Received: 4 May 2020 | Revised: 3 July 2020 | Accepted: 9 July 2020

DOI: 10.1111/1753-0407.13085

REVIEW ARTICLE

Journal of Diabetes WILEY

Factors leading to high morbidity and mortality of COVID-19 in patients with type 2 diabetes

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Abstract

Coronavirus disease 2019 (COVID-19) is a recent pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus. Diabetes (mostly type 2 diabetes mellitus, T2DM) and hyperglycemia are among the major comorbidities in patients with COVID-19 leading to poor outcomes. Reports show that patients with diabetes and COVID-19 are at an increased risk for developing severe complications including acute respiratory distress syndrome, multi-organ failure, and death. Here we explore potential mechanistic links that could explain the observed higher morbidity and mortality in this patient population. Patients with T2DM have an underlying increased level of inflammation associated with obesity and insulin resistance in addition to other comorbidities including hypertension, obesity, cardiovascular disease, dyslipidemia, and being older. We review evidence that T2DM with hyperglycemia are among factors that lead to elevated expression of angiotensin-converting enzyme 2 (ACE2) in lungs and other tissues; ACE2 is the cellular "receptor" and port of viral entry. The preexisting chronic inflammation with augmented inflammatory response to the infection and the increasing viral load leads to extreme systemic immune response ("cytokine storm") that is strongly associated with increased severity of COVID-19. Based on the available evidence, it is recommended by a panel of experts that safe but stringent control of blood glucose, blood pressure, and lipids be carried out in patients with T2DM, measures that could potentially serve to decrease the severity of COVID-19 should these patients contract the viral infection. Once the infection occurs, then attention should be directed to proper glycemic control with use of insulin and frequent monitoring of blood glucose levels.

KEYWORDS

COVID-19, cytokine storm, diabetes mellitus, inflammation, insulin resistance, mortality

Highlights

- Type 2 diabetes mellitus (T2DM) is associated with chronic inflammation due to underlying insulin resistance and other comorbidities including obesity, older age, hypertension, cardiovascular disease, and dyslipidemia.
- Insulin resistance, hyperglycemia, and elevated angiotensin-converting enzyme 2 (which acts as cellular "receptor" for the virus) leads to heightened inflammation in T2DM.
- We hypothesize that exacerbation of preexisting chronic inflammation and the intense hyperimmune response ("cytokine storm") play a critical role in increased morbidity and mortality of coronavirus disease 2019 (COVID-19).
- Safe and rigorous blood glucose, blood pressure, and lipid control is recommended in patients with T2DM and COVID-19.

1 | INTRODUCTION

In December 2019, Wuhan City in Hubei Province of China experienced an outbreak of pneumonia caused by a novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), and the disease was subsequently named coronavirus disease 2019 (COVID-19).[1,2] This highly infectious RNA virus has now spread to many parts of the world causing ever-increasing morbidity and mortality. The protein envelope of the virus contains "crown like" spike projections (S protein) that binds to angiotensin-converting enzyme 2 (ACE2), a membrane-bound aminopeptidase that is expressed on the surface of pulmonary epithelial and alveolar cells as well as many other cells throughout the body; ACE2 mediates the internalization of the virus following the action of transmembrane protease serine 2 (TMPRSS2).[3,4] Following intracellular replication, the virus stimulates humoral and cellular immunity pathways, and in severe cases leads to a strong inflammatory and hyperimmune response ("cytokine storm") that can cause massive bilateral viral pneumonia, acute respiratory distress syndrome (ARDS), cardiac and kidney injury, hypercoagulation and strokes, liver damage, infection of pancreatic islets, and multiple organ failure.[5] The spectrum of symptoms of COVID-19 spans from being asymptomatic to having a mild upper respiratory tract infection or diarrhea to severe illness.[6] A high percentage of severely ill patients have one to several preexisting comorbidities including increased age, hypertension (HTN), type 2 diabetes mellitus (T2DM), obesity, dyslipidemia, and renal and cardiovascular disease (CVD).[6,7] It is not known whether patients with T2DM are more vulnerable to contract the infection (as they are to other infections), but it is clear that once infected, they are at high risk for severe disease.[8]

This review is focused on patients with T2DM who develop COVID-19. However, many of the aspects of the clinical course of the disease are also applicable to patients with type 1 diabetes mellitus (T1DM), especially older patients who have become overweight or obese and have microvascular and macrovascular disease.

