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

Viurcos-Sanabria R *et al*. Immunometabolic mechanisms in diabetes and 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.

**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 Β-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, 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.

**REFERENCES**

1 **Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]

2 **Ceccarelli M**, Berretta M, Venanzi Rullo E, Nunnari G, Cacopardo B. Differences and similarities between Severe Acute Respiratory Syndrome (SARS)-CoronaVirus (CoV) and SARS-CoV-2. Would a rose by another name smell as sweet? *Eur Rev Med Pharmacol Sci* 2020; **24**: 2781-2783 [PMID: 32196628 DOI: 10.26355/eurrev\_202003\_20551]

3 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]

4 **Centers for Disease Control and Prevention.** Symptomps of Coronavirus. COVID-19 Testing Overview [cited 22 Dec 2020]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html#:~:text=Symptoms%20may%20appear%202%2D14,Cough

5 **Adhikari SP**, Meng S, Wu YJ, Mao YP, Ye RX, Wang QZ, Sun C, Sylvia S, Rozelle S, Raat H, Zhou H. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. *Infect Dis Poverty* 2020; **9**: 29 [PMID: 32183901 DOI: 10.1186/s40249-020-00646-x]

6 **Zou L**, Ruan F, Huang M, Liang L, Huang H, Hong Z, Yu J, Kang M, Song Y, Xia J, Guo Q, Song T, He J, Yen HL, Peiris M, Wu J. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med* 2020; **382**: 1177-1179 [PMID: 32074444 DOI: 10.1056/NEJMc2001737]

7 **Liu Y**, Yan LM, Wan L, Xiang TX, Le A, Liu JM, Peiris M, Poon LLM, Zhang W. Viral dynamics in mild and severe cases of COVID-19. *Lancet Infect Dis* 2020; **20**: 656-657 [PMID: 32199493 DOI: 10.1016/S1473-3099(20)30232-2]

8 **Lai CC**, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *Int J Antimicrob Agents* 2020; **55**: 105924 [PMID: 32081636 DOI: 10.1016/j.ijantimicag.2020.105924]

9 **Khan M**, Khan H, Khan S, Nawaz M. Epidemiological and clinical characteristics of coronavirus disease (COVID-19) cases at a screening clinic during the early outbreak period: a single-centre study. *J Med Microbiol* 2020; **69**: 1114-1123 [PMID: 32783802 DOI: 10.1099/jmm.0.001231]

10 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]

11 **Yang JK**, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, Sun GZ, Yang GR, Zhang XL, Wang L, Xu X, Xu XP, Chan JC. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabet Med* 2006; **23**: 623-628 [PMID: 16759303 DOI: 10.1111/j.1464-5491.2006.01861.x]

12 **Li B**, Yang J, Zhao F, Zhi L, Wang X, Liu L, Bi Z, Zhao Y. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol* 2020; **109**: 531-538 [PMID: 32161990 DOI: 10.1007/s00392-020-01626-9]

13 **Knapp S**. Diabetes and infection: is there a link?--A mini-review. *Gerontology* 2013; **59**: 99-104 [PMID: 23182884 DOI: 10.1159/000345107]

14 **Wu Z**, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323**: 1239-1242 [PMID: 32091533 DOI: 10.1001/jama.2020.2648]

15 **Onder G**, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA* 2020; **323**: 1775-1776 [PMID: 32203977 DOI: 10.1001/jama.2020.4683]

16 **DeFronzo RA**, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ, Hu FB, Kahn CR, Raz I, Shulman GI, Simonson DC, Testa MA, Weiss R. Type 2 diabetes mellitus. *Nat Rev Dis Primers* 2015; **1**: 15019 [PMID: 27189025 DOI: 10.1038/nrdp.2015.19]

17 **Daryabor G**, Kabelitz D, Kalantar K. An update on immune dysregulation in obesity-related insulin resistance. *Scand J Immunol* 2019; **89**: e12747 [PMID: 30593678 DOI: 10.1111/sji.12747]

18 **Feng YM**, Zhao D, Zhang N, Yu CG, Zhang Q, Thijs L, Staessen JA. Insulin Resistance in Relation to Lipids and Inflammation in Type-2 Diabetic Patients and Non-Diabetic People. *PLoS One* 2016; **11**: e0153171 [PMID: 27073920 DOI: 10.1371/journal.pone.0153171]

19 **Sattar N**, Gill JM. Type 2 diabetes as a disease of ectopic fat? *BMC Med* 2014; **12**: 123 [PMID: 25159817 DOI: 10.1186/s12916-014-0123-4]

20 **Yagihashi S**, Mizukami H, Sugimoto K. Mechanism of diabetic neuropathy: Where are we now and where to go? *J Diabetes Investig* 2011; **2**: 18-32 [PMID: 24843457 DOI: 10.1111/j.2040-1124.2010.00070.x]

21 **Di Fatta C,** Spiga R, Mancuso E, Fuoco A, Averta C, Mannino GC, Andreozzi F, Sesti G. Glucagon induces the expression of inflammatory markers in the liver through NLRP3 inflammasome. Session: Inflammatory events in type 2 diabetes. 2018 Oct 2; Berlin, Germany

22 **Leite NC**, Salles GF, Araujo AL, Villela-Nogueira CA, Cardoso CR. Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus. *Liver Int* 2009; **29**: 113-119 [PMID: 18384521 DOI: 10.1111/j.1478-3231.2008.01718.x]

23 **Nielsen TB**, Pantapalangkoor P, Yan J, Luna BM, Dekitani K, Bruhn K, Tan B, Junus J, Bonomo RA, Schmidt AM, Everson M, Duncanson F, Doherty TM, Lin L, Spellberg B. Diabetes Exacerbates Infection via Hyperinflammation by Signaling through TLR4 and RAGE. *mBio* 2017; **8** [PMID: 28830942 DOI: 10.1128/mBio.00818-17]

24 **Blair M**. Diabetes Mellitus Review. *Urol Nurs* 2016; **36**: 27-36 [PMID: 27093761]

25 **Muniyappa R**, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. *Am J Physiol Endocrinol Metab* 2020; **318**: E736-E741 [PMID: 32228322 DOI: 10.1152/ajpendo.00124.2020]

26 **Ye Q**, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. *J Infect* 2020; **80**: 607-613 [PMID: 32283152 DOI: 10.1016/j.jinf.2020.03.037]

