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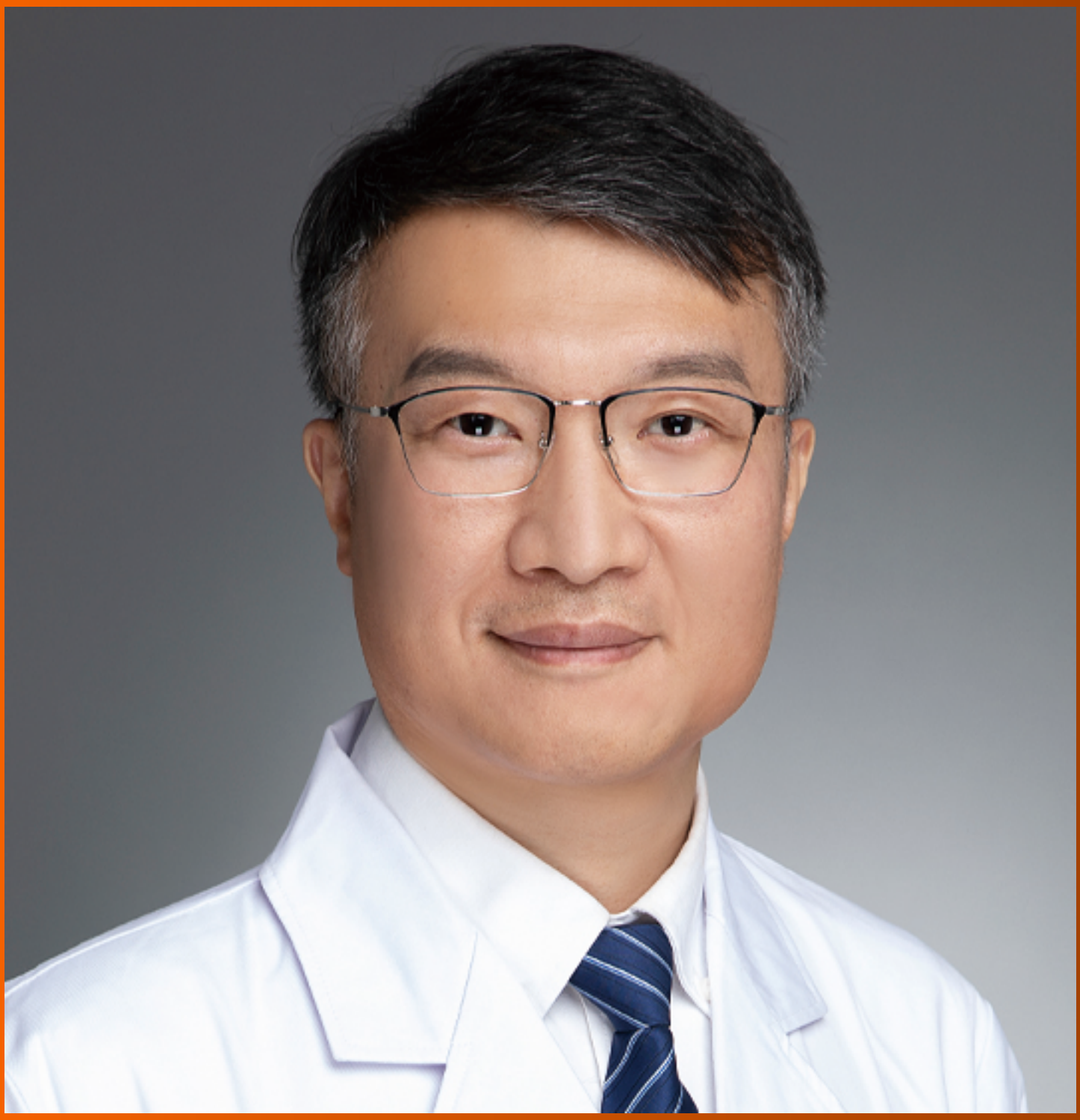

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The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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REVIEW