Here we explore the factors and pathways that could explain the observed higher morbidity and mortality of patients with T2DM and COVID-19.[9,10] Figure 1 shows the relationship of the common conditions that are present in most patients with T2DM; each of these factors is associated with increased susceptibility for developing severe COVID-19. The diagram illustrates the interrelationship of multiple factors and how they can collectively contribute to the severity of the disease. We postulate that multiple factors including obesity, preexisting insulin resistance, hypoglycemia, and the elevated chronic state of inflammation potentially lead to increased susceptibility to develop severe infection with SARS-CoV-2. Increased expression of ACE2 and introduction of the virus through binding to ACE2 in the lungs lead to systemic infection that exacerbates the existing chronic inflammation and leads to an intense immunological reaction which underlies the development of the severe COVID-19. We will briefly discuss these factors and their interrelationships in the following sections. We will also review treatment modalities focused on diabetes and the inflammation/immune response in patients with diabetes and COVID-19.

2 | INCREASED SUSCEPTIBILITY OF PATIENTS WITH T2DM TO INFECTIONS

Patients with T2DM are not only vulnerable to various infections caused by bacteria and fungi, they also develop

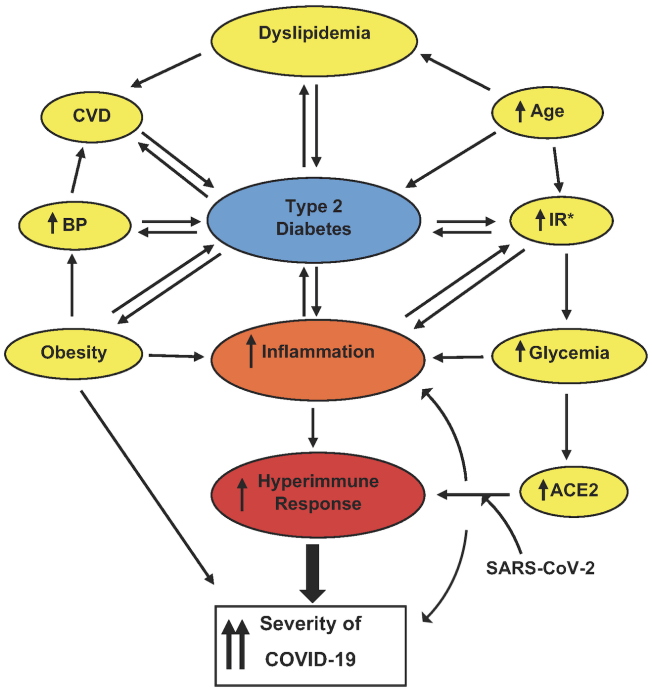

FIGURE 1 Conditions and factors present in patients with T2DM that could lead to the severity of COVID-19. The diagram shows the inter-relationship of the various factors that are present in patients with T2DM, factors and conditions that are associated with increased severity of COVID-19 among these patients. The various factors shown are inter-related and often re-enforcing with the insulin resistant state and T2DM. Entry of SARS-Cov-2 virus following its binding to ACE2 augments the already present chronic inflammatory state. The viral infection in conjunction with the stimulated inflammatory state leads to a hyperimmune response that appears to be the hallmark of severe COVID-19. Also shown is the role of increased expression of ACE2 (cell "receptor" for SARS-Cov-2) in patients with diabetes and hyperglycemia; this potentially explains the increased susceptibility of patients with diabetes for acquiring a severe form of the infection. The available evidence suggest that the elevated state of inflammation becomes greatly augmented by the viral infection and that together with the resulting hyperimmune response ("cytokine storm") represent the major common pathway through which patients with T2DM are at an increased risk of developing severe COVID-19 illness

more severe illness as compared to patients without diabetes.[11,12] There are various mechanisms that are possibly responsible for this higher susceptibility and severity of infections. There is impaired polymorphonuclear function, including chemotaxis, adherence, phagocytosis, and intracellular killing,[13] as well as impairment of T lymphocyte function.[14] Also, there is dysregulation of nitric oxide production in response to bradykinin leading to vasoconstriction, which could attenuate the ability of phagocytes to reach their targets.[15,16] T2DM is also associated with decreased host defense immunity, thereby further increasing the susceptibility to infections.[17] Hyperglycemia and hyperinsulinemia can impair complement receptor-3 and Fcg receptor-mediated phagocytosis in neutrophils by activating protein kinase Ca or protein kinase Cb.[18]

Unlike bacterial infections, the physiological response in normal individuals to viral infection and replication is activation of transcription factors including interferon regulator factors and nuclear factor kappa B (NF-KB).[19,20] This in turn leads to antiviral response by induction of type I interferon (IFN-I) and IFN-III and recruitment of specific subsets of leukocytes stimulated by chemokine secretion.[21-23] One study showed that patients with T2DM had decreased antiviral response demonstrated by a diminished production of IFN-α.[24] Another study performed on human peripheral blood mononuclear cells and human monocyte cell lines in vitro showed that hyperglycemia suppressed IFN-1 production and that pre-exposure to high glucose concentrations rendered monocytes more sensitive to IFN-α stimulation with heightened signaling.[25] Additionally, they found that high glucose levels promoted the production of other pro-inflammatory cytokines.[25] Therefore, it is probable that patients with T2DM may have alterations in their innate immune system that promotes pro-inflammatory cytokines as well as having a defective host defense system against viral infections by impeding IFN-1 production and signaling.

