

Diabetes and COVID-19: Role of insulin resistance as a risk factor for COVID-19 severity

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Abstract

Patients with diabetes are more susceptible to coronavirus disease 2019 (COVID-19), and as a consequence, develop more severe form of disease. This is partly due to a systemic inflammatory state and pro thrombotic milieu seen in metabolic syndrome. In this review, we attempt to explore the pathogenetic links between insulin resistance and COVID-19 disease severity. Insulin resistance is an underlying condition for metabolic syndromes, including type 2 diabetes, which impairs insulin signaling pathways affecting metabolic and cardiovascular homeostasis. A high concentration of circulating insulin shifts the balance to mitogen activated protein kinase (MAPK)-dependent signaling and causes endothelial cell damage. The phosphatidylinositol 3 kinase and MAPK dependent signaling pathways maintain a balance between nitric oxide-dependent vasodilator and endothelin-1 dependent vasoconstriction actions of insulin. Vascular smooth muscle cell dysfunction is responsible for inflammation and blood coagulation leading to microvascular and macrovascular complications in diabetes. Hyperactivity in renin-angiotensin system is implicated in development of islet oxidative stress and subsequent β -cell dysfunction, as it alters the islet blood flow. These deleterious effects of insulin resistance involving altered blood pressure, vascular dysfunction, and inflammation could be associated with increased severity in COVID-19 patients. We conclude that clinical and/or biochemical markers of insulin resistance should be included as prognostic markers in assessment of acute COVID-19 disease.

Key Words: Insulin resistance; Renin-angiotensin system; Blood flow measurements; Inflammation; Thrombosis; Severity of COVID-19

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Core Tip: Diabetes has been associated with an increased risk of developing coronavirus disease 2019 (COVID-19) as well as more severe outcomes as a consequence. The pathogenetic link between insulin resistance and COVID-19 disease severity is not fully understood. Establishing an association between insulin resistance and COVID-19 severity can help to develop targeted therapeutic interventions and potentially improve outcomes amongst the at-risk group.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a viral infection caused by a single stranded RNA virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and first identified in Wuhan, China. World Health Organization declared COVID-19 a global pandemic on March 11, 2020, with confirmed positive cases reported from more than 200 countries[1]. The most common signs and symptoms of SARS-CoV-2 infections range from asymptomatic to mild (20%-80% restricted to upper respiratory tract), while some may rapidly develop acute respiratory distress syndrome (ARDS), regional inflammation leading to pneumonia, respiratory failure, arrhythmias, acute cardiac injury, shock, multiple organ failure, and death. The severity of infection is manifested particularly in patients with concomitant conditions, including diabetes, cardiovascular disease, hypertension, obesity, and chronic obstructive pulmonary disease[2]. Epidemiological data has revealed that the mortality rate is higher amongst the older population with pre-existing comorbidities, including diabetes[3]. The clinical features of hospitalized COVID-19 patients reported by Liu *et al*[3] showed that elderly patients had underlying comorbidities including hypertension (27.78%), diabetes (16.67%), coronary heart disease (11.11%), and liver disease (5.56%). Elderly patients (median age 68) have had more complications following hospital admission, including ARDS (22.22%) and need for invasive ventilator support (22.22%)[3].

COVID-19 AND DIABETES MELLITUS

During the first wave, compared to Asia, a greater percentage of people in Europe had worse outcomes from COVID-19[4]. An analysis on comorbidities amongst Italian subjects infected with COVID-19 revealed diabetes mellitus as the highest-ranking condition, followed by systemic hypertension and ischemic heart disease[1]. A study from Wuhan, China on the characteristics of COVID-19 patients showed that those with pre-existing diabetes (prevalence of 9.7%)[5] were more likely to require admission to an intensive care unit (20%) or to die as a result of severe COVID-19[6]. A study on glycemic characteristics and clinical outcomes of COVID-19 inpatients in United States showed that poor glycemic control correlated with longer stays in the hospital and a higher mortality rate (28.8% *vs* 6.2%; $P < 0.001$) in the diabetic group compared to nondiabetic group[7]. It is now well recognized that advanced age, presence of diabetes mellitus, hypertension, and severe obesity (body mass index > 40 kg/m²) are associated with increased hospital admissions, morbidity, and mortality in patients with COVID-19[8].