Immunometabolic bases of type 2 diabetes in the severity of COVID-19

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Abstract

The outbreak of coronavirus disease 2019 (COVID-19) is caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). COVID-19 and type 2 diabetes (T2D) have now merged into an ongoing global syndemic that is threatening the lives of millions of people around the globe. For this reason, there is a deep need to understand the immunometabolic bases of the main etiological factors of T2D that affect the severity of COVID-19. Here, we discuss how hyperglycemia contributes to the cytokine storm commonly associated with COVID-19 by stimulating monocytes and macrophages to produce interleukin IL-1β, IL-6, and TNF-α in the airway epithelium. The main mechanisms through which hyperglycemia promotes reactive oxygen species release, inhibition of T cell activation, and neutrophil extracellular traps in the lungs of patients with severe SARS-CoV-2 infection are also studied. We further examine the molecular mechanisms by which proinflammatory cytokines induce insulin resistance, and their deleterious effects on pancreatic β-cell exhaustion in T2D patients critically ill with COVID-19. We address the effect of excess glucose on advanced glycation end product (AGE) formation and the role of AGEs in perpetuating pneumonia and acute respiratory distress syndrome. Finally, we discuss the contribution of preexisting endothelial dysfunction secondary to diabetes in the development of neutrophil trafficking, vascular leaking, and thrombotic events in patients with severe SARS-CoV-2 infection. As we outline here, T2D acts in synergy with SARS-CoV-2 infection to increase the progression, severity, and mortality of COVID-19. We think a better understanding of the T2D-related immunometabolic factors that contribute to exacerbate the severity of COVID-19 will improve our ability to identify patients with high mortality risk and prevent adverse outcomes.

Key Words: COVID-19; SARS-CoV-2; Type 2 diabetes; Inflammation; Hyperglycemia; Prothrombotic state

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Core Tip: Type 2 diabetes (T2D) acts in synergy with severe acute respiratory syndrome coronavirus-2 infection to increase the progression, severity, and mortality of coronavirus disease 2019 (COVID-19). Thus, the immunometabolic bases of the main etiological factors of T2D that contribute to the severity of COVID-19 should be studied. Here, we discuss the molecular mechanisms by which immune cells, hyperglycemia, hyperinsulinemia, loss of pancreatic β-cell mass, insulin resistance, advanced glycation end products, endothelial dysfunction, and prothrombotic state contribute to the severity of COVID-19. The syndemic between COVID-19 and T2D has challenged our ability to identify patients with high mortality risk based on scientific evidence.

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INTRODUCTION

The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first identified in the city of Wuhan, China in December 2019[1]. Unlike the SARS-CoV and the middle east respiratory syndrome coronavirus, SARS-CoV-2 is highly transmissible to humans, with case fatality rates ranging from 3% to 11%[2]. A study conducted in 1099 patients from China showed that incubation of SARS-CoV-2 takes a median of 4 d on average[3], while in the United States, the Centers for Disease Control and Prevention has estimated that symptoms can appear within 2-14 d after exposure[4]. The main modes of SARS-CoV-2 transmission are respiratory droplets produced by infected individuals, aerosols, and direct contact with contaminated surfaces or objects[5]. Transmission of SARS-CoV-2 is more likely to occur in the early stage of infection; by day 10 after the onset of symptoms, 90% of patients with mild disease show a negative RNA test[6,7]. SARS-CoV-2 is the causal agent of the coronavirus disease 2019 (COVID-19), an ongoing global pandemic that is affecting the lives of millions of people worldwide[8].

Although more than 85% of patients with COVID-19 experience a self-limiting illness with symptoms such as fever, headache, myalgia, and diarrhea, some patients develop the most severe forms of the disease including pneumonia, acute respiratory distress syndrome (ARDS), sepsis, multiple organ failure, and death[9]. For this reason, there is a deep need to understand the variety of factors that increase the severity of COVID-19.

The most severe and fatal cases of COVID-19 have been reported to occur in patients with preexisting comorbidities such as cancer, hypertension, and diabetes mellitus[10,11]. In fact, diabetes mellitus is one of the most prevalent comorbidities in patients critically ill with COVID-19[12]. Diabetes mellitus is a complex disorder characterized by abnormally high blood glucose levels that affect blood vessels and nerves. Diabetes ultimately results in chronic damage to skin, feet, immune system, eyes, kidneys, brain, and heart[13]. People living with diabetes do not exhibit increased susceptibility to SARS-CoV-2 infection compared to non-diabetic individuals [12]. However, patients with diabetes and COVID-19 are at much higher risk for adverse outcomes including admission to intensive care units, invasive ventilatory support, hospital-acquired infections, and death[14,15]. Diabetic patients with COVID-19 have a mortality rate of 7.3% with respect to non-diabetic subjects, among whom a mortality of 2.3% has been reported[14].

Type 2 diabetes (T2D), formerly known as adult-onset diabetes, is the most common form of diabetes and is characterized by multiple disorders including hyperglycemia, insulin resistance, systemic inflammation, hyperinsulinemia, β-cell exhaustion, vascular damage, endothelial dysfunction, nerve degeneration, increased platelet reactivity and prothrombotic state, and dyslipidemia, among others[16,17]. These conditions affect the immune response to pathogens through different mechanisms that are not yet fully understood and might influence the severity of COVID-19, as will

be further reviewed[16,18-23].