3 | ACE2, SARS-CoV-2, AND COVID-19

Angiotensin-2 is an 8-amino acid peptide produced by action of angiotensin-converting enzyme 1 (ACE1) on angiotensin-1. Angiotensin-2 stimulates aldosterone secretion, increases sodium retention and BP, and increases vascular permeability in the lungs thereby increasing the risk for ARDS; it also elicits inflammatory responses.[26,27] Angiotensin-converting enzyme 2 (ACE2) is a plasma membrane protein expressed largely in the lungs as well as in many other tissues and endothelial cells including the heart, kidneys, and importantly in insulin producing β-cells.[4,28-30] SARS-CoV-2 has a high affinity toward ACE2, and upon binding the virus, the complex is internalized resulting in intracellular replication of the virus[3]; hence, ACE2 acts as the "receptor" for SARS-CoV-2 and is the dominant path of the virus's entry into the lungs and other cells in the body.[4,31,32]

Expression of ACE2 is increased in patients with diabetes and in response to elevated glucose levels[4,29,33,34]; this in part may explain the apparent higher susceptibility of patients with diabetes to contract the disease and could contribute to the severe course of infection by

increasing the patient's viral load. ACE2 expression is also increased by ACE-inhibitors and angiotensin receptor blockers (ARBs).[4,35-38] ACE2 converts angiotensin-2 to angiotensin 1-7.[39] The 7-amino acid peptide product acts through the Mas receptor pathway and stimulates anti-inflammatory and antifibrotic pathways that could counteract some of the untoward effects of angiotensin-2.[33,40] This would be favorable to the recovery of patients with COVID-19. Hence, the balance between ACE1 and ACE2 activity seems to be critical to the outcome of patients suffering from COVID-19, and discontinuation of ACE inhibitors and ARBs is not recommended by many scientific societies and regulatory bodies.[41] Intriguingly, glucocorticoids also attenuate angiotensin 1-7 and Mas receptor expression.[42]

4 | T2DM, HYPERGLYCEMIA, AND SEVERITY OF COVID-19

Many reports show that T2DM is a frequent preexisting condition that is associated with severe disease and death in patients with COVID-19.[43-45] Bode et al reported that patients admitted with COVID-19 with either diabetes or uncontrolled hyperglycemia (defined by two blood glucoses of >180 mg/dL within a 24-hour period) had higher mortality and longer hospitalizations.[10] In these patients, those with uncontrolled hyperglycemia had a higher mortality (41.7%) with or without known history of diabetes as compared to 14.8% in patients with controlled diabetes.[10] Similar to reports of the SARS epidemic,[28] a recent study of patients with COVID-19 showed that a fasting plasma glucose ≥126 mg/dL is an independent predictor for in-hospital mortality.[46] Another recent study among 7300 hospitalized patients with COVID-19 found that although the presence of T2DM was associated with higher mortality, patients with diabetes and poorly controlled glycemia had an even higher death rate compared to patients with better controlled blood glucose.[45]

Acute (stress) hyperglycemia per se in the setting of severe illness or surgery is associated with longer length of hospital stay, higher infection rates, longer duration of ventilator management, and increased mortality.[47] Stress hyperglycemia occurs in individuals without diabetes and is thought to result from a surge of catecholamines and especially cortisol in response to acute stress.[48] In COVID-19 illness, direct damage of β-cells due to entry of the virus through cell surface ACE2 protein can lead to cell damage and apoptosis causing relative insulin deficiency and acute hyperglycemic state.[28,29] Indeed, new-onset diabetes with diabetic ketoacidosis has been described in previously healthy individuals; this may well be due to the β-cell damage induced by the infection.[49,50] Acute hyperglycemia was also identified as a significant predictor of severity and death in patients infected with 2003 SARS, 2009 pandemic novel influenza A virus (H1N1), and Middle East respiratory syndrome coronavirus (MERS-CoV).[28,51-53]

ACE2 protein is expressed on alveolar cells of the lungs and serves as the site of entry for the virus into the body,[3,31,32] and ACE2 expression is increased in patients with diabetes and in response to hyperglycemia.[29,33,34] Higher expression of "receptor" sites in the pulmonary system could help explain the greater propensity of patients with diabetes and hyperglycemia for developing a more severe disease.

