=0.0002$ ).[24] Preceding hyperglycemia (HbA1c  $>86$  mmol/mol; HR 2.23 [95% CI 1.50–3.30,  $P<0.0001$ ]) was also strongly associated with COVID-19-related mortality.[24] A body mass index (BMI) of  $<20.0$  kg/m<sup>2</sup> (HR 2.45 [95% CI 1.60–3.75,  $P<0.0001$ ]), 35.0–39.9 kg/m<sup>2</sup> (1.72 [1.21–2.46,  $P=0.0028$ ]), and  $>40.0$  kg/m<sup>2</sup> (2.33 [1.53–3.56,  $P<0.0001$ ]) was seen to be associated with significantly increased COVID-19-related deaths.[24] Impaired renal function and previous hospital admissions with stroke or heart failure were also associated with significantly increased COVID-19-related mortality ( $P<0.0001$ ).[24]

A cross-sectional, web-based survey involved all Italian pediatric diabetes centers in determining if the diagnosis of pediatric T1DM or its acute complications were altered during the early phase of COVID-19.[25] Compared with 2019, a 23% reduction was observed in new diabetes cases in 2020.[25] Among newly diagnosed patients with diabetic ketoacidosis (DKA), the proportion of patients with severe DKA in 2020 was 44.3% compared to 36.1% in 2019 ( $P=0.03$ ).[25] Hence, the COVID-19 pandemic might have changed the presentation of diabetes and the severity of DKA[25].

### **Drug therapy of DM among COVID-19 patients:**

Herein we discuss both oral and injectable non-insulin antidiabetics[summarized in Table 1] as well as insulin and their relation to COVID-19 management and outcomes.

<b>Anti-diabetic drug</b>	<b><i>Potential benefit</i></b>	<b><i>Final results</i></b>
<b><i>Metformin</i></b>	It has been described a potential reduction in mortality with its use in patients with type 2 diabetes and covid-19 infection.	Its use should be continued in patients with type 2 diabetes mellitus until hospitalized or unless contraindicated. It is unclear at this point whether its potential mortality benefit extends to inpatient use or in non-diabetic covid-19 patients.
<b><i>Pioglitazone</i></b>	Possible reduction in inflammatory markers.	There is no significant evidence to promote its use in patients with diabetes mellitus and covid-19 infection. Further studies are needed to elucidate its potential benefit.
<b><i>Sulfonylureas</i></b>	Potential reduction in disease severity.	Studies have not demonstrated a significant difference in rate of ICU admissions or disease severity with its use.
<b><i>DPP-4 inhibitors</i></b>	It has been proposed that DPP-4 could be involved with the receptor binding domain of SARS-CoV-2. Furthermore, it could offer anti-inflammatory, anti-fibrotic and immunomodulatory effects. Several researchers have proposed its use as a repurposed agent for COVID-19.	Several studies found no significant difference in rate mortality rate, poor prognosis, or rate of ICU admission. However, others did find some benefit in rate of intubation, severity of disease, and discharge rate. Further studies are needed to elucidate its potential benefit.
<b><i>SLGT-2 inhibitors</i></b>	Anti-inflammatory properties; decrease in lactic acidosis of dapagliflozin, which could potentially reverse acid-base balance in hypoxia.	Studies have not demonstrated a significant difference in disease severity or mortality rates.
<b><i>GLP-1 receptor agonists</i></b>	Improvement in right ventricular function and anti-inflammatory effects during acute lung injury.	There is limited data available. Some studies have shown no significant difference in rate of ICU admissions or mortality.

Table 1 Antidiabetics and COVID-19 adapted from singh et al[26].

### **Metformin:**

Most type 2 DM patients on oral hypoglycemics take Metformin, either alone or with other drugs. Metformin is the preferred initial drug to treat type 2 DM.

Metformin therapy may be associated with lactic acidosis. This is rare in the absence of other factors predisposing to lactic acidosis but could happen in patients suffering renal impairment, severe infections, or sepsis.[27] Metformin can be continued in asymptomatic COVID-19 patients or patients with mild symptoms. However, Metformin should be stopped in patients hospitalized with severe COVID-19 infection due to the risk of lactic acidosis [28].

