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Review

COVID-19 and diabetes: What does the clinician need to know?

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ABSTRACT

COVID-19 and diabetes are currently two global pandemics. Epidemiological studies indicate that diabetes is the second most common comorbidity in COVID-19. This review aims to summarize currently available data about prevalence, possible pathophysiological mechanisms and management of patients with diabetes and COVID-19.

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1. Introduction

In December 2019, a series of pneumonia cases of unknown cause was reported in Wuhan, Hubei, China. Shortly a novel coronavirus was isolated from respiratory tract samples named as SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2). The new virus rapidly spread globally resulting in a pandemic. SARS-CoV-2 belongs to betacoronavirus as the severe acute respiratory syndrome (SARS) and the middle east respiratory syndrome (MERS) viruses responsible for serious outbreaks in China in 2002–2003 and in the Middle East in 2012, respectively [1].

The disease caused by SARS-CoV-2, known as COVID-19 (coronavirus disease 2019) ranges from mild acute respiratory illness to severe pneumonia with respiratory failure, acute respiratory distress syndrome and septic shock. Severe disease mainly occurs in older adults and those with underlying medical comorbidities, such as hypertension, diabetes, cardiovascular disease, chronic lung disease, cancer and chronic kidney disease [2].

2. Association of diabetes with previous coronavirus outbreaks

In a study with 115 patients diagnosed with SARS-CoV in Hong Kong in 2003, the presence of diabetes was independently associated with an increased mortality risk (HR 4.7, 95 % CI 1.5–14.3; p = 0.008) [3]. Similarly, a systematic analysis of 637 MERS-CoV cases identified diabetes as a comorbidity in approximately 50 % of patients [4]. Diabetes was also associated with increased risk of complications during the 2009 pandemic influenza A (H1N1) infection [5].

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Despite higher transmissibility, SARS-CoV-2 appears to have a lower case fatality rate than SARS-CoV (9.5 %) and Middle East respiratory syndrome (MERS-CoV) (34.4 %), but higher than that of influenza (0.1 %) [6].

3. Association of diabetes with SARS-CoV-2 pandemic

The prevalence of diabetes in patients with COVID-19 depends on the size and characteristics of study population. Early estimates came from China. In a multicenter study with 1099 patients hospitalized with COVID-19 illness in China, the overall prevalence of diabetes was 7.4 % [2]. In a meta-analysis of 7 studies including 1576 patients from China, diabetes was the second most common comorbidity following hypertension, and was present in 9.7 % of patients [7]. In another meta-analysis of 21 studies mainly from China, hypertension and diabetes were the most prevalent comorbidities present in 15.6 % and 7.7 %, respectively, among 47,344 patients with COVID-19 [8]. In a retrospective study of 1591 critically ill patients admitted in ICU in the Lombardy region of Italy, hypertension was the most common comorbidity (49 %), followed by cardiovascular disorders (21 %), hypercholesterolemia (18 %), and diabetes (17 %) [9].

Observational studies so far indicate that diabetes is associated with higher morbidity and mortality in patients with COVID-19. Diabetic patients are at higher risk to develop complications of COVID-19 and been admitted to intensive care unit [10]. A study evaluating the metabolic cardiovascular comorbidities in patients with COVID-19 found that hypertension, cardia-cerebrovascular disease and diabetes were present in 17.1 %, 16.4 % and 9.7 %, respectively, among 1527 patients. The overall proportion of hypertension, cardia-cerebrovascular diseases and diabetes was about 2-fold, 3-fold and 2-fold, respectively, higher in intensive care unit (ICU)/severe cases than in non-ICU/severe counterparts. Diabetes accounted for 4.0 % of non-ICU/severe cases and 11.7 % of ICU/severe cases in this study [11]. In a meta-analysis of 1558 COVID-19 patients from 6 studies, diabetes was an independent risk factor for disease progression (OR: 2.47, $P < 0.001$) along with hypertension (OR: 2.29, $P < 0.001$), chronic obstructive pulmonary disease (COPD) (OR: 5.97, $P < 0.001$), cardiovascular disease (OR: 2.93, $P < 0.001$), and cerebrovascular disease (OR:3.89, $P = 0.002$) [12]. Diabetes also significantly increased the risk of ICU admission (OR: 2.79, 95 % CI 1.85–4.22, $p < 0.0001$) among 1382 patients with COVID-19 [13]. Diabetic patients were at higher mortality risk (OR 3.21, 95 % CI 1.82–5.64, $P < 0.0001$) in an analysis of 471 patients [13]. In a larger meta-analysis of 6452 patients from 30 studies, diabetic patients were at increased risk for death (RR 2.12, $P < 0.001$), severe COVID-19 (RR 2.45 $p < 0.001$), acute respiratory distress syndrome (ARDS) (RR 4.64 $p < 0.001$), and disease progression (RR 3.31, $p < 0.04$) [14].