HYPERGLYCEMIA

Hyperglycemia is the most common metabolic alteration associated with T2D and is characterized by persistently high blood sugar levels[24]. Hyperglycemia and the immune response are known to affect each other in ways that directly impact the severity of the SARS-CoV-2 infection. It is well known that high glucose levels can activate multiple immune cell types, leading to enhanced production of proinflammatory cytokines such as interleukin IL-1 beta, IL-6, and TNF-α, among others[25]. This phenomenon is especially relevant to SARS-CoV-2 infection, because patients with T2D and COVID-19 exhibit increased serum levels of proinflammatory cytokines including IL-1β, IL-6, TNF-α, IL-8, and IFN-γ[26-30]. In patients with SARS-CoV-2 infection, this so-called "cytokine storm" is accompanied by other inflammation-related markers such as C-reactive protein, D-dimer, and ferritin, and linked to the severity of COVID-19[31]. Exacerbation of the inflammatory response causes a more severe acute infection that leads to ARDS and multiple organ failure[26]. Elevated levels of IL-6 have been found in both the airway epithelium and blood stream of patients with COVID-19 that develop severe ARDS[32].

Accumulating evidence confirms that hyperglycemia is a negative predictor in COVID-19 due to increased release of inflammatory mediators, endothelial dysfunction, thrombosis, and production of reactive oxygen species (ROS)[33-35]. Accordingly, T2D patients critically ill with COVID-19 that show acute hyperglycemic peaks at hospital admission have a worse prognosis than patients with glycated hemoglobin (HbA1c) levels near to 6.5%[36,37]. Therefore, a high blood glucose value at hospital admission is a risk factor for mortality in patients with severe SARS-CoV-2 infection[11,38].

Persistent hyperglycemia promotes mitochondrial oxidative stress and ROS production[39] that in turn leads to blood vessel damage, pancreatic beta cell dysfunction, and impaired insulin secretion[40,41]. Hyperglycemia-induced mitochondrial dysfunction triggers release of intracellular signaling molecules that can in turn inhibit the T cell response, a phenomenon that has been consistently reported in patients with severe COVID-19[42]. Moreover, SARS-CoV-2 can also directly induce mitochondrial ROS production by activating the HIF-1α that in turn is able to promote the proinflammatory cytokine storm[42,43]. Therefore, it is feasible that hyperglycemia and ROS production from T2D act in synergy with SARS-CoV-2 infection to aggravate the cellular damage, organ failure, and progression of COVID-19.

In parallel, high blood sugar levels stimulate lactate dehydrogenase (LDH) activity and increase lactate production[44]. This phenomenon is of particular interest in COVID-19, where it has been reported that increased LDH levels are accurate predictors of mortality in patients with severe SARS-CoV-2 infection[45]. Notably, increased lactate levels in T2D patients might delay clearance of SARS-CoV-2 by inhibiting the retinoic acid-inducible RIG-1-like receptor *via* the mitochondrial antiviral-signaling protein, which results in blockage of interferon production and reduced anti-viral response[44].

Likewise, natural killer (NK) cells are innate lymphocytes that eliminate virally infected cells. In T2D patients, hyperglycemia appears to increase NK cells that express low levels of the NKG2D and the natural cytotoxicity receptor NKp46, resulting in decreased degranulation capacity and inefficient anti-viral activity[46-48]. In addition, hyperglycemia promotes viral replication in monocytes with concomitant inhibition of T cell activation[42]. Some studies have also found low numbers of dendritic cells (DCs) in T2D patients with poor glycemic control. In line with this finding, high glucose conditions in *in vitro* cultures appears to prevent monocyte differentiation into DCs[49,50]. Moreover, DCs from T2D patients poorly induce T cell proliferation *in vitro*[51]. Taken together, all of this evidence supports a decisive role for hyperglycemia in exacerbating COVID-19 progression, since T2D patients with severe SARS-CoV-2 infection exhibit low cell counts of NK cells, functional DCs, and CD4+ and CD8+ T cells[52].

Hyperglycemia in T2D patients has deleterious effects on numerous neutrophil functions including migration, phagocytosis, and bacterial killing[53]. Additionally, T2D patients have low numbers of IFN-γ-producing cells, which affects viral clearance in multiple infections such as those provoked by cytomegalovirus, Epstein-Barr virus, and influenza[54]. Moreover, hyperglycemia reduces antibody titers and the ability to kill bacteria able to invade the lungs and cause pneumonia such as *Staphylococcus*

pneumoniae and *Staphylococcus aureus*[55]. Considering the immune effects of hyperglycemia within the context of SARS-CoV-2 infection, the mechanisms discussed above might partially explain why T2D patients are at a higher risk of developing severe COVID-19 and adverse outcomes including increased viral load, sepsis, and death. For this reason, uncontrolled hyperglycemia should be considered as a crucial risk factor for COVID-19 progression in T2D patients.