It is worth mentioning that better outcomes have been reported in COVID-19 patients receiving Metformin.[29] 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) signaling pathway [30].

#### **Sulfonylureas:**

Sulfonylureas may induce hypoglycemia, so in patients with severe COVID-19 with inadequate oral intake, it is safer to stop them. In addition, simultaneous use of hydroxychloroquine may increase the risk of hypoglycemia[31].

#### **Dipeptidyl peptidase 4 (DPP-4) Inhibitors:**

DPP-4 inhibitors are well tolerated and can be continued safely in COVID-19 patients. [29] They are associated with a low risk of hypoglycemia. DPP-4 may act as a receptor for some coronaviruses. DPP-4 inhibitors might inhibit such binding and mitigate COVID-19 infection. [32] However, this hypothetical advantage has not been proven in clinical trials.[29]

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

GLP-1 agonists may decrease water intake[15]. They may also cause nausea and vomiting. Thus, GLP-1 agonist therapy is associated with an increased risk of dehydration and aspiration pneumonia. [33] GLP-1 agonists should be stopped in patients with severe COVID-19. [31] If GLP-1 agonists are given to COVID-19

patients, patients should be closely monitored, and fluid intake should be adequate. [28] GLP-1 agonists may have an anti-inflammatory effect and may attenuate pulmonary inflammation in rats with a respiratory syncytial virus (RSV) infection and experimental lung injury. [34] Whether GLP-1 agonists may have an anti-inflammatory effect in patients with COVID-19 or not needs further evaluation and assessment.

### **Pioglitazone**

Pioglitazone upregulates Angiotensin converting-2 enzyme (ACE-2) in rat tissues, [35] leading 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) to enter cells [36].

Wu et al. showed that using virtual computer screening, Pioglitazone may be a potent inhibitor of 3 chymotrypsin-like protease, which is necessary for RNA synthesis and replication of SARS CoV-2. [37] However, this still needs 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. [38]

### **Sodium-glucose cotransporter 2 (SGLT2) inhibitors**

SGLT2-inhibitors may have a potent antiviral effect by increasing lactate concentration and decreasing the intracellular pH, resulting in a possible viral load reduction. [39] Canagliflozin therapy, an SGLT2-inhibitor, could induce a reduction in interleukin-6 (IL-6) levels, which plays an essential role in triggering the cytokine release syndrome (CRS) in COVID-19 patients. [40]

SGLT2 inhibitors increase sodium and glucose urinary excretion, leading to osmotic diuresis and possibly dehydration. Also, SGLT2 inhibitors can cause euglycemic ketosis. SGLT2 inhibitors should not be given for critically ill patients with severe

COVID-19. However, there is no need to stop them in patients with mild disease. [28]

The DARE-19 trial is a recent study that aims to evaluate the role of sodium-glucose cotransporter 2 (SGLT-2) inhibitors in non-critically ill patients hospitalized due to covid-19 infection. The investigation is a double-blinded, placebo-controlled, phase III study centered on evaluating the impact of dapagliflozin on the incidence of complications and all-cause mortality in patients with respiratory failure infected with covid-19. Patients with and without diabetes were included in the study. Its primary endpoint was to assess organ failure or death in patients treated with this SGLT-2 inhibitor versus placebo. Secondary outcomes included the evaluation of composite kidney endpoint and all-cause mortality [41]. The patients were randomized to receive either dapagliflozin 10 mg daily or a placebo for 30 days. A total of 1,250 patients were enrolled and followed for a total of 90 days. Those who were critically ill at the time of presentation, with significantly impaired kidney function (GFR <25 ml/min/1.73m<sup>2</sup>), type 1 diabetes mellitus, or prior history of diabetic ketoacidosis were excluded. The study results have shown no significant reduction in organ dysfunction, death, or improvement in recovery in patients treated with dapagliflozin compared to placebo[42].