In a study that included 72,314 cases of COVID-19 from the Chinese Center for Disease Control and Prevention, the overall case-fatality rate (CFR) was 2.3 %, but patients with diabetes had a 3-fold higher mortality rate than those without diabetes (7.3 % vs 2.3 %) [15]. The overall fatality rate of persons with confirmed COVID-19 in the Italian population was 7.2 %, which was substantially higher than in China (2.3 %). This difference may be partly explained due to the older age of patients in Italy [16].

In a study that included 5700 patients hospitalized with COVID-19 in 12 hospitals in New York city, the most common comorbidities were hypertension (56.6 %), obesity (41.7 %) and diabetes (33.8 %). Mortality was high (88.1 %) for those who required mechanical ventilation. Among those who died, patients with diabetes were more likely to have received invasive mechanical ventilation (55.8 % vs 47.7 %) or ICU care (57.6 % vs 49.2 %) compared with non-diabetics. Moreover, patients with diabetes were more likely to develop acute kidney injury than those without (13.5 % vs 8% among discharged patients) [17].

4. Possible pathophysiological mechanisms

The pathophysiological mechanisms implicated with the increased frequency and severity of COVID-19 in people with diabetes are not yet elucidated. There are several hypotheses to explain why COVID-19 is more frequent in diabetes and associated with worse outcomes.

In general, diabetes is associated with an increased risk of various infections, including viral ones [18]. Alterations in innate immunity play a major role in increased susceptibility to infections in diabetics, while humoral immunity appears relatively unaffected. Hyperglycemia depresses neutrophil chemotaxis, phagocytosis, opsonization, adherence to vascular endothelium and intracellular bactericidal activity [19]. The presence of diabetic complications, such as vascular insufficiency and peripheral neuropathy may also predispose to infections [20]. Moreover, poor glycemic control contributes to this increased risk of infections in people with diabetes [21]. Diabetes and obesity are associated with a low grade subclinical chronic inflammation due to increased secretion of adipose tissue hormones and cytokines that contribute to the development of insulin resistance, such as leptin, tumor necrosis factor-a (TNFa) and interleukin-6 (IL-6) [22]. Moreover, diabetes and insulin resistance are associated with endothelial dysfunction, and enhanced platelet aggregation and activation, which predispose to the development of a hypercoagulable prothrombotic state [23]. The low-grade chronic inflammation along with the hypercoagulable state in diabetes may promote the cytokine storm, a complication of severe COVID-19 which is characterized by excessive production of inflammatory cytokines (IL-6, IL-10 and TNFa) [24].

Guo et al. compared laboratory parameters between 37 diabetic and 137 non-diabetic COVID-19 patients and found that absolute counts of neutrophils, C-reactive protein (CRP), D-dimers, serum ferritin, erythrocyte sedimentation rate (ESR), IL-6, and fibrinogen were significantly higher ($P < 0.01$) in diabetes compared to non-diabetes group [24]. It is possible that higher inflammatory and hypercoagulable state may contribute to the development of cytokine storm and rapid deterioration of COVID-19 in patients with diabetes [25].

Other studies have also demonstrated enhanced inflammation response in diabetic patients with severe COVID-19 compared with patients without diabetes. Yan et al. compared the clinical characteristics and outcomes in 48 severe COVID-19 patients with diabetes and 145 patients with severe COVID-19 without diabetes in a retrospective observational study in China [26]. White cell count, neutrophil count, CRP, IL-2R, IL-6, IL-8, D-dimer, lactate dehydrogenase (LDH) as well as N-terminal pro-B- type natriuretic peptide (NT-proBNP) were higher in diabetics. Patients with diabetes were more likely to receive mechanical ventilation, been admitted to ICU and die [26].