POTENTIAL MECHANISMS

Individuals with type 2 diabetes as part of a metabolic syndrome are characterized by increased activation of the renin angiotensin system, resulting in the development of diabetic complications, including micro and macro vascular diseases[9]. Renin

angiotensin system activation also triggers pro-inflammatory and procoagulant pathways, which further contribute to endothelial dysfunction and impaired vascular tone. Circulating levels of renin-angiotensin system (RAS) components, especially angiotensin II (ATII), have a potential role in endothelial cell dysfunction, insulin resistance, inflammation, and proliferation. Evidence has shown that insulin resistance is also positively associated with high prevalence of subclinical coronary artery disease and an altered adaptive immune response[10]. In addition, immune dysregulation and hyper inflammatory response induced by SARS-CoV-2 causes a delayed and impaired interferon response, lymphocyte exhaustion and cytokine storm in patients with diabetes and underlying insulin resistance[11,12]. However, the extent to which insulin resistance contributes to COVID-19 disease severity, along the underlying mechanisms involved, remain largely unexplored. In this review we explore the potential mechanisms linking insulin resistance and disease severity of COVID-19.

COVID-19-INFLAMMATORY PATHWAYS

SARS-CoV-2 is transmitted primarily *via* respiratory droplets, direct and indirect contact, with possible, but unproven, fecal-oral route. Following infection of SARS-CoV-2 in patients, the onset of symptoms occurs within 4 to 5 d, and 97.5% of symptomatic patients develop the disease within 2 wk. A common feature in a subgroup of severely ill patients admitted to hospital exhibit severe respiratory failure with dyspnea and bilateral lung infiltration as observed on chest computerized tomography scans, lymphopenia, diarrhea, and hemoptysis[12]. Thus, the spectrum of disease is broad, including a few reported cases from China involving neurological symptoms, including strokes[13]. It is believed that the disease severity and mortality could be due to the cytokine storm or an imbalance in the function of angiotensin converting enzyme 2 (ACE2) caused by the virus, which disrupts the RAS[14].

The entry of SARS-CoV-2 into the human body is facilitated by the RAS and its regulator ACE2[15]. The RAS and ACE2 play a key role in maintaining physiological functions of kidneys, heart, and lungs. The kidneys, lungs, heart, and endothelium abundantly express ACE2 protein. Further, ACE2 regulates and maintains homeostasis of local concentration of ATII, a potent vasoconstrictor and pro-inflammatory agent, which enhances fibrosis and is a vital component of the RAS system in maintaining cardiovascular functions[16]. Two independent research groups proved that the viral spike (S) protein binds to ACE2 protein on tissue cells leading to direct membrane fusion between the host cell and the virus, facilitating the viral entry and release of viral RNA genome into the host cell[15,17]. Binding of SARS-CoV-2 to ACE2 protein results in the loss of ACE2 expression due to internalization and shedding with decreased degradation of ATII, which leads to several pro-inflammatory and pro-fibrotic actions with lung injury[18]. The viral entry is also dependent on the expression of transmembrane serine protease 2 (TMPRSS2), and the endosomal cysteine protease cathepsin B and L (CatB/L). In vitro studies have shown that the TMPRSS2 inhibitor camostat mesylate, along with the CatB/L inhibitor E-64d, inhibited viral entry into Caco-2 cells[19]. During the late phase of infection, SARS-CoV-2 can infect cells with Fc receptors which are involved in antibody mediated internalization in macrophages, monocytes, or B cells, even without ACE2 protein and TMPRSS2 expression[20], contributing further to a dampened immune response.