Histopathological changes in the lungs of patients with diabetes includes thickened alveolar, epithelial, and pulmonary capillary basal lamina.[54] Hyperglycemia can cause microangiopathy of alveolar capillaries and non-enzymatic glycation of proteins in the lungs. This makes collagen less susceptible to proteolysis, leading to its accumulation in the connective tissue in the lungs, and causes restrictive lung disease. The loss of elastic recoil of the lungs leads to collapse of small airways during exhalation.[54,55] Hyperglycemia also reduces mucociliary clearance that can lead to increased lung infection.[56] In addition, insulin resistance and systemic inflammation results in oxidative stress and inflammatory response in the pulmonary system. It can also reduce respiratory muscle strength leading to functional lung abnormality.[54,56]

Finally, high glucose levels promote glycation of proteins and stimulate the synthesis of pro-inflammatory cytokines leading to oxidative stress; in addition, the production of adhesion molecules that mediate tissue inflammation is stimulated.[57] It is also possible that ACE2 on the surface of lung epithelial cells or the viral spike protein itself becomes glycated due to the hyperglycemia, thereby altering the binding of the viral spike protein to ACE2 and perhaps magnifying the degree of inflammation and the immune response to the virus.[58]

5 | AGE AND SUSCEPTIBILITY FOR DEVELOPING SEVERE COVID-19

Increasing age was reported as an important independent predictor of mortality in SARS and MERS,[59,60] and recent data in patients with COVID-19 have shown similar findings.[6] In addition, insulin resistance, CVD, HTN, T2DM, dyslipidemia, and obesity are more prevalent in the elderly. Age-dependent defects in T cell and B cell function and excess production of type 2 cytokines can lead to a deficiency in control of viral replication and more

prolonged pro-inflammatory responses, potentially leading to poor outcomes.[61] The above age-related factors are associated with and lead to higher basal levels of chronic inflammation.

6 | HYPERTENSION AND COVID-19

Multiple reports from China and the United States have shown that HTN is associated with increased prevalence and severity of COVID-19.[36,62-66] A pooled analysis found that HTN is associated with a ~2.5-fold increased risk for both severity and mortality in patients with COVID-19.[67] Chronically elevated blood pressure is one of the hallmarks of both the insulin resistant state and T2DM,[68,69] and HTN is strongly associated with and can lead to worsening of CVD.[70,71]

High blood pressure is a known risk factor for unfavorable progression of ARDS in patients with pneumonia.[72,73] Hypertension can also cause a decline in ACE2 expression,[74] and it has been proposed that the interaction of the virus with ACE2 leading to its internalization can reduce the residual surface ACE2. This could lead to increased angiotensin-2 and decreased angiotensin 1-7 levels that can cause worsening of ARDS.[75] Hence, an interplay between HTN and COVID-19 could lead to a synergistically increased risk for adverse outcomes. Given that HTN is highly prevalent in patients with T2DM[69] and in the elderly population, the combination could lead to poor prognosis for COVID-19. Also, a topic of interest is the use of ACE inhibitors and ARBs in patients with HTN and their effect on ACE2 expression; this issue is discussed in more detail under "Medical Management of Diabetes and COVID-19."

7 | OBESITY AND COVID-19

Various reports show a high prevalence of obesity in patients with COVID-19 including data from New York City where out of 5700 patients with COVID-19, 42% were obese,[63] and severe obesity (BMI > 40 kg/m^2) placed patients at a much higher risk for complications from COVID-19. Among 383 COVID-19 patients in Shenzhen, China, after adjusting for other risk factors, obesity was associated with ~2.4-fold higher odds for developing severe pneumonia compared to patients with normal weight.[76] Another study from New York City reported that after old age, severe obesity was the second strongest independent predictor for hospitalization (OR of 6.2).[77] Most recently, a detailed study of the role of comorbidities in patients with T2DM who developed severe COVID-19 reported that obesity was the single most important comorbidity that was associated with high rates of intensive care unit (ICU) admissions and mortality.[78]

It is well known that severe obesity increases the risk of ARDS[79] and can lead to difficult intubation in those requiring respiratory support. Possible underlying mechanisms for respiratory failure include impaired breathing mechanics, increased airway resistance, and impaired gas exchange with low respiratory muscle strength and lung volumes.[80] Similar to T2DM, obesity with underlying insulin resistance is associated with a state of chronic inflammation that can lead to poor outcomes in patients with COVID-19.[81]

Obesity is strongly associated with HTN, and various mechanisms including activation of the sympathetic nervous system, stimulation of the renin-angiotensin system, increased leptin levels, endothelial dysfunction, and renal functional abnormalities causing sodium retention mediate the HTN in these individuals.[82,83] Also, obesity-related underlying insulin resistance and heightened inflammatory state are linked to HTN.[68,84] Hence, the strong association of obesity with HTN, CVD, insulin resistance, and T2DM[85] can further increase the severity of COVID-19.