### **Insulin**

Insulin therapy is preferred for hospitalized patients, including moderate to severe hospitalized COVID-19 patients. For non-critically ill hospitalized patients, a basal plus bolus correction regimen is recommended with a target blood sugar range of 140-180 mg/dl. [43] Critically ill COVID-19 diabetic patients in ICU can be managed by intravenous insulin infusion. Intensive insulin therapy was found to exert an anti-inflammatory effect in critically ill patients and reduce the levels of inflammatory markers (C-reactive protein (CRP) and mannose-binding lectin

(MBL)) compared to conventional insulin therapy. [44] Whether the anti-inflammatory effect of insulin is beneficial in COVID-19 patients or not needs further assessment and evaluation.

A possible therapeutic regimen in non-critically ill COVID-19 diabetic patients is a combination of basal Insulin with GLP-1 agonist, given as a single injection. The rationale beyond this therapeutic strategy is giving a single daily injection minimizing exposure to COVID-19 patients. Also, both insulin and GLP-1 agonists have a glucose-lowering effect and a possible anti-inflammatory effect. [45]

### **Effects of hyperglycemia on complications of COVID-19**

Hyperglycemia is a well-known, established risk factor for mortality due to infections, mainly due to pneumonia. COVID-19 is characterized by pneumonia that has led to the death of over 1.65 million individuals worldwide.[46] According to a retrospective, observational study involving adult patients (n=184) with laboratory-confirmed COVID-19 and uncontrolled hyperglycemia (blood glucose [BG] >180 mg/dL within any 24 hours), the mortality rate was 28.8% versus 6.2% in patients without diabetes or hyperglycemia (n=386,  $P<0.001$ ). Additionally, 41.7% of patients with uncontrolled hyperglycemia died versus 14.8% of patients with diabetes ( $P<0.001$ ) [47]. Furthermore, the median length of stay in patients with diabetes and/or uncontrolled hyperglycemia was more prolonged than in patients without diabetes or hyperglycemia ( $P<0.001$ ) [47].

Another retrospective study involving consecutive patients with COVID-19 (n=605) reported that fasting BG (FBG  $\geq 7.0$  mmol/l) was an independent predictor for 28-day mortality in patients with COVID-19, who were not previously diagnosed with diabetes (hazard ratio [H.R.] 2.30 [95% CI 1.49-3.55] [48]. In a retrospective, multicenter study involving patients (n=952) with COVID-19 and pre-existing type 2 diabetes (T2D), patients with T2D were found to have more medical interventions



and significantly higher mortality and multiple organ injury versus patients without T2D (7.8% vs. 2.7%) [49].

A retrospective single-center case series involving consecutive Chinese patients (n=138) hospitalized with COVID-19-associated pneumonia reported a history of diabetes to be associated with 22.2% of intensive care unit (ICU) admissions compared with 5.9% of non- ICU admissions ( $P=0.009$ ) [50].

A recent meta-analysis that assessed the outcomes of COVID-19 in patients with hyperglycemia reported 17% (0.10-0.25) to have died, 11% to have been admitted to the ICU, and 23% to have required mechanical or non-mechanical ventilation [51]. Additionally, severe or critical COVID-19 was seen to develop in 72% of patients, acute cardiac injury in 14%, acute respiratory distress syndrome in 15%, and acute kidney injury in 5% [51]. It is worth mentioning that acute kidney injury, whether associated with hyperglycemia or not, is a predictor of a bad outcome in COVID-19 patients. This meta-analysis confirms that hyperglycemia is a predisposing factor for the death and progression of non-critical diseases to critical diseases in patients with COVID-19, both in diabetes and diabetes [51].

### **DKA and COVID-19**

Hyperglycemic complications of diabetes mellitus include Diabetic Ketoacidosis (DKA), hyperosmolar hyperglycemic syndrome (HHS). DKA is the commonest of these complications, with the highest hospitalizations rates that also increased in the last decade in developed countries, but fortunately, mortality decreased to less than 0.5% [52].