During an acute infection, an effective immune response is elicited for optimal pathogen clearance. In most individuals with SARS-CoV-2 infection, both innate and adaptive immune responses are activated leading to successful recovery. However, in severe cases of COVID-19, an excessive inflammatory innate response and deregulated adaptive host immune defense may cause tissue damage at both the viral entry site and systemic level. Autopsy findings in COVID-19 related deaths shows interstitial mononuclear inflammatory infiltrates lymphocytes in the lung and severe lymphopenia, with hyper activated T cells in the peripheral blood[21]. In addition, a decreased level of regulatory T cells was observed in severe COVID-19 cases. In severe cases of COVID-19 requiring intensive care in hospitals showed higher levels of inflammatory cytokines, including interleukin (IL)-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), tumour necrosis factor- α (TNF- α), and monocyte chemoattractant protein-1 (MCP-1) in serum, suggest a dysfunctional immune response triggering a cytokine storm that mediates wide-spread lung inflammation[22]. The release of free radicals along with cytokine storm causes damage to the host with multiple organ failure and severe ARDs. The circulating levels of G-CSF, interferon gamma-induced protein 10, MCP-1, macrophage inflammatory protein1 α , and TNF- α

are elevated in intensive care unit patients compared to those not requiring intensive care, further confirming the relation between cytokine storm, severity of COVID-19, mortality, and multiple organ failure[23].

Thromboembolism is another complication and cause of death in COVID-19. The main function of thrombin is to promote clot formation by activating platelets and converting fibrinogen to fibrin. Thrombin can augment inflammation *via* proteinase activated receptor-1, and its production is tightly controlled by the level of physiological anticoagulants like anti thrombin III, tissue factor pathway inhibitor and protein C system. During hyper inflammation, an imbalance in pro-coagulant-anticoagulant systems, which predisposes the patient to the development of micro-thrombosis, disseminated intravascular coagulation, and multi organ failure, were reported in severe COVID-19 pneumonia[24]. Disseminated intravascular coagulation, lower platelet count, and an increased d-Dimer evidenced in non survivors of COVID-19 is associated with poor prognosis[24]. Notably, endothelial cell death caused by COVID-19 leads to vascular leakage and induces cytopathic effect on airway epithelial cells[25]. Thus, the inflammatory mediators lead to vascular hyper permeability and stimulate endothelial cells that express ACE2 protein on blood vessels, which together with viral particles cause systemic inflammation, higher concentration of ATII, and induces tissue factor and plasminogen activator inhibitor 1 expression by endothelial cells *via* ATI receptors, leading to a hypercoagulable state. Thus, it is likely that dysregulation in RAS pathways contribute to cross talk between inflammation and thrombosis contributing to increased mortality. Patients with diabetes are now known to be at higher risk of severe clinical outcomes of COVID-19. Furthermore, insulin therapy itself has proven fatal in patients with COVID-19 and concurrent diabetes[26]. It is becoming increasingly apparent that an impaired adaptive immune response, characterized by chronic inflammation as seen amongst type 2 diabetes as well as obesity, can lead to abrupt systemic metabolic alterations contributing to increased production of inflammatory cytokines, fueling a cytokine storm resulting in poor outcomes[27]. Recent evidence also suggests that COVID-19 infection could precipitate acute metabolic complications of diabetes such as diabetic ketoacidosis and hyperglycemia[28]. The proposed mechanism is likely to involve ACE2 protein, which is expressed in pancreas including β -cells, and serve as a binding site or receptor for the SARS-CoV-2[29]. It is assumed that elevated circulating insulin levels with insulin resistance in type 2 diabetes underpins increased ACE2 expression in lung epithelial cells, and hence, contributes to severe disease associated with COVID-19 infection. Insulin resistance, a hallmark feature of type 2 diabetes, is known to elevate inflammatory cytokines[30], endothelial dysfunction[31] and procoagulant state[30] in this high-risk subgroup even before SARS-CoV-2 infection. Hence, as a result, insulin resistance potentially contributes to severity of COVID-19 associated with poorer outcomes amongst patients with pre-existing diabetes.