HYPERINSULINEMIA AND PANCREATIC B-CELL EXHAUSTION

Pancreatic β-cells play a key role in the control of blood glucose levels by secreting insulin[56]. During the evolution of T2D, pancreatic β-cells are exposed to glucotoxicity, ROS, and endoplasmic reticulum stress, all of which increase β-cell apoptosis and dysfunction[56,57]. Additionally, chronic hyperglycemia increases M1-like macrophage infiltration in pancreatic islets, where these immune cells can secrete IL-1β, IL-6, and TNF-α, promoting islet inflammation, β-cell malfunction, and apoptosis [58,59]. In response, pancreatic β-cells enhance insulin secretion in order to counteract persistently high glucose levels, leading to a state of hyperinsulinemia[60]. Nevertheless, β-cell mass is eventually exhausted, resulting in impaired insulin production. By the time diabetes is typically diagnosed, β-cells show less than fifty percent activity and are no longer able to secrete enough insulin to effectively maintain blood glucose levels[61,62].

In T2D patients, β-cell dysfunction can be aggravated during COVID-19 due to the ability of SARS-CoV-2 to enter the human pancreatic islets *via* angiotensin-converting enzyme 2 (ACE2)[62]. After SARS-CoV-2 invasion, inflammatory cells are recruited to pancreatic tissue, where they intensify local inflammation and injury resulting in increased peri- and intra islet fibrosis, β-cell mass loss, and hyperglycemia in both non-diabetic and diabetic patients[63]. Additionally, COVID-19 is characterized by persistent acute hypoxia that can affect numerous organs, including pancreatic islets, and provoke β-cell apoptosis directly[64]. In this way, SARS-CoV-2-induced pancreatic damage contributes to impaired insulin secretion that in turn may accelerate diabetes pathogenesis and/or aggravate preexisting diabetes[65]. Similarly, β-cell dysfunction that leads to chronic hyperglycemia is accompanied by ROS release, advanced glycation end product (AGE) formation, mitochondrial oxidative stress, and low antioxidant activity, worsening pancreatic β-cell damage during COVID-19[66-69].

A growing body of evidence suggests that SARS-CoV-2 infection not only affects the endocrine pancreas but also the exocrine pancreas[70]. In fact, SARS-CoV-2 appears to bind and enter the exocrine pancreatic ductal cells *via* ACE2[71]. Some studies estimate that the prevalence of the development of acute pancreatitis in patients with severe COVID-19 is as high as 17%[72].

The mechanisms discussed above highlight the importance of inflammation, hyperglycemia, and pancreatic dysfunction as potential contributors to the development of severe COVID-19 in patients with T2D[73].

INSULIN RESISTANCE

Insulin resistance is defined as the inability of insulin to exert its functions in insulin-dependent tissue such as liver, adipose tissue, and skeletal muscle[74]. Insulin resistance is the most important etiological factor contributing to the development of T2D[75]. There are multiple mechanisms whereby insulin resistance occurs in humans, however, systemic inflammation is one of the most recently studied. Obese subjects show a constant systemic proinflammatory state characterized by abnormally high circulating levels of TNF-α, IL-1β, IL-6, IL-12, and MCP-1[76,77]. In adipose tissue, TNF-α induces insulin resistance by activating protein-tyrosine phosphatase 1B that in turn can dephosphorylate the insulin receptor substrate-2 (IRS-2) resulting in glucose transport arrest and hyperglycemia[78,79]. IL-6 and the NF-κB pathway are also involved in insulin resistance and progressive loss of normal glucose tolerance[80,81]. In diabetic patients, NF-κB upregulates PKC-θ, AP-1, and c-Jun kinase, which all act together to inhibit the insulin receptor *via* serine/threonine phosphorylation of the IRS [82].

SARS-CoV-2 infection in pancreatic β-cells not only reduces insulin secretion but also provokes a proinflammatory cytokine storm that exacerbates insulin resistance [15]. It is well known that even mild SARS-CoV-2 infection can trigger a proinflammatory cascade that mainly increases TNF-α, IL-6, MCP-1, and IL-1β in the lungs and

blood stream[83]. Similarly, SARS-CoV-2 infection produces high levels of IFN-γ inducible protein-10 (IP-10) that can itself lower insulin sensitivity[84]. Thus, release of proinflammatory molecules in non-diabetic and diabetic patients with untreated insulin resistance might aggravate COVID-19 symptoms and increase its severity.