As with other severe infections, DKA can occur in diabetic patients with COVID-19. Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-CoV-1) was found to bind to the ACE2 receptor in the pancreatic islets, which causes cellular damage

leading to acute onset of diabetes DKA[53]; hence COVID-19 was expected to have a similar mechanism.

One study in Wuhan, China, reported the prevalence of ketonemia or ketonuria among hospitalized COVID-19 patients to be 6.4%, with 7% of them meeting American Diabetes Association (ADA) DKA criteria and all of them had a prior diagnosis of diabetes mellitus [54].

Many studies and case reports later reported new-onset diabetes with DKA as the presenting symptom in COVID-19 or DKA without respiratory symptoms, and even euglycemic DKA was reported [55]. COVID-19 has also been linked to new onset T1DM with DKA and pancreatic autoantibodies [56].

Data were presented from many countries with variable presentations, In a study done in Peru, 14 patients were admitted with DKA, and four of them were diagnosed with COVIDs-19, and two of them had associated findings suggestive of pancreatitis.[57] An Australian hospital's number of DKA diagnoses during the COVID-19 pandemic was increased but comparable, while the number of severe DKA was significantly higher (45% vs. 5%;  $P < 0.003$ ).[58] In the UK, it was noticed that diabetes mellitus was overrepresented in hospitalized COVID-19 patients (31%) while its national prevalence is 7% and data of T2DM hospital bed occupancy was 18% before the pandemic, with DKA present in 2% of hospitalized COVID-19 patients [59].

A recent systematic review evaluated 110 cases of DKA with COVID-19, with the majority (91/110) presenting with DKA and (19/110) had DKA/HHS; males represented 63% of the cohort, and 77% had a prior diagnosis of T2DM. Unfortunately, mortality reached 45%, and it was higher in the DKA/HHS group than the DKA group (67% vs. 29%). This high mortality rate could be related to COVID-19 or combining both factors. A single study done at Jacobi center in New York had DKA mortality of 50% when patients had concomitant COVID-19 [60],

likely due to the severity of their respiratory illness and the overwhelming pandemic on the healthcare system in New York.

Management of DKA with COVID-19 follows the standard protocol, although it was noted that patients required higher than usual insulin doses.[61] However, due to limited resources and personal protective equipment (PPE), hospitals initiated different protocols utilizing fewer infusion pumps to use them for pressors and started using subcutaneous insulin analogs.

DKA has always been famous for thrombotic complications, which was increased when combined with COVID-19 due to its potential thrombotic complications [62], highlighting the role of prophylactic anticoagulation in patients with DKA and COVID-19.

### **Corticosteroids and COVID-19**

Steroids have been diabetes rivals for decades, although used in almost every specialty in medicine with many short-term and long-term treatment courses for their anti-inflammatory and immunosuppressive actions with subsequent undesirable side effects such as osteoporosis, hypertension, hyperglycemia, and steroid-induced diabetes [63].

Many factors contribute to the degree of hyperglycemia, including duration of treatment, dosage, relative potency, and associated infection. The higher the dose of steroid therapy, the higher the risk of developing steroid-induced diabetes. The use of steroids in diabetic patients increases the risk of hospitalization due to uncontrolled blood sugar[64].

In the first few months of the pandemic, World Health Organization (WHO) recommended against corticosteroid treatment, based on historical evidence in clinical studies of Middle East Respiratory Syndrome-corona Virus (MERS-CoV) and SARS-CoV [65] that showed treatment complications as delayed viral clearance, opportunistic infections, and hyperglycemia.

Following the warning, many institutions initiated observational studies and randomized controlled trials (RCT) on steroid therapy for COVID-19, with the most extensive study in the UK, also known as The RECOVERY trial, which showed dexamethasone as opposed to usual care reduced 28-day mortality in patients requiring oxygen therapy or mechanical ventilation [66].

Following this study and as of September 2, 2020, the WHO changed prior recommendations, and now steroids remain the only drug of proven benefit for Covid-19 patients.