8 | DYSLIPIDEMIA AND COVID-19

Dyslipidemia is present in 30% to 60% of patients with T2DM.[86] Dyslipidemia in T2DM is characterized by elevated triglycerides (TGs) in most patients and somewhat elevated low-density lipoprotein (LDL) and low high-density lipoprotein.[86] Insulin resistance in T2DM is virtually present in all insulin-responsive cells, including adipocytes, where it results in increased release of free fatty acids (FFAs) and inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNFα), and leptin.[87] Elevated FFAs are taken up by the liver and deposited as triacylglycerols in fat droplets or are secreted as very low-density lipoprotein (VLDL) particles leading to hypertriglyceridemia. The elevated blood TGs derived from VLDL are deposited in skeletal and cardiac muscle, and other insulin-responsive cells and decrease their sensitivity to insulin. Elevated FFAs also stimulate atypical protein kinase C that inhibits insulin signaling and glucose uptake in skeletal muscle and result in excess gluconeogenesis in the liver.[87,88] In addition, FFAs directly activate toll-like receptor 4 (TLR4), which is mainly expressed on immune system cells including monocytes, macrophages, and dendritic cells; activation of this receptor leads to cytokine secretion and inflammatory response.[87,89] TG-rich VLDL slowly loses some of its TG

and transforms into LDL molecules. In T2DM, the LDL particles are smaller and denser than normal and are more atherogenic.[90,91] This partly explains the increased premature atherosclerosis and CVD in patients with T2DM.[91]

The dyslipidemia present in T2DM contributes to the insulin resistant state in a self-reinforcing cycle. The preexisting inflammatory state associated with dyslipidemia and insulin resistance augment the inflammatory response by SAR-CoV-2 infection.

9 | PREEXISTING CVD AND COVID-19

Patients with preexisting CVD appear to have heightened vulnerability to develop severe COVID-19 with worse clinical outcome.[43,92,93] In a report of 52 critically ill patients with COVID-19, the prevalence of preexisting CVD was higher in those who did not survive compared to survivors (53% vs 20%).[94] Similarly, another report on fatality with COVID-19 showed a significantly higher rate of preexisting CVD compared with survivors (24% vs 1%).[6] A meta-analysis of six published studies from China including 1527 patients with COVID-19 reported that the presence of CVD was associated with a 3-fold greater risk for developing severe COVID-19 or requiring ICU admission.[93]

Various cardiovascular risk factors, including dyslipidemia, HTN, insulin resistance, and T2DM, can adversely affect the prognosis of COVID-19. Many of these factors can lead to a heightened inflammatory state, which could be a potential mechanism underlying the association between COVID-19 and new cardiac events, especially in patients with preexisting CVD.[95] It is known that inflammatory reaction following pneumonia or ARDS can result in plaque instability causing acute coronary events.[96] The acute inflammatory response may increase the demand for higher cardiac function and sympathetic hyperactivity thereby increasing the risk for arrhythmias and heart failure in patients with COVID-19 and preexisting CVD.[97]

10 | CHRONIC KIDNEY DISEASE AND COVID-19

The prevalence of mild to moderate chronic kidney disease (CKD) in older patients with established diabetes (aged ≥65 years) ranges from 35% to 40%.[98] CKD is associated with an increased risk for pneumonia and pneumonia-related mortality.[99,100] ACE2 is highly expressed in renal tubular epithelial cells and less so in glomerular epithelial cells and vasculature.[101] Increased ACE2 leading to direct viral invasion along with hypercoagulation could possibly explain the high risk of acute kidney injury in patients with COVID-19 even without preexisting renal disease.[102]

A meta-analysis of four studies in 1389 patients showed a 3-fold higher risk for severe COVID-19 in patients with CKD.[103] There is a suggestion that plasma ACE2 activity is increased in patients with CKD,[104,105] but by the time end-stage renal disease is reached and dialysis is initiated, a relative deficiency in plasma ACE2 activity ensues.[106] Still, there is higher risk of severe illness in patients on hemodialysis with COVID-19.[107]

ACE2 activity has been shown to be altered in diabetes kidney disease (DKD).[105] ACE2 and ACE-1 mRNA and protein expression are altered in mouse models of DKD and in patients with DKD.[108,109] Thus, patients with DKD who develop COVID-19 may be at higher risk of acute kidney injury because of upregulation of the ACE-1 and downregulation of ACE2, a combination that can lead to increased angiotensin levels with pro-inflammatory and profibrotic actions in the kidneys.