INSULIN AND VASCULAR INFLAMMATION

Insulin is a potent anabolic hormone, involved in stimulating glucose uptake in skeletal muscles and adipocytes, promoting glycogen synthesis in skeletal muscles, suppressing hepatic glucose production, and inhibiting lipolysis in adipocytes. The biological actions of insulin are initiated by binding to its insulin receptor, a heterotetrameric tyrosine receptor kinase which phosphorylates intracellular substrates like insulin receptor substrate (IRS-1). Interaction of tyrosine phosphorylated IRS-1 creates Src Homology, recruit's phosphatidylinositol 3 kinase (PI3K) and growth factor receptor-bound protein 2 (Grb-2). Upon phosphorylation and activation of PI3K, it subsequently phosphorylates and activates other downstream serine/threonine kinase, including Akt and atypical protein kinase C, culminating in many metabolic actions of insulin including glucose uptake through insulin responsive glucose transporter (GLUT) 4[32]. In addition to PI3K dependent insulin signaling, activation of Src homology Grb-2 results in the activation of GTP binding protein Ras, Raf, mitogen activated protein kinase (MAPK). MAPK dependent insulin signaling regulates the biological actions related to growth, mitogenesis, and differentiation. Thus, there are two major insulin signaling pathways: PI3K dependent signaling mediates metabolic actions and MAPK dependent signaling regulates non-metabolic mitogenic cardiovascular physiology. In the presence of insulin resistance and hyperglycaemia, shared insulin signaling pathways are impaired in metabolic and cardiovascular tissues, contributing to reciprocal relationship between insulin resistance and endothelial dysfunction[33].

The vascular functions of insulin are complex, with either protective or deleterious effects on vasculature[34]. A normal endothelial cell function is important in maintaining vascular tone and homeostasis by regulating vasodilation and constriction, thrombosis and fibrinolysis, platelet activation and leukocyte recruitment, and smooth muscle function. In addition to metabolic actions of insulin, PI3K signaling regulates the production of vasodilator nitric oxide (NO)[35]. Vasodilation increases blood flow and augments metabolic actions of insulin in skeletal muscle, regulates sodium homeostasis by enhancing sodium reabsorption in kidneys and thereby regulating blood pressure. A counterbalance is established by MAPK signaling in the endothelium, secreting vasoconstrictor endothelin-1, vascular smooth muscle cell (VSMC) proliferation, and pro-inflammatory activity. Expression of cellular adhesion molecules, including intercellular adhesion molecule-1 vascular cell adhesion molecule, are regulated by MAPK for modulating cell-cell interactions between vascular endothelium and circulatory inflammatory cells[36].

Under physiological conditions, insulin maintains a quiescent phenotype in VSMC [37]. VSMCs express both insulin receptor and insulin like growth factor receptor-1 (IGF-IR). At physiological concentrations of insulin stimulate translocation of insulin receptor and IGF-IR on VSMCs and increases cyclic guanosine monophosphate levels by releasing endothelial NO synthase 3 that evoke vasorelaxation. Insulin further attenuates VSMC contractility by regulating Rho induced increases in cytosolic calcium through calcium channels and inactivates myosin light chain phosphatase through PI3K/Akt insulin signaling. Insulin maintains a dedifferentiating state on VSMC through PI3K pathway and mediates VSMC migration through MAPK dependent pathway. In insulin resistant states, PI3K/Akt pathway is impaired and MAPK/RAS/Raf is increased, which preferentially signals to the mitogenic pathway as demonstrated in endothelial VSMCs[31]. A study in murine models has shown that both hyperglycemia and insulin resistance downregulate IRS-1 in VSMC and blood vessels with enhanced VSMC migration and proliferation in diabetic mice aorta promoting the formation of atherosclerotic lesions[38]. Hyperinsulinemia, in insulin resistant conditions can activate inflammatory pathways through enhanced advanced glycated end products (AGE) formation, reactive oxygen species (ROS) production, and elevated levels of circulating free fatty acids. Increased ROS and free fatty acids activate nuclear factor Kappa B (NF-kB) signaling pathway, which stimulates the production of pro-inflammatory cytokines, including TNF- α and IL-6. TNF- α through activation of Jun N terminal kinase pathway reduces insulin stimulated activation of PI3K/Akt/NO in endothelial cells and promotes atherosclerotic lesions. Furthermore, TNF- α stimulates expression of inflammatory proteins like C-reactive protein (CRP), an important marker of vascular inflammation and IL-6[38]. Thus, glucotoxicity and lipotoxicity associated with insulin resistance induce a pro-inflammatory milieu impairing vascular and endothelial function, promoting coronary heart diseases and atherosclerosis.