ACE2 is an important link between insulin resistance and severe COVID-19, since it acts as the main cellular entry point for SARS-CoV-2[85]. Under normal conditions, ACE2 converts angiotensin II into angiotensin 1-7 in order to prevent angiotensin II-related physiological disturbances such as vasoconstriction, inflammation, oxidative stress, and insulin resistance[86]. In mice fed a high-sucrose diet, ACE2 is upregulated to remove excess angiotensin II and mitigate its negative effects on insulin sensitivity and glucose transport *via* the glucose transporter protein family[87,88]. T2D patients demonstrate increased ACE2 receptor levels that in turn may help SARS-CoV-2 extend cellular binding, thus boosting viral load and severity of infection.

Likewise, IFN-γ increases in patients with severe SARS-CoV-2 infection and reduces insulin sensitivity *via* IP-10[89]. Also, IFN-γ produced in response to multiple viral infections can cause insulin resistance in skeletal muscle and adipose tissue by downregulating PI3K[90,91]. It is thus reasonable to speculate that increased IFN-gamma production in patients with COVID-19 may aggravate pre-existing insulin resistance in both non-diabetic and diabetic patients.

Insulin resistance also seems to prevent the anti-inflammatory T-helper type 2 differentiation of CD4+ lymphocytes *via* the extracellular signal-regulated kinase[92]. In fact, CD4+ T cells appear to induce abnormal responses to insulin in conditions characterized by insulin resistance such as obesity and T2D[93]. Insulin resistance can also influence macrophages, an immune cell type thought to play a key role in preventing COVID-19-related organ damage[94]. Consistent with these findings, monocytes and macrophages that lack insulin signaling show impaired responses to a variety of pathogens[95]. In T2D patients, insulin resistance is also associated with high blood neutrophil count, which is of particular importance in severe COVID-19 that is characterized by neutrophilia and monocytopenia[18,96].

FORMATION OF ADVANCED GLYCATION END PRODUCTS

Pathogenesis of T2D is also characterized by the non-enzymatic covalent attachment of glucose to molecules such as proteins, lipids, and/or nucleic acids, a process that results in the formation of AGEs[97]. In addition to their negative effects on the insulin signaling pathway, AGEs have been shown to bind several surface receptors such as CD36, scavenger receptors type I and II, and galectin-3[98,99]. Upon receptor recognition, AGEs stimulate the release of pro-inflammatory cytokines in lymphocytes, monocytes, and macrophages and promote vascular inflammation and endothelial dysfunction[101]. AGEs can also directly bind to the receptor for advanced glycation end products (RAGE), a multi-ligand binding protein that promotes sustained inflammatory responses[100]. Notably, the lungs can express high RAGE levels, which may increase pulmonary inflammation in T2D patients in whom a wide variety of AGEs are produced[101]. RAGE is expressed in alveolar epithelial cells, vascular smooth muscle pulmonary cells, airway smooth muscle cells, and endothelial cells[102-105]. The AGE-RAGE interaction activates the NLRP3 inflammasome pathway. NLRP3 polarizes macrophages toward M1, inducing neutrophil extracellular trap formation and increasing the Th17 Lymphocyte population. Altogether, these inflammatory actions can perpetuate the cytokine storm, leading to pulmonary inflammation and fibrosis in patients with COVID-19[101,106]. This hypothesis is supported by the finding that RAGE-dependent inflammatory pathways play a detrimental role in pneumonia and ARDS[107].

AGEs produced in diabetic patients are also known to activate the classical complement pathway by recognizing C1q, which in turn inactivates CD59 and increases vascular injury in blood vessels of T2D patients[108]. In agreement with this concept, membrane attack complex deposits present in lung tissue from patients with severe COVID-19 has revealed complement-mediated damage which in turn induces vascular inflammation and results in extended lung damage[109].

It is well known that excess glucose can be non-enzymatically attached to hemoglobin to form HbA1c. This is particularly relevant to T2D and COVID-19 since SARS-CoV-2 is capable of altering the 1-beta chain of hemoglobin. This causes iron dissociation and porphyrin formation, thus affecting oxygen affinity and bioavailability in peripheral tissues[110]. It follows that excess glycation of hemoglobin in T2D patients may contribute to breathing difficulty that progresses to ARDS, a key

pathophysiological component of severe COVID-19. Indeed, a recent study reported that ACE2 can be glycated in hyperglycemic conditions[111]. Interestingly, ACE2 glycation appears to increase SARS-CoV-2 affinity and entry into pancreatic and lung tissue[112,113]. Good glycemic control has been shown to lower the amount of glycated ACE2 in lung tissue, ameliorating pneumonia and COVID-19 severity presumably by reducing the availability of viral entry points[113]. Conversely, uncontrolled hyperglycemia leads to aberrant formation of glycated ACE2 not only in lungs but also in nasal airways, tongue, and oropharynx, which may increase viral entry points and disease severity[113].