27 **Mangalmurti N**, Hunter CA. Cytokine Storms: Understanding COVID-19. *Immunity* 2020; **53**: 19-25 [PMID: 32610079 DOI: 10.1016/j.immuni.2020.06.017]

28 **Hu B**, Huang S, Yin L. The cytokine storm and COVID-19. *J Med Virol* 2021; **93**: 250-256 [PMID: 32592501 DOI: 10.1002/jmv.26232]

29 **Chi Y**, Ge Y, Wu B, Zhang W, Wu T, Wen T, Liu J, Guo X, Huang C, Jiao Y, Zhu F, Zhu B, Cui L. Serum Cytokine and Chemokine Profile in Relation to the Severity of Coronavirus Disease 2019 in China. *J Infect Dis* 2020; **222**: 746-754 [PMID: 32563194 DOI: 10.1093/infdis/jiaa363]

30 **Wang J**, Jiang M, Chen X, Montaner LJ. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. *J Leukoc Biol* 2020; **108**: 17-41 [PMID: 32534467 DOI: 10.1002/JLB.3COVR0520-272R]

31 **Yang X**, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**: 475-481 [PMID: 32105632 DOI: 10.1016/S2213-2600(20)30079-5]

32 **Zhang C**, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. *Int J Antimicrob Agents* 2020; **55**: 105954 [PMID: 32234467 DOI: 10.1016/j.ijantimicag.2020.105954]

33 **Bode B**, Garrett V, Messler J, McFarland R, Crowe J, Booth R, Klonoff DC. Glycemic Characteristics and Clinical Outcomes of COVID-19 Patients Hospitalized in the United States. *J Diabetes Sci Technol* 2020; **14**: 813-821 [PMID: 32389027 DOI: 10.1177/1932296820924469]

34 **Ceriello A**, Zarich SW, Testa R. Lowering glucose to prevent adverse cardiovascular outcomes in a critical care setting. *J Am Coll Cardiol* 2009; **53**: S9-13 [PMID: 19179217 DOI: 10.1016/j.jacc.2008.09.054]

35 **Ceriello A**. Acute hyperglycaemia: a 'new' risk factor during myocardial infarction. *Eur Heart J* 2005; **26**: 328-331 [PMID: 15618047 DOI: 10.1093/eurheartj/ehi049]

36 **Singh AK**, Singh R. Hyperglycemia without diabetes and new-onset diabetes are both associated with poorer outcomes in COVID-19. *Diabetes Res Clin Pract* 2020; **167**: 108382 [PMID: 32853686 DOI: 10.1016/j.diabres.2020.108382]

37 **Liao WI**, Wang JC, Chang WC, Hsu CW, Chu CM, Tsai SH. Usefulness of Glycemic Gap to Predict ICU Mortality in Critically Ill Patients With Diabetes. *Medicine (Baltimore)* 2015; **94**: e1525 [PMID: 26356728 DOI: 10.1097/MD.0000000000001525]

38 **Iacobellis G**, Penaherrera CA, Bermudez LE, Bernal Mizrachi E. Admission hyperglycemia and radiological findings of SARS-CoV2 in patients with and without diabetes. *Diabetes Res Clin Pract* 2020; **164**: 108185 [PMID: 32360710 DOI: 10.1016/j.diabres.2020.108185]

39 **Robertson RP**, Harmon J, Tran PO, Tanaka Y, Takahashi H. Glucose toxicity in beta-cells: type 2 diabetes, good radicals gone bad, and the glutathione connection. *Diabetes* 2003; **52**: 581-587 [PMID: 12606496 DOI: 10.2337/diabetes.52.3.581]

40 **Zhang ZY**, Miao LF, Qian LL, Wang N, Qi MM, Zhang YM, Dang SP, Wu Y, Wang RX. Molecular Mechanisms of Glucose Fluctuations on Diabetic Complications. *Front Endocrinol (Lausanne)* 2019; **10**: 640 [PMID: 31620092 DOI: 10.3389/fendo.2019.00640]

41 **Lowell BB**, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. *Science* 2005; **307**: 384-387 [PMID: 15662004 DOI: 10.1126/science.1104343]

42 **Codo AC**, Davanzo GG, Monteiro LB, de Souza GF, Muraro SP, Virgilio-da-Silva JV, Prodonoff JS, Carregari VC, de Biagi Junior CAO, Crunfli F, Jimenez Restrepo JL, Vendramini PH, Reis-de-Oliveira G, Bispo Dos Santos K, Toledo-Teixeira DA, Parise PL, Martini MC, Marques RE, Carmo HR, Borin A, Coimbra LD, Boldrini VO, Brunetti NS, Vieira AS, Mansour E, Ulaf RG, Bernardes AF, Nunes TA, Ribeiro LC, Palma AC, Agrela MV, Moretti ML, Sposito AC, Pereira FB, Velloso LA, Vinolo MAR, Damasio A, Proença-Módena JL, Carvalho RF, Mori MA, Martins-de-Souza D, Nakaya HI, Farias AS, Moraes-Vieira PM. Elevated Glucose Levels Favor SARS-CoV-2 Infection and Monocyte Response through a HIF-1α/Glycolysis-Dependent Axis. *Cell Metab* 2020; **32**: 437-446.e5 [PMID: 32697943 DOI: 10.1016/j.cmet.2020.07.007]

43 **Ceriello A**. Hyperglycemia and COVID-19: What was known and what is really new? *Diabetes Res Clin Pract* 2020; **167**: 108383 [PMID: 32853690 DOI: 10.1016/j.diabres.2020.108383]

44 **Zhang W**, Wang G, Xu ZG, Tu H, Hu F, Dai J, Chang Y, Chen Y, Lu Y, Zeng H, Cai Z, Han F, Xu C, Jin G, Sun L, Pan BS, Lai SW, Hsu CC, Xu J, Chen ZZ, Li HY, Seth P, Hu J, Zhang X, Li H, Lin HK. Lactate Is a Natural Suppressor of RLR Signaling by Targeting MAVS. *Cell* 2019; **178**: 176-189.e15 [PMID: 31155231 DOI: 10.1016/j.cell.2019.05.003]