Insulin resistant states with impaired sensitivity to insulin mediated glucose disposal display impaired insulin mediated vasodilation, as well as endothelial dysfunction. In type 2 diabetes mellitus with underlying insulin resistance, insulin stimulated PI3K/NO pathway is selectively impaired and the compensatory hyperinsulinemia activate MAPK pathway, leading to enhanced vasoconstriction, pro-inflammation, increased sodium and water retention, and elevated blood pressure. Insulin resistance is also characterized by the presence of free fatty acids and AGE products, both are pro-inflammatory in nature. Hyperglycemia and insulin resistance supports viral proliferation in human monocytes, involves glycolysis with subsequent ROS production, and cytokine release including IL-1 β [38]. No studies have evaluated surrogate markers of insulin resistance for prognostic scoring in COVID-19 patients or the underlying mechanisms that contribute to disease severity in this group.

PORTAL CIRCULATION, RAS SYSTEM AND INFLAMMATION

The pancreas is a highly vascularized salivary gland which produces an array of digestive enzymes (acinar or exocrine cells), such as amylase, pancreatic lipase and trypsinogen, (released into duodenum) and pancreatic hormones (released into blood stream *via* splenic artery). The endocrine cells are distributed in cellular aggregates forming the islet of Langerhans, which are small, island-like structures within exocrine pancreatic tissue. The exocrine compartment constitutes 98% to 99% of the gland and the remaining 1% to 2% constitute endocrine cells with five different cell types, α -cells producing glucagon (15%-20%), β -cells producing amylin-, C-peptide and insulin-

(65%-80%), γ -cells producing pancreatic polypeptide (3%-5%), δ -cells producing somatostatin (3%-10%), and ϵ -cells producing ghrelin (< 1%)[39]. The dissimilar functions between the two compartments manifests different vascular organization, including vascular morphology and blood flow. The pancreatic islet blood flow (IBF), both basal and stimulated, is 5-10 times higher than that of exocrine pancreas, which is regulated autonomously from one another. The blood flow through islet capillaries significantly impacts nutrient sensing, paracrine communication, and final hormonal output, and hence any alterations in blood perfusion, either induced physiologically (*e.g.*, nervous input) or because of pathological changes (*e.g.*, fibrosis), could affect islets function[40].

The pancreas receives 1% of the cardiac output supplied by celiac artery (70%) and the superior mesenteric artery (30%). The venous pancreatic blood is drained into the portal vein. The islets are supplied with arterioles, branching into fenestrated capillaries constituting 7% to 8% of islet volume. The acini are drained through venules into intra lobular veins and islet into ductal venous system. A part of the venous blood enters the insula-acinar portal system where venules bridge islet capillaries to acinar capillaries to provide an interface[41]. There is compelling evidence that metabolic regulation of islet blood perfusion is done by metabolites like adenosine and adenosine triphosphate/adenosine diphosphate[42]. The perfusion of blood in islets and exocrine compartments are modified by local endothelial mediators, the nervous system (the parasympathetic and sympathetic nerves), and gastrointestinal hormones. The islets are more sensitive to endothelial mediators especially NO and the incretin hormones, and adipokines preferentially act on islet vasculature. The evidence from literature so far suggests that insulin present in high local concentrations stimulates IBF and is independently regulated from the whole pancreatic blood flow (PBF)[42].