Last but not least, CD147 is a glycoprotein expressed in type II pneumocytes that binds the spike S1 protein, thus favoring SARS-CoV-2 entry into lung cells[114]. Evidence in T2D patients suggests that CD147 can be glycated in hyperglycemic conditions, which is linked to metalloproteinase upregulation and loss of tight junctions that may favor cell entry of SARS-CoV-2 and increase viral load[115]. As we have outlined, formation of AGEs appears to play a key role in the severity of COVID-19, which becomes more relevant in T2D patients with poor glycemic control, a condition that favors protein glycation.

ENDOTHELIAL DYSFUNCTION, VASCULAR DAMAGE, AND PROTHROMBOTIC STATE

The vascular endothelium maintains homeostasis by modulating blood flow, fybrinolysis, coagulation, platelet adherence, and immune cell trafficking in response to cell injury[116]. Impaired vascular endothelium function in patients with diabetes mellitus is considered a risk factor for cardiovascular disease[117]. Emerging evidence suggests that COVID-19 aggravates vascular pathology due to proliferation of SARS-CoV-2 in endothelial cells. This induces cellular damage, apoptosis, and disruption of the vascular barrier, which is especially relevant in T2D patients that show impaired angiogenesis[118-120]. Notably, endothelial dysfunction is a central feature in COVID-19 pathogenesis[121]. Patients with COVID-19 have nitric oxide (NO) deficiencies that lead to increased vascular contraction and reduced ROS neutralization[122,123]. Upon SARS-CoV-2 infection, the vascular endothelium undergoes vascular leakage and enhanced blood clotting. Subsequent recruitment of immune mediators results in inflammation that perpetuates tissue damage and vascular impairment[124]. As mentioned above, COVID-19 is accompanied by a high number of neutrophils, proinflammatory immune cells that also contribute to vascular damage in T2D. Diabetic patients have neutrophils with enhanced oxidative activity that produce high free radical levels and neutrophil extracellular traps (NETs) which can cause direct injury to blood vessels[125,126]. Neutrophils are also major producers of myeloperoxidase, a peroxidase enzyme that binds to the vascular endothelium and increases blood vessel damage in T2D patients[127]. These lines of evidence support a deleterious synergistic effect of T2D on COVID-19, wherein hyper-reactive neutrophils may directly injure the vascular endothelium and worsen the patient's outcome[96]. Interestingly, SARS-CoV-2 can increase NET release by infecting neutrophils. Increased formation of NETs can then directly injure the lung epithelium.

Proinflammatory cytokines play a decisive role in endothelial dysfunction. It is well known that IL-6 is upregulated in T2D and is associated with endothelial damage and atherosclerosis[128]. In patients with severe COVID-19, IL-6 induces chemokine expression, leukocyte trafficking, immune cell extravasation toward arterial walls, NO reduction, increased oxidative stress, and exacerbated inflammation of blood vessels [129]. TNF-α, another important proinflammatory cytokine involved in the COVID-19 cytokine storm, accelerates atherosclerosis *via* vascular cell adhesion molecule-1, E-selectin, and MCP1, which impairs vasodilatation and promotes endothelial cell apoptosis[81]. Post-mortem examination of lung tissue from patients severely infected with SARS-CoV-2 revealed massive mononuclear and polymorphonuclear cell infiltration, supporting the role of immune cell recruitment in COVID-19 progression[118]. These findings indicate that chemoattraction and recruitment of immune cells act together with endothelial dysfunction to induce vascular damage in patients with T2D, which may worsen the severity of COVID-19 by increasing vascular leaking and prothrombosis.

Disruption of vascular integrity promotes basement membrane exposure, coagulopathy, D-dimer release, and fibrinogen and platelet activation, all of which are important biomarkers for poor prognosis in COVID-19[130-133]. It is well known that the prothrombotic state common in patients with T2D may increase the occurrence of

severe coagulopathy in patients critically ill with COVID-19[134]. In fact, the severity of COVID-19 increases in parallel with pulmonary embolism, microcirculatory malfunction, and disseminated intravascular coagulation[135,136]. Microvascular and macrovascular thromboembolic events have been documented in the kidneys, lungs, spleen, and brains of SARS-CoV-2 infected patients[137-140]. Thrombotic incidence of about 30% has been reported in lungs[141] and incidence of deep venous thrombosis as occurs in the lower limbs of T2D patients has been reported at 46%[142].