45 **Li X**, Xu S, Yu M, Wang K, Tao Y, Zhou Y, Shi J, Zhou M, Wu B, Yang Z, Zhang C, Yue J, Zhang Z, Renz H, Liu X, Xie J, Xie M, Zhao J. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol* 2020; **146**: 110-118 [PMID: 32294485 DOI: 10.1016/j.jaci.2020.04.006]

46 **Piątkiewicz P**, Miłek T, Bernat-Karpińska M, Ohams M, Czech A, Ciostek P. The dysfunction of NK cells in patients with type 2 diabetes and colon cancer. *Arch Immunol Ther Exp (Warsz)* 2013; **61**: 245-253 [PMID: 23456207 DOI: 10.1007/s00005-013-0222-5]

47 **Berrou J**, Fougeray S, Venot M, Chardiny V, Gautier JF, Dulphy N, Toubert A, Peraldi MN. Natural killer cell function, an important target for infection and tumor protection, is impaired in type 2 diabetes. *PLoS One* 2013; **8**: e62418 [PMID: 23638076 DOI: 10.1371/journal.pone.0062418]

48 **Angelidi AM**, Belanger MJ, Mantzoros CS. Commentary: COVID-19 and diabetes mellitus: What we know, how our patients should be treated now, and what should happen next. *Metabolism* 2020; **107**: 154245 [PMID: 32320742 DOI: 10.1016/j.metabol.2020.154245]

49 **Summers KL**, Marleau AM, Mahon JL, McManus R, Hramiak I, Singh B. Reduced IFN-alpha secretion by blood dendritic cells in human diabetes. *Clin Immunol* 2006; **121**: 81-89 [PMID: 16859998 DOI: 10.1016/j.clim.2006.05.015]

50 **Gilardini Montani MS**, Granato M, Cuomo L, Valia S, Di Renzo L, D'Orazi G, Faggioni A, Cirone M. High glucose and hyperglycemic sera from type 2 diabetic patients impair DC differentiation by inducing ROS and activating Wnt/β-catenin and p38 MAPK. *Biochim Biophys Acta* 2016; **1862**: 805-813 [PMID: 26769359 DOI: 10.1016/j.bbadis.2016.01.001]

51 **Macia L**, Delacre M, Abboud G, Ouk TS, Delanoye A, Verwaerde C, Saule P, Wolowczuk I. Impairment of dendritic cell functionality and steady-state number in obese mice. *J Immunol* 2006; **177**: 5997-6006 [PMID: 17056524 DOI: 10.4049/jimmunol.177.9.5997]

52 **Zhong J**, Tang J, Ye C, Dong L. The immunology of COVID-19: is immune modulation an option for treatment? *Lancet Rheumatol* 2020; **2**: e428-e436 [PMID: 32835246 DOI: 10.1016/S2665-9913(20)30120-X]

53 **Alba-Loureiro TC**, Munhoz CD, Martins JO, Cerchiaro GA, Scavone C, Curi R, Sannomiya P. Neutrophil function and metabolism in individuals with diabetes mellitus. *Braz J Med Biol Res* 2007; **40**: 1037-1044 [PMID: 17665039 DOI: 10.1590/S0100-879X2006005000143]

54 **Kalantar F**, Dabbaghmanesh MH, Martinuzzi E, Moghadami M, Amirghofran Z. Islet amyloid polypeptide is not a target antigen for CD8+ T-cells in type 2 diabetes. *Iran J Immunol* 2014; **11**: 1-12 [PMID: 24632583]

55 **Mathews CE**, Brown EL, Martinez PJ, Bagaria U, Nahm MH, Burton RL, Fisher-Hoch SP, McCormick JB, Mirza S. Impaired function of antibodies to pneumococcal surface protein A but not to capsular polysaccharide in Mexican American adults with type 2 diabetes mellitus. *Clin Vaccine Immunol* 2012; **19**: 1360-1369 [PMID: 22761295 DOI: 10.1128/CVI.00268-12]

56 **Butler AE**, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes* 2003; **52**: 102-110 [PMID: 12502499 DOI: 10.2337/diabetes.52.1.102]

57 **Weir GC**. Glucolipotoxicity, β-Cells, and Diabetes: The Emperor Has No Clothes. *Diabetes* 2020; **69**: 273-278 [PMID: 31519699 DOI: 10.2337/db19-0138]

58 **Inoue H**, Shirakawa J, Togashi Y, Tajima K, Okuyama T, Kyohara M, Tanaka Y, Orime K, Saisho Y, Yamada T, Shibue K, Kulkarni RN, Terauchi Y. Signaling between pancreatic β cells and macrophages via S100 calcium-binding protein A8 exacerbates β-cell apoptosis and islet inflammation. *J Biol Chem* 2018; **293**: 5934-5946 [PMID: 29496993 DOI: 10.1074/jbc.M117.809228]

59 **Westwell-Roper CY**, Ehses JA, Verchere CB. Resident macrophages mediate islet amyloid polypeptide-induced islet IL-1β production and β-cell dysfunction. *Diabetes* 2014; **63**: 1698-1711 [PMID: 24222351 DOI: 10.2337/db13-0863]

60 **Guardado-Mendoza R**, Davalli AM, Chavez AO, Hubbard GB, Dick EJ, Majluf-Cruz A, Tene-Perez CE, Goldschmidt L, Hart J, Perego C, Comuzzie AG, Tejero ME, Finzi G, Placidi C, La Rosa S, Capella C, Halff G, Gastaldelli A, DeFronzo RA, Folli F. Pancreatic islet amyloidosis, beta-cell apoptosis, and alpha-cell proliferation are determinants of islet remodeling in type-2 diabetic baboons. *Proc Natl Acad Sci USA* 2009; **106**: 13992-13997 [PMID: 19666551 DOI: 10.1073/pnas.0906471106]

61 **Jallut D**, Golay A, Munger R, Frascarolo P, Schutz Y, Jéquier E, Felber JP. Impaired glucose tolerance and diabetes in obesity: a 6-year follow-up study of glucose metabolism. *Metabolism* 1990; **39**: 1068-1075 [PMID: 2215253 DOI: 10.1016/0026-0495(90)90168-C]

62 **Hayden MR**. An Immediate and Long-Term Complication of COVID-19 May Be Type 2 Diabetes Mellitus: The Central Role of β-Cell Dysfunction, Apoptosis and Exploration of Possible Mechanisms. *Cells* 2020; **9** [PMID: 33202960 DOI: 10.3390/cells9112475]