The changes in the PBF are clinically relevant as changes in the blood perfusion may affect the pathogenesis of diabetes mellitus and other pancreatic diseases. The effects of other hormone system, like the RAS, in the pathogenesis of glucose intolerance, insulin resistance, and hypertension, are well reported. The presence of local RAS is reported in many tissues including heart, vasculature, brain, retina, liver, and pancreas [9]. Evidence from human and animal studies suggests that the local hyperactive RAS/ATII signaling pathways contribute to pathogenesis of diabetes and related complications. The relative risk of developing diabetes mellitus is reduced 25% by inhibiting RAS[43]. RAS components are found in acini, ducts, islets, endothelial cells, and its expression is modulated in different conditions, including hypoxia, pancreatitis, hyperglycemia, and diabetes mellitus. The conversion of angiotensinogen to vasoactive peptide angiotensin I (ATI) by renin, and further to ATII by ACE, occurs in most vascular systems in the body. The physiological activity of ATII is mediated by ATI and ATII receptors. The ATI receptors cause sympathetic activation facilitating norepinephrine release, vasoconstriction, sodium water retention, oxidative stress, and cell growth stimulation, while the ATII receptors cause anti-proliferative effects through kinins and vasodilation[9].

Under physiological concentrations, ATII constricts both exocrine and endocrine blood vessels and regulate the release of enzymes and hormones. Elevated levels of ATII in islet micro vessels, decreases IBF in healthy nondiabetic Sprague Dawley rats, and RAS blockade by ACE/ATI inhibitors increases blood flow to islet micro vessels, suggesting a role played by pancreatic RAS in maintaining islet perfusion and regulation of glucose stimulated insulin secretion[41]. Infusion of ATII in *in vivo* models, such as rats, caused vasoconstriction and delayed the first phase of insulin release after stimulus, the earliest detectable defect (insulin resistance) in development of diabetes mellitus. ATII has shown to induce vasoconstriction in a dose-dependent manner in islet arterioles and islet blood vessels regulating IBF. Furthermore, ATII stimulates the release of pancreatic juice *via* cholinergic afferent pathway thus regulating perfusion in exocrine pancreas as well[44].

Chronic hyper-glycemia or insulin resistance is characterized by vascular dysfunction especially with regard to the endothelium. The decreased bioavailability of NO diminishes endothelium dependent vasodilation, further favoring vasoconstriction in vascular beds. The mechanisms that diminish NO production are partially regulated by increasing the NO synthesis inhibitor, and increased formation of ROS leads to degradation of NO and dysfunction of VSMC, which lead to macro and micro vascular complications of diabetes[31]. In addition, chronic hyperglycemia causes endothelial cell death by affecting the serine threonine kinase Akt pathway. Diabetes mellitus is often associated with islet inflammation, and reduction in β -cell mass/cell number and cytoarchitecture, which of course may affect IBF. Studies on islet vasculature in insulin resistance mice models (ob/ob positive mice and GLUT4

negative mice) revealed a vascular plasticity with increased islet vessel area and decreased intra islet vessel density affecting β -cells and increased IBF is proposed to contribute to this [45]. Experimental studies in mice models have found that initial stages of disturbed metabolism increase IBF, as disease progresses β -cell mass decreases followed by decreased islet volume and IBF. Insulin resistance would stimulate an increase in IBF and increase delivery of insulin to the systemic circulation and insulin biosynthesis, a compensatory mechanism adopted by β -cells to restore euglycemic state seen as a prodrome to overt diabetes mellitus[45]. The secondary changes in the pancreatic and IBF associated with glucose intolerance could modulate the pathophysiology of diabetes mellitus.

Blood flow measurements have shown that the local inflammation mediated by the release of adipokines, and macrophage derive cytokines may augment IBF. Evidence from vagotomised rats after portal vein infusion of Intralipid® increases PBF 2-3-fold and IBF > 10-fold[46]. Administration of inhibitors of inflammation like palmitate decreases both PBF and IBF. Thus, pathological activation of innate immune system and inflammation may alter IBF as a secondary phenomenon[46]. Thus, therapies aiming to decrease augmented islet blood perfusion would improve clinical outcomes in these patients.