The mechanisms underlying thromboembolic events in T2D patients with severe COVID-19 remain unclear, but persistent inflammation has now emerged as a potential contributor[143]. As described above, levels of several proinflammatory cytokines, including TNF-α, IL-6, and IL-8 are elevated in patients with COVID-19 who required hospitalization[144,145]. Interestingly, some of these cytokines have prothrombotic effects by themselves[146]. For instance, there is a positive association between elevated IL-6 and increased fibrinogen levels[146]. During sepsis, monocytes and macrophages release TNF-α as well as tissue factors that activate clotting pathways[147]. Besides inducing proinflammatory cytokine production, SARS-CoV2 has been shown to induce expression of procoagulant genes such as fibrinogen, tissue factor, factor II, and factor X[148,149] *in vitro* culture models. During numerous viral infections and sepsis, activation of the innate immune system leads to increased activation of the complement system, von Willebrand factor, tissue factor, and factor VIIa[148,150,151]. Likewise, complement activation during COVID-19-related sepsis intensifies the cytokine storm and perpetuates microvascular damage[152].

T2D increases mortality risk in COVID-19 due to the preexisting prothrombotic state secondary to diabetes, where hyperglycemia by itself appears to play a contributing role[151]. Human aortal endothelial cells cultured in high glucose *in vitro* were shown to trigger both inflammatory and prothrombotic pathways[153]. Similarly, hyperglycemia acts in synergy with neutrophils to release calprotectin, a protein that can bind RAGE on Kupffer cells and induce IL-6 synthesis. IL-6 increases thrombopoietin production, which enhances proliferation and expansion of thrombotic precursors and leads to thrombocytosis[154]. Similarly, P2Y12, a receptor expressed on the surface of platelets that plays essential roles in platelet activation, may be elevated in T2D patients, and facilitate platelet adhesion to vascular endothelium[155,156]. Consistent with these findings, numerous reports have demonstrated that the prothrombotic state can be mitigated by lowering blood glucose concentration[154]. Thus, several factors associated with T2D including endothelial dysfunction, vascular damage, systemic inflammation, and hyperglycemia can directly aggravate the prothrombotic state and increase mortality risk in patients with severe COVID-19[138,141,157].

CONCLUSION

COVID-19 is an ongoing global pandemic that has challenged the ability of healthcare providers to treat the most vulnerable patient populations, such as those living with preexisting T2D. Indeed, managing the syndemic between the two current pandemics of COVID-19 and T2D has become a major contemporary public health challenge. We have shown that T2D acts in synergy with SARS-CoV-2 infection to accelerate disease progression, increase severity, and heighten the mortality risk of COVID-19. We have discussed the mechanisms whereby hyperglycemia contributes to the "cytokine storm" characteristic of severe SARS-CoV-2 infection by stimulating monocytes and macrophages to produce IL-1β, IL-6, and TNF-α in the airway epithelium. The main mechanisms whereby hyperglycemia promotes ROS release, inhibition of T cell activation, and NET formation in the lungs of patients with severe SARS-CoV-2 infection have also been examined. We have reviewed the molecular mechanisms by which proinflammatory cytokines induce insulin resistance and exert deleterious effects on pancreatic β-cell exhaustion in T2D patients critically ill with COVID-19. We have also studied the effect of excess glucose on AGE formation and the role of AGEs in perpetuating pneumonia and ARDS. Finally, we have discussed the contribution of preexisting endothelial dysfunction secondary to diabetes to the development of neutrophil trafficking, vascular leaking, and thrombotic events in patients with severe SARS-CoV-2 infection (Table 1). We have not, however, addressed the possible contribution of other components of T2D such as nerve injury, hyperglucagonemia, adiposity, dyslipidemia, endoplasmic reticulum stress, glomerular and myocardial damage, and hypovitaminosis D to the severity of COVID-19. Importantly, the efficacy of vaccines against SARS-CoV-2 should be rigorously scrutinized in patients with T2D,

Table 1 Immunometabolic mechanisms of the main etiological factors associated with type 2 diabetes and their implications in the development of severe severe acute respiratory syndrome coronavirus-2 infection