11 | HYPERCOAGULABILITY AND COVID-19

SARS-CoV-2 can directly induce inflammation of vascular endothelial cells following viral entry into endothelial cells via the ACE2 receptor.[110] Endothelial damage can activate coagulation pathways, leading to microthrombi in small and large vessels of the lung and other organs.[111]

T2DM, hyperglycemia, and insulin resistance are associated with endothelial cell dysfunction and stimulate platelet activation and aggregation, changes that lead to a hypercoagulable state.[8,112] Elevated proinflammatory cytokines in patients with T2DM that are a known cause of coagulation activation[113] and endothelial dysfunction may constitute a trigger for procoagulant imbalance in patients with COVID-19. Furthermore, poor prognosis of COVID-19 is associated with hypercoagulability and high blood d-dimer levels.[114,115] In addition, patients who developed acute respiratory failure had hyperfibrinogenemia, a known cause of hypercoagulability.[116] In keeping with this are recent reports of blood clot formation in large arterial and venous vessels leading to strokes, especially in relatively young persons with no preexisting conditions, and the finding of multiple microemboli and clots in lungs of patients with COVID-19.[117]

12 | T2DM AND STATE OF CHRONIC INFLAMMATION

T2DM is a disorder of β-cell function and insulin resistance of tissues that develops over many years.[118] There are multiple genetic and environmental factors that lead to the development of the disease. There is evidence that the chronic inflammation and dysfunction of the innate immune system play important roles in the pathogenesis of T2DM.[119] C-reactive protein (CRP), IL-1β, IL-6, and other cytokines are elevated in patients with T2DM,[120] and there is increasing evidence that activation of immune system, high oxidative stress, and adipose tissue inflammation are related to pathogenesis and progression of T2DM.[81,121,122]

Upon infection with SARS-CoV-2 and the increased viral load due to replication of the virus in many cells throughout the body, the preexisting chronic inflammation is further increased and plays a critical role in the progression of COVID-19.[66,123] A meta-analysis by Zeng et al evaluated 16 retrospective studies and found that inflammatory markers, especially CRP, procalcitonin, IL-6, and erythrocyte sedimentation rate (ESR), were positively correlated with the severity of COVID-19.[124] Another retrospective, multicenter cohort study reported a significant elevation of IL-6 in COVID-19 nonsurvivors as compared to survivors.[6]

In patients with T2DM, macrophages, adipocytes, and endothelial cells release pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-10.[125-127] T2DM is therefore associated with a general activation of the innate immune system in which there is a chronic cytokine-mediated state of low-grade inflammation.[120,128] Hyperglycemia also increases the formation of advanced glycation end products that stimulate the production of reactive oxygen species (ROS); this leads to increased oxidative stress and activation of immune response. In addition, high insulin levels can induce an inflammatory reaction.[129]

13 | T2DM, immune dysfunction and COVID-19

Evidence suggests that SARS-CoV-2 produces a vigorous innate immune response,[130] leading to a so called "cytokine storm" that appears to mediate severe disease. "Cytokine storm," a condition without an exact definition, is characterized by a powerful activation of the immune system. It was noted in previous coronavirus pneumonias due to SARS and MERS that circulating levels of pro-inflammatory cytokines, such as IFN-γ, IL-1B, IL-6, and IL-12, and chemokines, such as CXCL10 and CCL2, are increased and are associated with pulmonary inflammation and extensive lung damage.[131,132] Similarly, the "cytokine storm" induced by SARS-CoV-2 infection and the sustained inflammatory response is thought to play a critical role in the high mortality of patients with COVID-19.[43,133] Lymphocytopenia is one of the prominent markers of COVID-19 and can be used as part of the diagnostic criteria for COVID-19 and its severity.[134] Also, there is evidence that coronaviruses can activate multiple complement pathways, further leading to severe disease.[135]

Blanco-Melo et al studied the host response to SARS-CoV-2 in cell lines, primary cell cultures, ferrets, and patients with COVID-19.[136] They found that SARS-CoV-2 infection induces low IFN-I and IFN-III levels along with a strong chemokine expression. Chen et al characterized the immunological features of COVID-19 in patients with different degrees of disease severity and found that patients with severe disease displayed significantly higher serum levels of IL-6, IL-10, and TNF-α and lower absolute numbers of T lymphocytes, CD4+T cells, and CD8+T cells as compared to patients with moderate disease. Also, severe cases were characterized by a lower expression of IFN-γ by CD4+T cells as compared with moderately severe cases.[137] These results are consistent with the premise that low innate antiviral defense and high pro-inflammatory cytokines contribute to severe COVID-19.