63 **Yang JK**, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol* 2010; **47**: 193-199 [PMID: 19333547 DOI: 10.1007/s00592-009-0109-4]

64 **Zheng X**, Zheng X, Wang X, Ma Z, Gupta Sunkari V, Botusan I, Takeda T, Björklund A, Inoue M, Catrina SB, Brismar K, Poellinger L, Pereira TS. Acute hypoxia induces apoptosis of pancreatic β-cell by activation of the unfolded protein response and upregulation of CHOP. *Cell Death Dis* 2012; **3**: e322 [PMID: 22695615 DOI: 10.1038/cddis.2012.66]

65 **Maddaloni E**, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. *Diabetes Metab Res Rev* 2020: e33213321 [PMID: 32233018 DOI: 10.1002/dmrr.3321]

66 **Hayden MR**, Sowers JR. Isletopathy in Type 2 diabetes mellitus: implications of islet RAS, islet fibrosis, islet amyloid, remodeling, and oxidative stress. *Antioxid Redox Signal* 2007; **9**: 891-910 [PMID: 17516840 DOI: 10.1089/ars.2007.1610]

67 **Pina AF**, Patarrão RS, Ribeiro RT, Penha-Gonçalves C, Raposo JF, Gardete-Correia L, Duarte R, M Boavida J, L Medina J, Henriques R, Macedo MP. Metabolic Footprint, towards Understanding Type 2 Diabetes beyond Glycemia. *J Clin Med* 2020; **9** [PMID: 32785111 DOI: 10.3390/jcm9082588]

68 **Hayden MR**, Sowers JR. Redox imbalance in diabetes. *Antioxid Redox Signal* 2007; **9**: 865-867 [PMID: 17477794 DOI: 10.1089/ars.2007.1640]

69 **Hayden MR**. Endothelial activation and dysfunction in metabolic syndrome, type 2 diabetes and coronavirus disease 2019. *J Int Med Res* 2020; **48**: 300060520939746 [PMID: 32722979 DOI: 10.1177/0300060520939746]

70 **Hayden MR**, Sowers JR. Pancreatic renin-angiotensin-aldosterone system in the cardiometabolic syndrome and type 2 diabetes mellitus. *J Cardiometab Syndr* 2008; **3**: 129-131 [PMID: 18983326 DOI: 10.1111/j.1559-4572.2008.00006.x]

71 **Hayden MR**, Karuparthi PR, Habibi J, Wasekar C, Lastra G, Manrique C, Stas S, Sowers JR. Ultrastructural islet study of early fibrosis in the Ren2 rat model of hypertension. Emerging role of the islet pancreatic pericyte-stellate cell. *JOP* 2007; **8**: 725-738 [PMID: 17993725]

72 **Aloysius MM**, Thatti A, Gupta A, Sharma N, Bansal P, Goyal H. COVID-19 presenting as acute pancreatitis. *Pancreatology* 2020; **20**: 1026-1027 [PMID: 32444169 DOI: 10.1016/j.pan.2020.05.003]

73 **Ceriello A**, De Nigris V, Prattichizzo F. Why is hyperglycaemia worsening COVID-19 and its prognosis? *Diabetes Obes Metab* 2020; **22**: 1951-1952 [PMID: 32463166 DOI: 10.1111/dom.14098]

74 **Garbossa SG**, Folli F. Vitamin D, sub-inflammation and insulin resistance. A window on a potential role for the interaction between bone and glucose metabolism. *Rev Endocr Metab Disord* 2017; **18**: 243-258 [PMID: 28409320 DOI: 10.1007/s11154-017-9423-2]

75 **Tabák AG**, Jokela M, Akbaraly TN, Brunner EJ, Kivimäki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. *Lancet* 2009; **373**: 2215-2221 [PMID: 19515410 DOI: 10.1016/S0140-6736(09)60619-X]

76 **Daniele G**, Guardado Mendoza R, Winnier D, Fiorentino TV, Pengou Z, Cornell J, Andreozzi F, Jenkinson C, Cersosimo E, Federici M, Tripathy D, Folli F. The inflammatory status score including IL-6, TNF-α, osteopontin, fractalkine, MCP-1 and adiponectin underlies whole-body insulin resistance and hyperglycemia in type 2 diabetes mellitus. *Acta Diabetol* 2014; **51**: 123-131 [PMID: 24370923 DOI: 10.1007/s00592-013-0543-1]

77 **Fève B**, Bastard JP. The role of interleukins in insulin resistance and type 2 diabetes mellitus. *Nat Rev Endocrinol* 2009; **5**: 305-311 [PMID: 19399017 DOI: 10.1038/nrendo.2009.62]

78 **Hotamisligil GS**, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. *Science* 1996; **271**: 665-668 [PMID: 8571133 DOI: 10.1126/science.271.5249.665]

79 **Méndez-García LA**, Trejo-Millán F, Martínez-Reyes CP, Manjarrez-Reyna AN, Esquivel-Velázquez M, Melendez-Mier G, Islas-Andrade S, Rojas-Bernabé A, Kzhyshkowska J, Escobedo G. Infliximab ameliorates tumor necrosis factor-alpha-induced insulin resistance by attenuating PTP1B activation in 3T3L1 adipocytes in vitro. *Scand J Immunol* 2018; **88**: e12716 [PMID: 30260514 DOI: 10.1111/sji.12716]

80 **Akbari M**, Hassan-Zadeh V. IL-6 signalling pathways and the development of type 2 diabetes. *Inflammopharmacology* 2018; **26**: 685-698 [PMID: 29508109 DOI: 10.1007/s10787-018-0458-0]

81 **Antuna-Puente B**, Feve B, Fellahi S, Bastard JP. Adipokines: the missing link between insulin resistance and obesity. *Diabetes Metab* 2008; **34**: 2-11 [PMID: 18093861 DOI: 10.1016/j.diabet.2007.09.004]

82 **Bastard JP**, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, Capeau J, Feve B. Recent advances in the relationship between obesity, inflammation, and insulin resistance. *Eur Cytokine Netw* 2006; **17**: 4-12 [PMID: 16613757]

83 **Pal R**, Bhadada SK. COVID-19 and diabetes mellitus: An unholy interaction of two pandemics. *Diabetes Metab Syndr* 2020; **14**: 513-517 [PMID: 32388331 DOI: 10.1016/j.dsx.2020.04.049]