INSULIN RESISTANCE INCREASES THE SEVERITY OF COVID-19 IN DIABETES PATIENTS

Hyperinsulinemia in patients with insulin resistance and diabetes can lead to increased SARS-CoV-2 viral load, as insulin increases membrane expression of ACE2, which functions as a viral dock for entry into cells[47]. ACE2 is upregulated in initial stages of diabetes as an adaptive mechanism to counter ACE over activity. ACE2 controls blood pressure in a stable microenvironment by transforming ATII to AT1-7, lowering insulin resistance, oxidative stress, and increasing GLUT4 activity. In the later phases of diabetes ACE2 is downregulated due to glycosylation. However it is markedly increased in patients with diabetes and hypertension being treated with ACE inhibitors. Thus, ACE2 expression is increased in insulin resistant states, including type 2 diabetes. This in turn facilitates SARS-CoV-2 viral entry, which contributes to increased propensity to infection[18]. However, the SARS-CoV-2 infection decreases ACE2 expression as it is internalized along with virus, further leading to exaggerated ATII. The SARS-CoV-2 viral infection enhances ACE2 deficiency, dysregulation between the 'adverse' $ACE \rightarrow ATII \rightarrow AT1$ axis, and the "protective" $ACE2 \rightarrow AT1-7 \rightarrow MAS1$ receptor axis would contribute to strengthening the progression of inflammatory and thrombotic processes. The underlying insulin resistance in patients with type 2 diabetes predispose them to COVID-19 by creating more affinity to spike proteins and an increased inflammatory response, leading to more severe forms of infection with increased mortality[47].

Insulin resistance by itself can cause inflammation. Several COVID-19 studies show a strong association between the severity of the disease and the degree of dysregulated systemic inflammation biomarkers. A total of 56 individuals were included in an observational study and 18 (32.14%) of them were elderly patients, median age ≥ 68 years. The CRP level was considerably greater in the older group ($P < 0.001$) than in the younger and middle-aged groups. This study suggests that severe COVID-19 was observed amongst older patients with diabetes where interrelation between aging and inflammation is well established[3]. IL-6 a pro-inflammatory cytokine circulation elevation of 2 to 3-fold is observed in conditions of insulin resistance[31]. In comparison to non-diabetic and diabetic patients without COVID-19 infection, patients with COVID-19 infection with diabetes mellitus have higher IL-6 levels[48]. The accumulation of activated immune cells in metabolic tissues and inflammatory mediators, in particular IL-1 β and TNF- α , contribute to the onset and progression of insulin resistance. Hyperglycemia produces ROS *via* advanced glycation end products and activates immune response in diabetes patients. CRP, an acute-phase reactant usually associated with serious infection and inflammation is strongly correlated in insulin resistance and a powerful predictor of future cardiovascular event. Patients with COVID-19 and coexistent diabetes characterized by low grade chronic inflammation are more likely to develop a cytokine storm, leading to high risk of vascular hyper permeability state, multi-organ failure, and death[49]. Whether COVID-19 accelerates the existing metabolic perturbations associated with diabetes and insulin resistance or virally induced inflammation leads to insulin resistance resulting in poor prognosis needs to be explored further.

The findings of rapidly worsening glycemic control in patients with diabetes and COVID-19, requiring high doses of insulin to control elevated blood glucose, increased ketosis in older individuals indicate the possibility of pancreatic invasion by the SARS-CoV-2[50]. Investigation of ACE2 expression confirmed a higher expression in pancreas than lungs, and single cell RNA sequencing confirmed the expression in both exocrine and endocrine glands of pancreas[50]. Thus, SARS-CoV-2 may cause direct damage to insulin secreting pancreatic beta cells, and this may partly explain the worsening of glucose control in people with diabetes who do have some functional β -cells in reserve. According to Wang *et al*[51], 9 (17%) of 52 admitted COVID-19 pneumonia patients in Wuhan experienced pancreatic injury as evidenced by irregular serum amylase or lipase levels. Six of the 9 pancreatic injury patients had developed glucose intolerance[51]. Following viral entry into beta cells, ACE2 is downregulated, resulting in an increase in angiotensin levels and impaired insulin secretion. The direct cytopathic effect of SARS-CoV-2 replication, the systemic reaction to respiratory failure, and the harmful immune response caused by SARS-CoV-2 infection are all possible mechanisms of pancreatic injury[51].