Similarly, in a multi-center study of 7337 cases of COVID-19 in China, patients with diabetes had a significantly higher incidence of lymphopenia, higher leukocytes and neutrophil counts in peripheral blood, higher inflammation markers like C-reactive protein and procalcitonin and increased D-dimers compared with non-diabetic patients [27]. Interestingly, diabetic patients with well controlled glycemia experienced less severe inflammatory response than those with poorly controlled glycemia, highlighting the importance of good glycemic control prior and during COVID-19 [27].

Pulmonary dysfunction is another aspect that may contribute to worse outcomes of COVID-19 in patients with diabetes. Sev-

eral functional abnormalities in the respiratory tract have been reported in patients with diabetes, such as reduced lung function (low FEV1), reduced forced vital capacity and peripheral airway obstruction. The pathophysiology of diabetic lung is complex and includes hyperglycemia, hyperinsulinemia, autonomic neuropathy, oxidative stress, micro/macroangiopathy of alveolar capillaries and pulmonary arterioles, glycosylation of tissue proteins, collagen and elastin changes, alteration of connective tissue, surfactant dysfunction and malfunction of respiratory muscles [28].

Obesity is a major risk factor for diabetes and most diabetics are overweight or obese. Obesity appears to be an independent risk factor for severe illness in COVID-19, thus the presence of both obesity and diabetes further poses to poor prognosis [29]. In a study of 383 Chinese patients, obese patients were at 3.40-fold odds of developing severe disease (OR 3.40, 95 % CI 1.40–2.86, P < 0.007), compared with patients with normal weight even after adjusting for comorbidities and other risk factors [30]. Similarly, obese patients had 3-fold greater likelihood (OR 3.00, 95 % CI 1.22–7.38) of progressing to severe disease in a matched cohort study of 75 Chinese patients, after adjustment for clinical characteristics, including the presence of diabetes [31]. Chronic inflammation in obesity impairs immune response. Moreover, obesity is associated with decreased expiratory reserve volume, functional capacity and respiratory system compliance predisposing to worse outcomes. In a retrospective study, obesity increased the risk for invasive ventilation in patients with COVID-19 [32]. Severe obesity (BMI $\geq$ 35 kg/m^2), was also independently associated with mortality among 200 patients hospitalized with COVID-19 in a tertiary hospital in New York [33].

The presence of multiple comorbidities correlates with greater disease severity and adverse outcomes on COVID-19 infection [34].The high incidence of diabetes in severe cases of COVID-19 could reflect the frequent coexistence with other comorbidities such as cardiovascular disease and older age. In a previous study, concurrent cardiovascular disease increased the risk for infection-related death in patients with diabetes [35]. In a retrospective study involving 153 COVID-19 patients with diabetes compared with age and sex-matched patients without diabetes, multivariable analyses showed that age >70 years (HR 2.39, 95 % CI 1.03–5.56) and hypertension (HR 3.10, 95 % CI 1.14–8.44) were independent risk factors for in-hospital death in patients with diabetes [36]. Another study identified older age as independent predictor of death among diabetic patients with COVID-19 [37].

5. Role of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs)

SARS-CoV-1 and SARS-CoV-2 entry into target cells, primarily the lung alveolar epithelial cells, after binding to angiotensin-converting enzyme 2 (ACE2). ACE2 is an enzyme that degrades angiotensin II to angiotensin (1–7) and angiotensin I to angiotensin (1–9). ACE2 is also expressed in many other tissues, such as the heart, kidneys, intestinal epithelium and pancreas [38]. It has been suggested that ACEIs and ARBs, which are widely used as antihypertensives in diabetic patients, result in the upregulation of ACE2, thus possibly increasing the risk for and the severity of COVID-19 infection [39].