A recent study by Guo et al showed that individuals with diabetes and COVID-19 had a lower lymphocyte count, higher absolute neutrophil count, and high levels of IL-6, ferritin, ESR, and CRP compared to patients with COVID-19 without diabetes.[44] Similarly, Zhu et al showed that IL-6, CRP, and LDH levels were significantly higher in patients with T2DM and COVID-19 during 28-day follow-up as compared to patients with COVID-19 without T2DM.[45]

Taken together, presence of T2DM with chronic inflammation and other comorbidities associated with defective immune response, especially the low levels of IFN-1, may allow unrestricted viral replication and trigger high levels of inflammation, hyperimmune reaction, and greatly exacerbate the response to SARS-CoV-2. In sum, "cytokine storm" has emerged as being potentially the main factor driving the more severe clinical course of COVID-19.

14 | MEDICAL MANAGEMENT OF DIABETES AND COVID-19

It is the advice of an international panel of diabetes experts that in the era of COVID-19 medical management of patients with either T1DM or T2DM should continue

with the aim of achieving near-normal levels of blood glucose, BP, and lipids safely considering patient choices and economic factors.[138] It is also advised that stringent control be continued if patients with diabetes develop COVID-19.[138] However, at the present time, not enough evidence has been accrued to enable strong recommendations for the use of any specific medications in patients with diabetes and COVID-19.

Uncontrolled or stress hyperglycemia is associated with increased severity of COVID-19 and mortality. In addition, very high levels of blood glucose often occur as the patient's illness advances and reaches severe levels. Hyperglycemia stimulates the expression of ACE2. Hyperglycemia can also induce glycation of ACE2, which may cause increased entry of SARS-CoV-2 into the cells, leading to increased inflammation and hyperimmune responses.[139] Hence, it is essential to closely monitor and manage blood glucose levels in patients hospitalized with diabetes and COVID-19. Glucose-lowering agents, especially insulin, play an important and critical role in management of T2DM under conditions that the disease becomes so severe that β-cells infected with the virus are under stress and may be undergoing apoptosis and cannot release adequate amounts of insulin. In keeping with this, new-onset diabetic ketoacidosis has been reported in individuals with severe COVID-19 in the absence of prior history of diabetes.[49,50] Insulin is the major glucose-lowering agent that can be used in COVID-19.

Some oral antidiabetic medications can potentially be effective in alleviating inflammation in patients with T2DM and COVID-19. Metformin and activation of adenosine monophosphate-activated protein kinase (AMPK)[140] increases the expression and phosphorylation of ACE2[141] that may lead to decreased SARS-CoV-2 binding.[142] In addition, metformin reduces the production of ROS, oxidative stress, and DNA damage.[143]

Sodium glucose cotransporter 2 inhibitors have been reported to increase ACE2 levels, leading to increase in angiotensin 1-7 that has vasodilatory effects and decreases inflammation in the lungs.[144] Additionally, they prevent the release of proinflammatory cytokines in the body.[145,146] On the other hand, the increase in ACE2 expression may have detrimental effects on the disease severity. Not enough information is available to make a rational judgment.

Thiazolidinediones in animal studies have been shown to decrease levels of ACE-1 and angiotensin-2 and increase the concentrations of circulating ACE2 and angiotensin 1-7 leading to alleviation of inflammation in the body.[147] Additionally, they can decrease inflammation and fibrosis in the lungs.[148]

Dipeptidyl peptidase IV (DPP-IV) is a transmembrane glycoprotein that increases inflammation by activating T cells, upregulates CD86 expression on macrophages and B cells, and stimulates the NF-KB pathway.[149,150] Hence, DPP-IV inhibitors can have anti-inflammatory effects in patients with COVID-19, in addition to glucose-lowering effects by increasing endogenous glucagon-like peptide 1 (GLP-1), an insulin-tropic polypeptide.[150] DPP-IV served as a functional receptor and entry site of the MERS virus; however, there is no evidence that DPP-IV plays a similar role in SARS-CoV-2 infection.[150,151]

GLP-1 receptor agonists can also potentially decrease inflammatory response in patients with COVID-19 by activation of AMPK and blockade of NF-KB.[152,153]

ACE inhibitors and ARBs have also been reported to increase ACE2 expression,[37,38] and it was suggested that perhaps their use should be discontinued in patients with diabetes and the medications be changed to other agents, if possible. However, detailed reports have not shown any negative effects of these agents in patients with diabetes who acquire COVID-19.[154] Furthermore, several regulatory bodies and scientific societies have recommended continuation of these agents in patients with T2DM and COVID-19.[77]

15 | ROLE OF ANTI-INFLAMMATORY AGENTS AND IMMUNOTHERAPY IN SEVERE COVID-19

Despite the many on-going studies, not enough large-scale randomized controlled trials using specific agents or treatment modalities have been completed to make informed decisions. While this review is focused on the pathogenesis of severe COVID-19 in patients with T2DM, we will briefly summarize some recent studies directed at treatment of COVID-19.