84 **Kassir R**. Risk of COVID-19 for patients with obesity. *Obes Rev* 2020; **21**: e13034 [PMID: 32281287 DOI: 10.1111/obr.13034]

85 **Kuba K**, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C, Penninger JM. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005; **11**: 875-879 [PMID: 16007097 DOI: 10.1038/nm1267]

86 **Underwood PC**, Adler GK. The renin angiotensin aldosterone system and insulin resistance in humans. *Curr Hypertens Rep* 2013; **15**: 59-70 [PMID: 23242734 DOI: 10.1007/s11906-012-0323-2]

87 **Takeda M**, Yamamoto K, Takemura Y, Takeshita H, Hongyo K, Kawai T, Hanasaki-Yamamoto H, Oguro R, Takami Y, Tatara Y, Takeya Y, Sugimoto K, Kamide K, Ohishi M, Rakugi H. Loss of ACE2 exaggerates high-calorie diet-induced insulin resistance by reduction of GLUT4 in mice. *Diabetes* 2013; **62**: 223-233 [PMID: 22933108 DOI: 10.2337/db12-0177]

88 **Rao S**, Lau A, So HC. Exploring Diseases/Traits and Blood Proteins Causally Related to Expression of ACE2, the Putative Receptor of SARS-CoV-2: A Mendelian Randomization Analysis Highlights Tentative Relevance of Diabetes-Related Traits. *Diabetes Care* 2020; **43**: 1416-1426 [PMID: 32430459 DOI: 10.2337/dc20-0643]

89 **Lee JS**, Park S, Jeong HW, Ahn JY, Choi SJ, Lee H, Choi B, Nam SK, Sa M, Kwon JS, Jeong SJ, Lee HK, Park SH, Park SH, Choi JY, Kim SH, Jung I, Shin EC. Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19. *Sci Immunol* 2020; **5** [PMID: 32651212 DOI: 10.1126/sciimmunol.abd1554]

90 **Šestan M**, Marinović S, Kavazović I, Cekinović Đ, Wueest S, Turk Wensveen T, Brizić I, Jonjić S, Konrad D, Wensveen FM, Polić B. Virus-Induced Interferon-γ Causes Insulin Resistance in Skeletal Muscle and Derails Glycemic Control in Obesity. *Immunity* 2018; **49**: 164-177.e6 [PMID: 29958802 DOI: 10.1016/j.immuni.2018.05.005]

91 **Duffaut C**, Zakaroff-Girard A, Bourlier V, Decaunes P, Maumus M, Chiotasso P, Sengenès C, Lafontan M, Galitzky J, Bouloumié A. Interplay between human adipocytes and T lymphocytes in obesity: CCL20 as an adipochemokine and T lymphocytes as lipogenic modulators. *Arterioscler Thromb Vasc Biol* 2009; **29**: 1608-1614 [PMID: 19644053 DOI: 10.1161/ATVBAHA.109.192583]

92 **Viardot A**, Grey ST, Mackay F, Chisholm D. Potential antiinflammatory role of insulin via the preferential polarization of effector T cells toward a T helper 2 phenotype. *Endocrinology* 2007; **148**: 346-353 [PMID: 17008395 DOI: 10.1210/en.2006-0686]

93 **Viardot A**, Heilbronn LK, Samocha-Bonet D, Mackay F, Campbell LV, Samaras K. Obesity is associated with activated and insulin resistant immune cells. *Diabetes Metab Res Rev* 2012; **28**: 447-454 [PMID: 22492715 DOI: 10.1002/dmrr.2302]

94 **Gómez-Rial J**, Rivero-Calle I, Salas A, Martinón-Torres F. Role of Monocytes/Macrophages in Covid-19 Pathogenesis: Implications for Therapy. *Infect Drug Resist* 2020; **13**: 2485-2493 [PMID: 32801787 DOI: 10.2147/IDR.S258639]

95 **Ieronymaki E**, Daskalaki MG, Lyroni K, Tsatsanis C. Insulin Signaling and Insulin Resistance Facilitate Trained Immunity in Macrophages Through Metabolic and Epigenetic Changes. *Front Immunol* 2019; **10**: 1330 [PMID: 31244863 DOI: 10.3389/fimmu.2019.01330]

96 **Rizo-Téllez SA**, Méndez-García LA, Flores-Rebollo C, Alba-Flores F, Alcántara-Suárez R, Manjarrez-Reyna AN, Baltazar-López N, Hernández-Guzmán VA, León-Pedroza JI, Zapata-Arenas R, González-Chávez A, Hernández-Ruíz J, Carrillo-Ruíz JD, Serrano-Loyola R, Guerrero-Avendaño GML, Escobedo G. The Neutrophil-to-Monocyte Ratio and Lymphocyte-to-Neutrophil Ratio at Admission Predict In-Hospital Mortality in Mexican Patients with Severe SARS-CoV-2 Infection (Covid-19). *Microorganisms* 2020; **8** [PMID: 33050487 DOI: 10.3390/microorganisms8101560]

97 **Maessen DE**, Stehouwer CD, Schalkwijk CG. The role of methylglyoxal and the glyoxalase system in diabetes and other age-related diseases. *Clin Sci (Lond)* 2015; **128**: 839-861 [PMID: 25818485 DOI: 10.1042/CS20140683]

98 **Hegab Z**, Gibbons S, Neyses L, Mamas MA. Role of advanced glycation end products in cardiovascular disease. *World J Cardiol* 2012; **4**: 90-102 [PMID: 22558488 DOI: 10.4330/wjc.v4.i4.90]

99 **Mulrennan S**, Baltic S, Aggarwal S, Wood J, Miranda A, Frost F, Kaye J, Thompson PJ. The role of receptor for advanced glycation end products in airway inflammation in CF and CF related diabetes. *Sci Rep* 2015; **5**: 8931 [PMID: 25754382 DOI: 10.1038/srep08931]

100 **Fehrenbach H**, Kasper M, Tschernig T, Shearman MS, Schuh D, Müller M. Receptor for advanced glycation endproducts (RAGE) exhibits highly differential cellular and subcellular localisation in rat and human lung. *Cell Mol Biol (Noisy-le-grand)* 1998; **44**: 1147-1157 [PMID: 9846897 DOI: 10.1161/ATVBAHA.120.315527]