Steroids have beneficial effects in states of hyper inflammation, which is the hallmark of Covid-19 but at the expense of worsening hyperglycemia, new-onset diabetes, and hyperglycemic complications.

### **Co-infections in diabetic patients with COVID 19**

DM is an important prognostic factor, as studies have shown a 10-fold higher risk of death in this patient population [67]. 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 [68]. As a result, these patients are more susceptible to other bacterial, viral, and fungal infections.

Candida species (Albicans and non-Albicans) are among the fungal co-infections observed in COVID-19 patients and present as invasive candidiasis. It can also cause fungal pneumonia. Another severe fungal superinfection is invasive pulmonary aspergillosis which is associated with high mortality rates. The diagnosis implies microbiological and/or histopathological evidence using special fungal staining [69]. Cryptococcal disease and pneumocystis jirovecii have also been detected in COVID-19 patients, particularly those treated with immunosuppressants [68]. Patients with diabetes mellitus, especially poorly controlled, 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 [70]. Fungal infections can be missed, as many of them manifest like COVID-19.

According to one case series in Washington, the rate of bacterial co-infection in COVID-19 patients was 4.8%. A study from China revealed *Mycoplasma pneumoniae* and *Legionella pneumophila* are among the most frequently isolated organisms causing respiratory illness in patients with COVID 19. The prevalence of diabetes was 54%, and a strong correlation was shown between hyperglycemia and co-infection [71]. Patients with bacterial co-infections were found to have higher mortality and higher rates of steroid use.

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 [72]. 71% of COVID-19 associated mucormycosis (CAM) cases are reported from India. This is explained by the fact that India has the highest burden of mucormycosis in the world and has the second-largest number of adults with diabetes [72]. This otherwise 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. DM was present in 94 % of CAM patients, 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 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 patients[73]. Also, blood glucose readings using various devices such as meter, pump, and sensor facilitate diabetic management by e-health. However, it 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[74].

Lockdown during the COVID-19 pandemic has a negative impact on blood glucose levels by changing diet habits, decreasing physical activities, 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[75]. Moreover, diabetic patients need regular foot checkups. Using video calling as triage for the diabetic foot could prevent catastrophic complications. A meta-analysis of 42 randomized control trials showed that telemedicine has a better impact on the control of hemoglobin A1C than standard care, especially in more than 40 years old and type 1 diabetic patient.[76] E-health should be part of the standard of care during and after the pandemic.

### **Conclusion:**

Diabetes mellitus carries a significant risk of complications, extended hospital stays, and mortality in COVID-19 infected patients. Therefore, insulin is preferred to oral hypoglycemic medications in the management of hospitalized COVID-19 infected

diabetic subjects. This cohort has recommended frequent blood sugar checks and prompt management of hypoglycemia, hyperglycemia, and DKA.