Experimental animal models have provided mixed results regarding the effects of ACEIs on ACE2 levels, while there are few studies in humans with inconclusive results [38]. At present, there is no clinical evidence supporting that the use of ACEIs or ARBs aggravate the susceptibility or severity of COVID-19. On the contrary, ARBs have shown a potentially protective pulmonary effect in experimental models [40]. During SARS-CoV-2 infection, alveolar ACE2 appears to be downregulated resulting in decreased levels of protective angiotensin (1–7) [41]. In this context, there is an ongoing study evaluating the effect of Recombinant Human Angiotensin-converting Enzyme 2 (rhACE2) and another study with losartan as a treatment for patients with COVID-19. Therefore, it can be speculated that having increased ACE2 expression by RAAS inhibitors treatment may actually be beneficial in the course of SARS-CoV-2 infection [38].

According to several scientific societies including the European Society of Cardiology [42], European Society of Hypertension [43], the American Heart Association and the American College of Cardiology [44], ACEIs/ARBs should not be withheld in stable patients who are at risk for or are infected with COVID-19, until further data are available. Withdrawal of ACEIs/ARBs may result in clinical instability, especially in high-risk patients, such as those with prior myocardial infarction, heart failure with impaired left ventricular function and proteinuric chronic kidney disease. Indeed, findings from observational studies support current recommendations for treating hypertension during the COVID-19 pandemic. In a retrospective study from China there was no difference in severity, complications, and risk of death from COVID-19 in patients on ACEIs/ARBs compared with those not treated with these medications [45]. Similarly, in a case control study from Italy, the use of ACEIs or ARBs did not influence the risk of COVID-19 [46].

6. Management of diabetes during the COVID-19 pandemic

An international expert panel has published practical recommendations for diabetes management in patients with COVID-19 both in and out of the hospital setting [47]. People with diabetes should follow general preventive measures including frequent hand hygiene and strict social distancing. Telemedicine should be encouraged when possible in order to avoid unnecessary routine clinical visits and prevent person-to-person transmission [47].

People with diabetes should intensify treatment and optimize glycemic control as better diabetes control is associated with improvement in cellular immunity [48]. Better control of hypertension and dyslipidemia should also be encouraged in order to achieve optimal metabolic control. Outpatient diabetics with mild COVID-19 should follow sick day rules, including frequent glucose monitoring, adequate hydration, monitor of ketones if on insulin therapy and frequent medical contact in order to identify possible clinical deterioration [49].

In cases of mild infection diabetes medications should be continued. Special attention should be paid on sodium-glucose transporter 2 (SGLT2) inhibitors because of the risk of euglycemic diabetic ketoacidosis and dehydration during acute illness. However, it is well established that SGLT2i exert cardioprotective and renoprotective effects in patients with type-2 diabetes, heart failure with reduced ejection fraction, and chronic kidney disease. Thus, it has been hypothesized that SGLT2i may actually be beneficial in patients with COVID-19 who frequently develop cardiovascular complications, acute myocardial injury and/or acute kidney injury. A randomized, double-blind, placebo-controlled, phase 3 Dapagliflozin in Respiratory Failure in Patients With COVID-19 (DARE-19) study is ongoing and will evaluate the effect of dapagliflozin in reducing disease progression, complications, and all-cause mortality in hospitalized patients with mild-moderate COVID-19 and type 2 diabetes, cardiovascular disease, and/or mild-moderate chronic kidney disease (CKD) [50]. Metformin may be stopped in those with acute illness and dehydration to minimize risk of lactic acidosis. Glucagon-like peptide-1 receptor agonist (GLP-1RA) therapy may be continued in non-critically ill patients, however, gastrointestinal side effects may predispose to volume depletion. Pioglitazone should be discontinued in critically ill patients [49]. A concern has been raised as pioglitazone and liraglutide were associated with upregulation of ACE2 in animal studies.

However, as with ACEIs/ARBs, there is currently absence of clinical evidence of harm in people affected by COVID-19 [51]. Dipeptidyl peptidase-4 (DPP4) inhibitors are associated with low risk of hypoglycaemia and may be continued in non-critically ill patients. DPP-4 is the receptor for MERS [52]. It has been hypothesized that DPP4 inhibitors might be a therapeutic strategy for preventing infection and decreasing the severity of COVID-19. However, there is currently no evidence that DPP4 serves as a receptor for SARS-CoV2 [53]. Doses of other antihyperglycemic drugs such as sulfonylureas and insulin may have to be adjusted depending on blood glucose levels. Frequent self-monitoring of blood-glucose is necessary especially when insulin is used with careful adjustment of the insulin dose. Patients with type 1 diabetes should monitor ketone levels and be vigilant for the development of symptoms of DKA [49].Indeed, in a registry of patients with type 1 diabetes and COVID-19 almost one third of the patients developed DKA [54].