101 **Oczypok EA**, Perkins TN, Oury TD. All the "RAGE" in lung disease: The receptor for advanced glycation endproducts (RAGE) is a major mediator of pulmonary inflammatory responses. *Paediatr Respir Rev* 2017; **23**: 40-49 [PMID: 28416135 DOI: 10.1016/j.prrv.2017.03.012]

102 **Katsuoka F**, Kawakami Y, Arai T, Imuta H, Fujiwara M, Kanma H, Yamashita K. Type II alveolar epithelial cells in lung express receptor for advanced glycation end products (RAGE) gene. *Biochem Biophys Res Commun* 1997; **238**: 512-516 [PMID: 9299542 DOI: 10.1006/bbrc.1997.7263]

103 **Prasad K**. AGE-RAGE Stress in the Pathophysiology of Pulmonary Hypertension and its Treatment. *Int J Angiol* 2019; **28**: 71-79 [PMID: 31384104 DOI: 10.1055/s-0039-1687818]

104 **Nakamura K**, Sakaguchi M, Matsubara H, Akagi S, Sarashina T, Ejiri K, Akazawa K, Kondo M, Nakagawa K, Yoshida M, Miyoshi T, Ogo T, Oto T, Toyooka S, Higashimoto Y, Fukami K, Ito H. Crucial role of RAGE in inappropriate increase of smooth muscle cells from patients with pulmonary arterial hypertension. *PLoS One* 2018; **13**: e0203046 [PMID: 30180189 DOI: 10.1371/journal.pone.0203046]

105 **Polverino F**, Celli BR, Owen CA. COPD as an endothelial disorder: endothelial injury linking lesions in the lungs and other organs? (2017 Grover Conference Series). *Pulm Circ* 2018; **8**: 2045894018758528 [PMID: 29468936 DOI: 10.1177/2045894018758528]

106 **Ahn M**, Anderson DE, Zhang Q, Tan CW, Lim BL, Luko K, Wen M, Chia WN, Mani S, Wang LC, Ng JHJ, Sobota RM, Dutertre CA, Ginhoux F, Shi ZL, Irving AT, Wang LF. Dampened NLRP3-mediated inflammation in bats and implications for a special viral reservoir host. *Nat Microbiol* 2019; **4**: 789-799 [PMID: 30804542 DOI: 10.1038/s41564-019-0371-3]

107 **Boteanu RM**, Uyy E, Suica VI, Antohe F. High-mobility group box 1 enhances the inflammatory process in diabetic lung. *Arch Biochem Biophys* 2015; **583**: 55-64 [PMID: 26254814 DOI: 10.1016/j.abb.2015.07.020]

108 **Chikazawa M**, Shibata T, Hatasa Y, Hirose S, Otaki N, Nakashima F, Ito M, Machida S, Maruyama S, Uchida K. Identification of C1q as a Binding Protein for Advanced Glycation End Products. *Biochemistry* 2016; **55**: 435-446 [PMID: 26731343 DOI: 10.1021/acs.biochem.5b00777]

109 **Manzo G**. COVID-19 as an Immune Complex Hypersensitivity in Antigen Excess Conditions: Theoretical Pathogenetic Process and Suggestions for Potential Therapeutic Interventions. *Front Immunol* 2020; **11**: 566000 [PMID: 33193337 DOI: 10.3389/fimmu.2020.566000]

110 **Means C**. Letter to the Editor: Mechanisms of increased morbidity and mortality of SARS-CoV-2 infection in individuals with diabetes: what this means for an effective management strategy. *Metabolism* 2020; **108**: 154254 [PMID: 32360397 DOI: 10.1016/j.metabol.2020.154254]

111 **Guo YR**, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. *Mil Med Res* 2020; **7**: 11 [PMID: 32169119 DOI: 10.1186/s40779-020-00240-0]

112 **Zhao P**, Praissman JL, Grant OC, Cai Y, Xiao T, Rosenbalm KE, Aoki K, Kellman BP, Bridger R, Barouch DH, Brindley MA, Lewis NE, Tiemeyer M, Chen B, Woods RJ, Wells L. Virus-Receptor Interactions of Glycosylated SARS-CoV-2 Spike and Human ACE2 Receptor. *bioRxiv* 2020 [PMID: 32743578 DOI: 10.1101/2020.06.25.172403]

113 **Brufsky A**. Hyperglycemia, hydroxychloroquine, and the COVID-19 pandemic. *J Med Virol* 2020; **92**: 770-775 [PMID: 32293710 DOI: 10.1002/jmv.25887]

114 **Bao W**, Min D, Twigg SM, Shackel NA, Warner FJ, Yue DK, McLennan SV. Monocyte CD147 is induced by advanced glycation end products and high glucose concentration: possible role in diabetic complications. *Am J Physiol Cell Physiol* 2010; **299**: C1212-C1219 [PMID: 20810913 DOI: 10.1152/ajpcell.00228.2010]

115 **De Francesco EM**, Vella V, Belfiore A. COVID-19 and Diabetes: The Importance of Controlling RAGE. *Front Endocrinol (Lausanne)* 2020; **11**: 526 [PMID: 32760352 DOI: 10.3389/fendo.2020.00526]

116 **Pober JS**, Sessa WC. Evolving functions of endothelial cells in inflammation. *Nat Rev Immunol* 2007; **7**: 803-815 [PMID: 17893694 DOI: 10.1038/nri2171]

117 **Almdal T**, Scharling H, Jensen JS, Vestergaard H. The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. *Arch Intern Med* 2004; **164**: 1422-1426 [PMID: 15249351 DOI: 10.1001/archinte.164.13.1422]

118 **Varga Z**, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395**: 1417-1418 [PMID: 32325026 DOI: 10.1016/S0140-6736(20)30937-5]

119 COVID-19 and vascular disease. *EBioMedicine* 2020; **58**: 102966 [PMID: 32829782 DOI: 10.1016/j.ebiom.2020.102966]

120 **Kahn MB**, Yuldasheva NY, Cubbon RM, Smith J, Rashid ST, Viswambharan H, Imrie H, Abbas A, Rajwani A, Aziz A, Baliga V, Sukumar P, Gage M, Kearney MT, Wheatcroft SB. Insulin resistance impairs circulating angiogenic progenitor cell function and delays endothelial regeneration. *Diabetes* 2011; **60**: 1295-1303 [PMID: 21317296 DOI: 10.2337/db10-1080]