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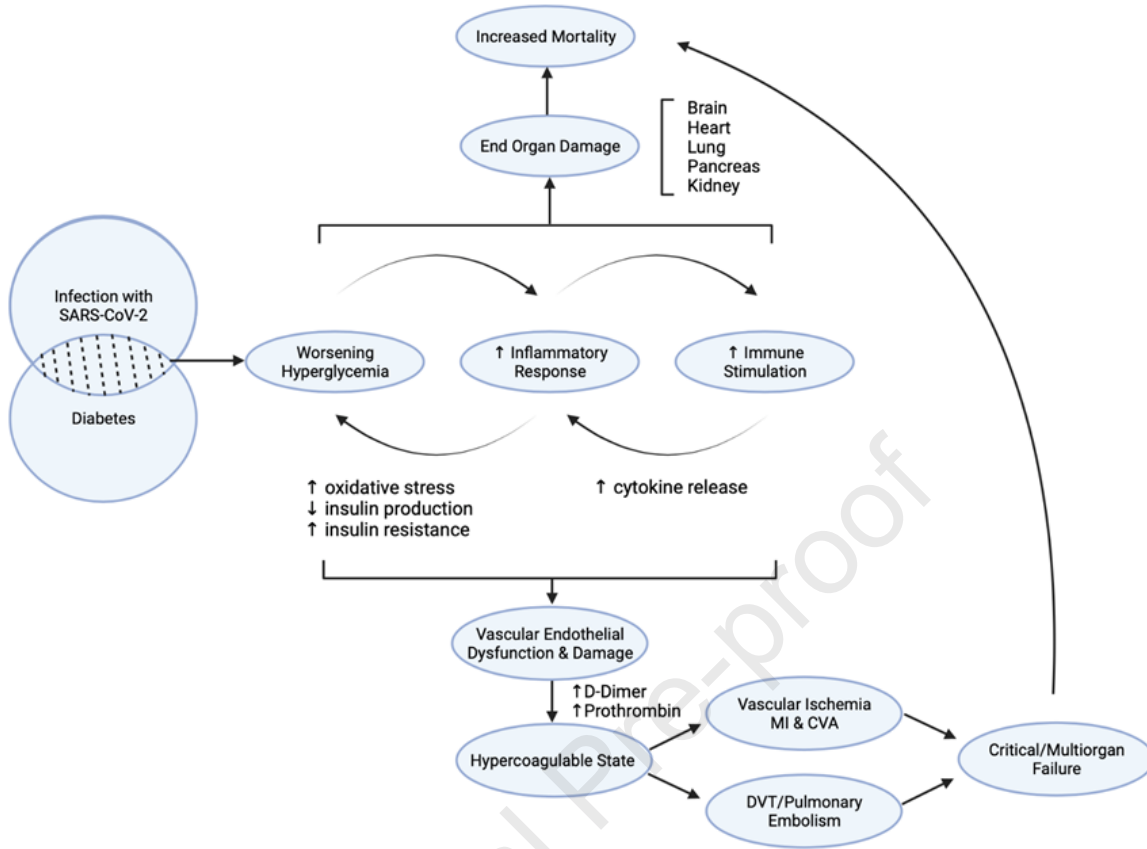
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Journal Pre-proof

<b>Anti-diabetic drug</b>	<b><i>Potential benefit</i></b>	<b><i>Final results</i></b>
<b><i>Metformin</i></b>	It has been described a potential reduction in mortality with its use in patients with type 2 diabetes and covid-19 infection.	Its use should be continued in patients with type 2 diabetes mellitus until hospitalized or unless contraindicated. It is unclear at this point whether its potential mortality benefit extends to inpatient use or in non-diabetic covid-19 patients.
<b><i>Pioglitazone</i></b>	Possible reduction in inflammatory markers.	There is no significant evidence to promote its use in patients with diabetes mellitus and covid-19 infection. Further studies are needed to elucidate its potential benefit.
<b><i>Sulfonylureas</i></b>	Potential reduction in disease severity.	Studies have not demonstrated a significant difference in rate of ICU admissions or disease severity with its use.
<b><i>DPP-4 inhibitors</i></b>	It has been proposed that DPP-4 could be involved with the receptor binding domain of SARS-CoV-2. Furthermore, it could offer anti-inflammatory, anti-fibrotic and immunomodulatory effects. Several researchers have proposed its use as a repurposed agent for COVID-19.	Several studies found no significant difference in rate mortality rate, poor prognosis, or rate of ICU admission. However, others did find some benefit in rate of intubation, severity of disease, and discharge rate. Further studies are needed to elucidate its potential benefit.
<b><i>SLGT-2 inhibitors</i></b>	Anti-inflammatory properties; decrease in lactic acidosis of dapagliflozin, which could potentially reverse acid-base balance in hypoxia.	Studies have not demonstrated a significant difference in disease severity or mortality rates.
<b><i>GLP-1 receptor agonists</i></b>	Improvement in right ventricular function and anti-inflammatory effects during acute lung injury.	There is limited data available. Some studies have shown no significant difference in rate of ICU admissions or mortality.

Table 1 Antidiabetics and COVID-19 adapted from singh et al[26].



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