Insulin is the treatment of choice in hospitalized COVID-19 patients. According to the American Diabetes Association guidelines, basal insulin or a basal plus bolus correction insulin regimen is the preferred treatment for noncritically ill hospitalized patients. Continuous intravenous insulin infusion is preferred in critically ill patients in the ICU. A target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for both critically ill patients and noncritically ill patients [55]. Optimizing glycemic control in hospitalized patients requires multiple daily glucose measurements from health care providers. The implementation of diabetes technology (i.e., continuous glucose monitoring, CGM) can be helpful in minimizing staff exposure during the COVID-19 pandemic as data can be remotely accessed and has been proven effective in maintaining blood glucose control [56,57].

UK's National Diabetes Inpatient COVID Response Team has released guidelines for management of inpatient hyperglycemia in COVID-19 patients with diabetes [58]. It is emphasized that COVID-19 increases the risk of diabetes emergencies, such as DKA and hyperosmolar hyperglycaemic state. Moreover, markedly increased insulin resistance has been detected in the ICU setting with patients requiring markedly elevated insulin drip rates up to 20 u/h [58]. Guidance is also provided regarding the use of subcutaneous insulin for the treatment of DKA when infusion pumps are not available. Noteworthy that all patients should be evaluated for diabetes at admission as there is evidence that SARS-CoV-2 predisposes to new onset diabetes [58]. ACE2 is widely expressed in several extrapulmonary tissues, including the liver and the pancreatic islets. Infection of the beta cells by SARS-CoV-2 could result in impaired insulin secretion and contribute to the exacerbation of pre-existing or development of new diabetes in acutely ill patients with COVID-19 [25].

7. Glycaemic control

It is well established that inpatient hyperglycemia contributes to a significant increase in morbidity and mortality, and that better glycemic control may improve clinical outcomes [59]. Improving glycemic control also correlates with better outcomes in patients with diabetes and COVID-19. Zhu et al. showed that among 7337 confirmed COVID-19 cases in China, diabetics with better glucose control (glycemic variability within 70–180 mg/dL; 3.9–10.0 mmol/L) had lower mortality rate than diabetics with poor control (upper limit of glycemic variability >180 mg/dL; >10.0 mmol/L) [27]. It is noteworthy that patients from the well-controlled group also had lower inflammatory and coagulation markers (CRP, procalcitonin, D-dimers), required significantly less treatment (antivirals, antibiotics, antifungals, systemic corticosteroids, immunoglobin and vasoactive drugs) and had less need for oxygen supplementation as well as invasive and non-invasive ventilation [27]. A retrospective study with 1122 patients in 88 U.S. hospitals showed that patients with COVID-19 and diabetes and/or uncontrolled hyperglycaemia had a longer length of hospital stay and markedly higher mortality than patients without diabetes and/or uncontrolled hyperglycaemia. In a subset analysis of patients without evidence of diabetes prior to admission who developed hyperglycemia in hospital, mortality was 7-fold greater, thus raising the possibility that acute hyperglycemia is an independent risk factor for mortality in COVID-19 [60]. Hyperglycemia at admission has also been associated with worse prognosis, while optimal glycemic control during hospitalization is associated with a significant reduction of inflammatory cytokines, procoagulative status and risk of severe disease and death in patients with COVID-19 [61].

8. Conclusions

People with diabetes are at increased risk of disease progression and developing COVID-19 complications, such as ARDS, ICU admission, mechanical ventilation and death. Diabetic patients demonstrate severe inflammatory response and are more prone to develop cytokine storm syndrome. Optimal glycemic control is crucial in the COVID-19 era and improves prognosis. Management of patients with diabetes and COVID-19 is challenging. Prevention and treatment strategies are urgently required to decrease morbidity and mortality in this high-risk population.

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Conflict of interest

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