121 **Iba T**, Levy JH, Levi M, Connors JM, Thachil J. Coagulopathy of Coronavirus Disease 2019. *Crit Care Med* 2020; **48**: 1358-1364 [PMID: 32467443 DOI: 10.1097/CCM.0000000000004458]

122 **Green SJ**. Covid-19 accelerates endothelial dysfunction and nitric oxide deficiency. *Microbes Infect* 2020; **22**: 149-150 [PMID: 32425647 DOI: 10.1016/j.micinf.2020.05.006]

123 **Akerström S**, Gunalan V, Keng CT, Tan YJ, Mirazimi A. Dual effect of nitric oxide on SARS-CoV replication: viral RNA production and palmitoylation of the S protein are affected. *Virology* 2009; **395**: 1-9 [PMID: 19800091 DOI: 10.1016/j.virol.2009.09.007]

124 **Teuwen LA**, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. *Nat Rev Immunol* 2020; **20**: 389-391 [PMID: 32439870 DOI: 10.1038/s41577-020-0343-0]

125 **Llorente L**, De La Fuente H, Richaud-Patin Y, Alvarado-De La Barrera C, Diaz-Borjón A, López-Ponce A, Lerman-Garber I, Jakez-Ocampo J. Innate immune response mechanisms in non-insulin dependent diabetes mellitus patients assessed by flow cytoenzymology. *Immunol Lett* 2000; **74**: 239-244 [PMID: 11064109 DOI: 10.1016/S0165-2478(00)00255-8]

126 **Joshi MB**, Baipadithaya G, Balakrishnan A, Hegde M, Vohra M, Ahamed R, Nagri SK, Ramachandra L, Satyamoorthy K. Elevated homocysteine levels in type 2 diabetes induce constitutive neutrophil extracellular traps. *Sci Rep* 2016; **6**: 36362 [PMID: 27811985 DOI: 10.1038/srep36362]

127 **Zhang C**, Yang J, Jennings LK. Leukocyte-derived myeloperoxidase amplifies high-glucose--induced endothelial dysfunction through interaction with high-glucose--stimulated, vascular non--leukocyte-derived reactive oxygen species. *Diabetes* 2004; **53**: 2950-2959 [PMID: 15504976 DOI: 10.2337/diabetes.53.11.2950]

128 **Andreozzi F**, Laratta E, Procopio C, Hribal ML, Sciacqua A, Perticone M, Miele C, Perticone F, Sesti G. Interleukin-6 impairs the insulin signaling pathway, promoting production of nitric oxide in human umbilical vein endothelial cells. *Mol Cell Biol* 2007; **27**: 2372-2383 [PMID: 17242212 DOI: 10.1128/mcb.01340-06]

129 **Didion SP**. Cellular and Oxidative Mechanisms Associated with Interleukin-6 Signaling in the Vasculature. *Int J Mol Sci* 2017; **18** [PMID: 29186034 DOI: 10.3390/ijms18122563]

130 **Siddiqi HK**, Libby P, Ridker PM. COVID-19 - A vascular disease. *Trends Cardiovasc Med* 2021; **31**: 1-5 [PMID: 33068723 DOI: 10.1016/j.tcm.2020.10.005]

131 **Sturtzel C**. Endothelial Cells. *Adv Exp Med Biol* 2017; **1003**: 71-91 [PMID: 28667554 DOI: 10.1007/978-3-319-57613-8\_4]

132 **Panigada M**, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, Pesenti A, Peyvandi F, Tripodi A. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost* 2020; **18**: 1738-1742 [PMID: 32302438 DOI: 10.1111/jth.14850]

133 **Figliozzi S**, Masci PG, Ahmadi N, Tondi L, Koutli E, Aimo A, Stamatelopoulos K, Dimopoulos MA, Caforio ALP, Georgiopoulos G. Predictors of adverse prognosis in COVID-19: A systematic review and meta-analysis. *Eur J Clin Invest* 2020; **50**: e13362 [PMID: 32726868 DOI: 10.1111/eci.13362]

134 **McFadyen JD**, Stevens H, Peter K. The Emerging Threat of (Micro)Thrombosis in COVID-19 and Its Therapeutic Implications. *Circ Res* 2020; **127**: 571-587 [PMID: 32586214 DOI: 10.1161/CIRCRESAHA.120.317447]

135 **Jabaudon M**, Blondonnet R, Roszyk L, Bouvier D, Audard J, Clairefond G, Fournier M, Marceau G, Déchelotte P, Pereira B, Sapin V, Constantin JM. Soluble Receptor for Advanced Glycation End-Products Predicts Impaired Alveolar Fluid Clearance in Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 2015; **192**: 191-199 [PMID: 25932660 DOI: 10.1164/rccm.201501-0020OC]

136 **Tang N**, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 2020; **18**: 1094-1099 [PMID: 32220112 DOI: 10.1111/jth.14817]

137 **Klok FA**, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb Res* 2020; **191**: 148-150 [PMID: 32381264 DOI: 10.1016/j.thromres.2020.04.041]

138 **Xu X**, Chang XN, Pan HX, Su H, Huang B, Yang M, Luo DJ, Weng MX, Ma L, Nie X. [Pathological changes of the spleen in ten patients with coronavirus disease 2019(COVID-19) by postmortem needle autopsy]. *Zhonghua Bing Li Xue Za Zhi* 2020; **49**: 576-582 [PMID: 32340089 DOI: 10.3760/cma.j.cn112151-20200401-00278]

139 **Vulliamy P**, Jacob S, Davenport RA. Acute aorto-iliac and mesenteric arterial thromboses as presenting features of COVID-19. *Br J Haematol* 2020; **189**: 1053-1054 [PMID: 32353183 DOI: 10.1111/bjh.16760]

140 **Wichmann D**, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, Heinrich F, Mushumba H, Kniep I, Schröder AS, Burdelski C, de Heer G, Nierhaus A, Frings D, Pfefferle S, Becker H, Bredereke-Wiedling H, de Weerth A, Paschen HR, Sheikhzadeh-Eggers S, Stang A, Schmiedel S, Bokemeyer C, Addo MM, Aepfelbacher M, Püschel K, Kluge S. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med* 2020; **173**: 268-277 [PMID: 32374815 DOI: 10.7326/M20-2003]