15.1 | Anti-inflammatory medications

Lipid ibuprofen has been shown to improve survival in animal models of ARDS by modulation of cytokine responses.[155] However, some investigators raised concerns that use of ibuprofen in patients with COVID-19 may increase the activity of ACE-2 that could be harmful.[36,156] Subsequent reviews found no evidence of severe adverse events in patients with COVID-19 as a result of usage of such agents.[157] The on-going LIBERATE trial is testing the effect of three dosages of lipid ibuprofen on progression of lung injury in patients with SARS-CoV-2 infection.[158]

Most recently, it has been reported that dexamethasone (used at a dose of 6 mg daily) has a positive effect in

patients severely affected with COVID-19 by reducing mortality.[159] Dexamethasone would be expected to increase blood glucose levels, especially in patients with T2DM who already have a high degree of insulin resistance. Nevertheless, it appears that the positive anti-inflammatory and immune-modulating effects of the agent override the negative effects of hyperglycemia; the elevated glucose levels can by managed by meticulous insulin treatment and careful monitoring. Colchicine may also have positive effects on the course of COVID-19.[160]

15.2 | Immunotherapy

Uncontrolled "cytokine storm" appears to be the most dangerous and potentially life-threatening event related to severity of COVID-19. Studies using inhibitors of cytokines including IL-1 and IL-6 are on-going in the management of the hyperimmune reaction in severely ill patients with COVID-19.

Chloroquine and hydroxylchloroquine (HCQ) with immunosuppressive effects are being evaluated as potential treatments for COVID-19. Two large retrospective studies using HCQ have found no beneficial effects in severity of COVID-19 or related mortality; interestingly, more patients in the treatment arm had diabetes.[161,162]

IL-6 appears to play an important role in the pathogenesis of the "cytokine storm."[163,164] Effects of tocilizumab (TCZ), a humanized anti-IL-6 receptor immunoglobulin G1 monoclonal antibody, was examined in an uncontrolled study in patients with COVID-19 and ARDS requiring mechanical ventilation; it was found that patients treated with TCZ showed a rapid, sustained, and significant clinical improvement.[165] Elevated IL-1 levels are also associated with disease severity. In a retrospective cohort study of patients with less severe COVID-19 and ARDS (not admitted to the ICU), treatment with high-dose anakinra (an IL-1 blocker) was associated with clinical improvement in the majority of patients.[166]

Use of dexamethasone (as an immune-modulating agent) in decreasing mortality in severe cases of COVID-19 is described above.

In sum, there is increasing evidence that immune-based therapies may improve outcomes of severe COVID-19. Results of more studies, especially focused on patients with T2DM, are anticipated.

16 | CONCLUSION

There is a heightened level of inflammation that is chronically present in patients with T2DM prior to being affected with COVID-19. This is largely due to the multiple conditions that are present in these individuals including older age, HTN, obesity, CVD, and dyslipidemia. However, as depicted in Figure 1, we hypothesize that the chronic inflammation becomes greatly amplified following the infection by the virus. Elevated expression of ACE2 in lungs and other tissues facilitates increased viral entry and viral load, thereby greatly stimulating preexisting inflammation in patients with T2DM. This in conjunction with a hyperactive immune response ("cytokine storm") appears to be the final common pathway leading to severe cases of COVID-19.

Based on the available evidence, it is recommended that safe but tight control of blood glucose, HTN, and lipids in patients with T2DM may serve to decrease the severity of COVID-19 illness, should they contract the viral infection.[138] Also, use of continuous glucose-monitoring devices (where available), especially in patients admitted to ICU, for frequent glucose monitoring to help adjust insulin therapy is recommended. Finally, recently it has been reported that a daily dose of 6 mg dexamethasone decreases mortality in patients severely affected by COVID-19.[159] The increase in glycemia due to use of glucocorticoid will require adjustment of insulin therapy.

ACKNOWLEDGEMENTS

No funding received. We appreciate Dr Laure Sayyed-Kassem, Chief of the Endocrine Section at Louis Stokes Cleveland VA Medical Center/Case Western Reserve University, for reviewing our manuscript.

DISCLOSURE

Aman Rajpal and Leili Rahimi have no disclosures. Faramarz Ismail-Beigi is a consultant for Sanofi and COVANCE. He has grants from the NIH, and has previously received grants from Novo Nordisk; he has shares in Thermalin Insulin.

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How to cite this article: Rajpal A, Rahimi L, Ismail-Beigi F. Factors leading to high morbidity and mortality of COVID-19 in patients with type 2 diabetes. *Journal of Diabetes*. 2020;12:895–908. https://doi.org/10.1111/1753-0407.13085