Etiological component of T2D	Effect on immune responses	Implications in COVID-19	Ref.
Hyperglycemia	Stimulation of monocytes and macrophages to release IL-1β, IL-6, and TNF-α	Promotion of the cytokine storm and exacerbated inflammatory responses	Nielsen *et al*[23], Blair *et al*[24]
	Mitochondrial oxidative stress and production of reactive oxygen species	Activation of the proinflammatory cytokine storm	Robertson *et al*[39]
	Stimulation of lactate dehydrogenase activity	Upregulation of lactate pathway during severe COVID-19	Zhang *et al*[40]
	Increased NK cells with low levels of NKG2D and NKp46	Decreased degranulation and inefficient antiviral activity	Berrou *et al*[47]
	Low number of dendritic cells	Inefficient antigen presentation and decreased T cell activation	Zhong *et al*[52]
	Inhibition of T cell activation and proliferation	Increased viral load and COVID-19 progression	Macia et *al*[51]
	Decreased neutrophil migration and phagocytosis	Impaired viral clearance	Alba-Loureiro *et al*[53]
	Low number of IFN-γ-producing cells	Impaired antiviral response	Kalantar *et al*[54]
	Reduction of antibody titers	Inability to kill infected cells and increased viral load	Mathews *et al*[55]
Pancreatic β-cell exhaustion and hyperinsulinemia	β-cell apoptosis	Enhanced pancreatic damage through SARS-CoV-2 direct binding to ACE2 in β-cells	Weir[57]
	β-cell dysfunction through endoplasmic reticulum stress	Increased pancreatic inflammation	Butler *et al*[56]
	M1-like macrophage infiltration	Islet fibrosis and β-cell mass loss	Inoue *et al*[58], Westwell-Roper *et al*[59]
	Impaired insulin production	Increased hyperglycemia and promotion of proinflammatory cell activation	Zheng *et al*[64]
	Deterioration of exocrine pancreas	Increased pancreatic inflammation	Hayden *et al*[66]
Insulin resistance	Stimulation of proinflammatory cytokine release into circulation	Exacerbated systemic inflammation	Tabák *et al*[75], Akbari *et al*[80]
	Inactivation of the insulin signaling pathway *via* NF-κB	Suppression of IP-10 production and reduced insulin sensitivity	Antuna-Puente *et al*[81]
	Increased ACE2 receptor levels	Increased viral load and COVID-19 progression	Kuba *et al*[85]
	Decreased Th2 cell differentiation	Reduction of lymphocytes with anti-inflammatory functions	Viardot *et al*[92]
	Impaired ability of macrophages to respond to pathogens	Monocytopenia, COVID-19 progression, increased mortality risk	Rizo-Téllez *et al*[96]
	High blood neutrophil count	Neutrophilia, COVID-19 progression, increased mortality risk	DeFronzo *et al*[16]
Advanced glycation end products	Activation of the RAGE and sustained inflammatory responses	Increased pulmonary inflammation and mortality risk	Oczypok *et al*[101]
	Increased Th17 lymphocytes	Perpetuation of the cytokine storm and pulmonary inflammation	Wang *et al*[30]
	Activation of the classical complement pathway	Complement-mediated damage and membrane attack complex formation in lung tissue	Lupu *et al*[150]
	Non-enzymatic attachment of glucose to hemoglobin	Alteration of the hemoglobin 1-β chain, less oxygen bioavailability in peripheral tissues and breathing difficulty	Means[110]
	Non-enzymatic attachment of glucose to ACE2	Increased SARS-CoV-2 affinity and infection in pancreatic and lung tissue	Zhao *et al*[112], Bao *et al*[114]
	Glycation of CD147 in type II	Promotion of SARS-CoV-2 cell entry and	De Francesco *et al*[115]

	pneumocytes	increased viral load in pneumocytes	
	Neutrophil trafficking impairment	Hyper-reactive neutrophils that injure the vascular endothelium	Kraakman *et al*[154]
Endothelial dysfunction and prothrombotic state	Increased prothrombotic state	Enhanced blood clotting and severe coagulopathy	McFadyen *et al*[134]
	Hyper-activation of neutrophils in blood vessels	Vascular damage, blood vessel leaking, and sepsis	Joshi *et al*[126]
	Impaired vasodilatation with release of IL-6 and TNF-α	Microcirculatory malfunction and increased fibrinogen levels	Chi *et al*[29], Mangalmurti *et al*[27]
	Recruitment of immune cells	Blood vessel leaking and thrombosis	Ranucci *et al*[146]
	IL-6 production	Increased thrombopoietin production	Kraakman *et al*[154]
	Increased P2Y12 platelet receptor	Enhanced platelet adhesion and thrombosis	Dorsam *et al*[155]

Summary of the main immunometabolic mechanisms by which immune cells and cytokines act in synergy with preexisting hyperglycemia, β-cell dysfunction, hyperinsulinemia, insulin resistance, advanced glycation end products, endothelial dysfunction, and prothrombotic state to increase the severity, progression, and mortality of coronavirus disease 2019 in patients with type 2 diabetes. COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; T2D: Type 2 diabetes; NK: Natural killer; ACE2: Angiotensin-converting enzyme 2; IP-10: IFN-γ inducible protein-10; RAGE: Receptor for advanced glycation end products.

with careful consideration for all of the factors discussed herein. A better understanding of the T2D-related immunometabolic agents that contribute to exacerbate the severity of COVID-19 will improve our ability to identify patients with high mortality risk and prevent adverse outcomes.

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