141 **Cattaneo M**, Bertinato EM, Birocchi S, Brizio C, Malavolta D, Manzoni M, Muscarella G, Orlandi M. Pulmonary Embolism or Pulmonary Thrombosis in COVID-19? Is the Recommendation to Use High-Dose Heparin for Thromboprophylaxis Justified? *Thromb Haemost* 2020; **120**: 1230-1232 [PMID: 32349132 DOI: 10.1055/s-0040-1712097]

142 **Zhang L**, Feng X, Zhang D, Jiang C, Mei H, Wang J, Zhang C, Li H, Xia X, Kong S, Liao J, Jia H, Pang X, Song Y, Tian Y, Wang B, Wu C, Yuan H, Zhang Y, Li Y, Sun W, Zhang Y, Zhu S, Wang S, Xie Y, Ge S, Zhang L, Hu Y, Xie M. Deep Vein Thrombosis in Hospitalized Patients With COVID-19 in Wuhan, China: Prevalence, Risk Factors, and Outcome. *Circulation* 2020; **142**: 114-128 [PMID: 32421381 DOI: 10.1161/CIRCULATIONAHA.120.046702]

143 **Karakike E**, Giamarellos-Bourboulis EJ. Macrophage Activation-Like Syndrome: A Distinct Entity Leading to Early Death in Sepsis. *Front Immunol* 2019; **10**: 55 [PMID: 30766533 DOI: 10.3389/fimmu.2019.00055]

144 **Chen G**, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, Zhang X, Zhang M, Wu S, Song J, Chen T, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020; **130**: 2620-2629 [PMID: 32217835 DOI: 10.1172/JCI137244]

145 **Henry BM**, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med* 2020; **58**: 1021-1028 [PMID: 32286245 DOI: 10.1515/cclm-2020-0369]

146 **Ranucci M**, Ballotta A, Di Dedda U, Bayshnikova E, Dei Poli M, Resta M, Falco M, Albano G, Menicanti L. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemost* 2020; **18**: 1747-1751 [PMID: 32302448 DOI: 10.1111/jth.14854]

147 **Subramaniam S**, Scharrer I. Procoagulant activity during viral infections. *Front Biosci (Landmark Ed)* 2018; **23**: 1060-1081 [PMID: 28930589 DOI: 10.2741/4633]

148 **Giannis D**, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *J Clin Virol* 2020; **127**: 104362 [PMID: 32305883 DOI: 10.1016/j.jcv.2020.104362]

149 **Ng LF**, Hibberd ML, Ooi EE, Tang KF, Neo SY, Tan J, Murthy KR, Vega VB, Chia JM, Liu ET, Ren EC. A human in vitro model system for investigating genome-wide host responses to SARS coronavirus infection. *BMC Infect Dis* 2004; **4**: 34 [PMID: 15357874 DOI: 10.1186/1471-2334-4-34]

150 **Lupu F**, Keshari RS, Lambris JD, Coggeshall KM. Crosstalk between the coagulation and complement systems in sepsis. *Thromb Res* 2014; **133 Suppl 1**: S28-S31 [PMID: 24759136 DOI: 10.1016/j.thromres.2014.03.014]

151 **Gragnano F**, Sperlongano S, Golia E, Natale F, Bianchi R, Crisci M, Fimiani F, Pariggiano I, Diana V, Carbone A, Cesaro A, Concilio C, Limongelli G, Russo M, Calabrò P. The Role of von Willebrand Factor in Vascular Inflammation: From Pathogenesis to Targeted Therapy. *Mediators Inflamm* 2017; **2017**: 5620314 [PMID: 28634421 DOI: 10.1155/2017/5620314]

152 **Irshad Z**, Xue M, Ashour A, Larkin JR, Thornalley PJ, Rabbani N. Activation of the unfolded protein response in high glucose treated endothelial cells is mediated by methylglyoxal. *Sci Rep* 2019; **9**: 7889 [PMID: 31133647 DOI: 10.1038/s41598-019-44358-1]

153 **Kraakman MJ**, Lee MK, Al-Sharea A, Dragoljevic D, Barrett TJ, Montenont E, Basu D, Heywood S, Kammoun HL, Flynn M, Whillas A, Hanssen NM, Febbraio MA, Westein E, Fisher EA, Chin-Dusting J, Cooper ME, Berger JS, Goldberg IJ, Nagareddy PR, Murphy AJ. Neutrophil-derived S100 calcium-binding proteins A8/A9 promote reticulated thrombocytosis and atherogenesis in diabetes. *J Clin Invest* 2017; **127**: 2133-2147 [PMID: 28504650 DOI: 10.1172/JCI92450]

154 **Guo W**, Li M, Dong Y, Zhou H, Zhang Z, Tian C, Qin R, Wang H, Shen Y, Du K, Zhao L, Fan H, Luo S, Hu D. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev* 2020: e3319 [PMID: 32233013 DOI: 10.1002/dmrr.3319]

155 **Dorsam RT**, Kunapuli SP. Central role of the P2Y12 receptor in platelet activation. *J Clin Invest* 2004; **113**: 340-345 [PMID: 14755328 DOI: 10.1172/JCI20986]

156 **Przygodzki T**, Luzak B, Kassassir H, Mnich E, Boncler M, Siewiera K, Kosmalski M, Szymanski J, Watala C. Diabetes and Hyperglycemia Affect Platelet GPIIIa Expression. Effects on Adhesion Potential of Blood Platelets from Diabetic Patients under In Vitro Flow Conditions. *Int J Mol Sci* 2020; **21** [PMID: 32370146 DOI: 10.3390/IJMS21093222]

157 **Gąsecka A**, Borovac JA, Guerreiro RA, Giustozzi M, Parker W, Caldeira D, Chiva-Blanch G. Thrombotic Complications in Patients with COVID-19: Pathophysiological Mechanisms, Diagnosis, and Treatment. *Cardiovasc Drugs Ther* 2021; **35**: 215-229 [PMID: 33074525 DOI: 10.1007/s10557-020-07084-9]

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**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 *etal*[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 pneumocytes | Promotion of SARS-CoV-2 cell entry and increased viral load in pneumocytes | De Francesco *et al*[115] |
| 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.



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