Diabetes is linked with coagulopathy and thrombosis contributing to long term micro and macro vascular pathological complications. Higher d-Dimer levels are found in COVID-19 patients with diabetes[23]. Additionally, individuals with both obesity and diabetes are reported to have worse prognosis associated with COVID-19 infection, including potential thrombotic events such as stroke[49]. Considering 80% of patients with diabetes have coexistent hypertension, infection by SARS-CoV-2 may lead to deregulated blood pressure, with further increased risk of cardiovascular complications. Several publications have reported an increased risk of venous thromboembolism and pulmonary embolism amongst diabetes patients compared to the control group[52].

Patients with diabetes mellitus are more susceptible to the severe form of COVID-19, which is associated with poorer outcomes. Based on the evidence so far, we hypothesize that insulin resistance could be a key facilitator driving severe disease in COVID-19 in patients with diabetes. A better understanding of clinical and biochemical markers of insulin resistance for evaluating diabetes status in patients with COVID-19 might help in developing patient tailored treatment strategies (Figure 1). In addition real world evidence is required to test the utility of markers of insulin resistance as prognostic indicators in predicting disease severity in COVID-19.

RATIONALE AND CLINICAL IMPLICATIONS OF INSULIN RESISTANCE IN COVID-19 SEVERITY

A hypothesis that may partially explain the propensity of individuals with insulin resistance and with type 2 diabetes to develop more severe forms of COVID-19 is inflammation associated with a high concentration of insulin and activation of the RAS. The SARS-CoV-2 uses ACE2 protein for the host entry. Hyperactivity of RAS pathway due to increased ROS is implicated in the pathogenesis of diabetes. In the islets, ACE2 may modulate blood flow and morphology in order to maintain insulin secretion. A higher concentration of circulating insulin shifts the balance towards vasoconstriction, disturbing cardiovascular homeostasis and resulting in increased risk of thromboembolism and multiple organ failure as explained in Figure 2. Diabetes mellitus alters cytokine profile and aggravates a dysregulated immune response. "Cytokine storm" implicated in mortality of COVID-19 patients reflecting, at least in part, a state of insulin resistance and elevated insulin levels driving ACE2 expression, altered blood pressure, inflammation, endothelial dysfunction, and coagulation. The triglyceride glucose index (a surrogate marker for insulin resistance) was found to be associated with poor clinical outcomes in patients with COVID-19, according to a recent study[53]. Thus, COVID-19 which is otherwise a mild infection in majority of the population but much more severe and fatal in the context of people with diabetes, could be explained by above hypothesis.

Using surrogate markers of insulin resistance in clinical setting as a prognostic tool in conjunction with other disease severity markers for β -cell damage, RAS pathway, inflammation, and thrombosis would help in developing tailored management strategies for patients with COVID-19 and diabetes (Table 1). This could potentially improve outcomes in severely ill patients. The hyperinsulinemic-euglycemic clamp technique is the gold standard to measure hepatic and skeletal muscle insulin sensitivity. However, it is technically demanding, time consuming, and inappropriate to perform in acutely ill patients. Alternative methods based on fasting insulin and

Table 1 Clinical studies that reported insulin resistance markers in patients with Diabetes and coronavirus disease 2019

Ref.	Study design	Sample size	T2DM	Markers of IR	Age	Outcomes	Country
Wang <i>et al</i> [57], 2021	Retrospective	172	72	Hypertriglyceridemia (Fibrinogen, triglycerides, Serum ferritin)	66 (Median)		China
Ren <i>et al</i> [53], 2020	Retrospective	151	39	Triglyceride-glucose index	59.5 (Mean)	Severity and mortality	China
Alcántara-Alonso [58], 2021	Observational cohort	43	25	Triglyceride to high density lipoprotein cholesterol	57.19 (Mean)	Incidence of acute kidney injury, requirement of invasive mechanical ventilation, vasopressor support, days of hospitalization and mortality	Mexico

IR: Insulin receptor; T2DM: Type 2 diabetes mellitus.

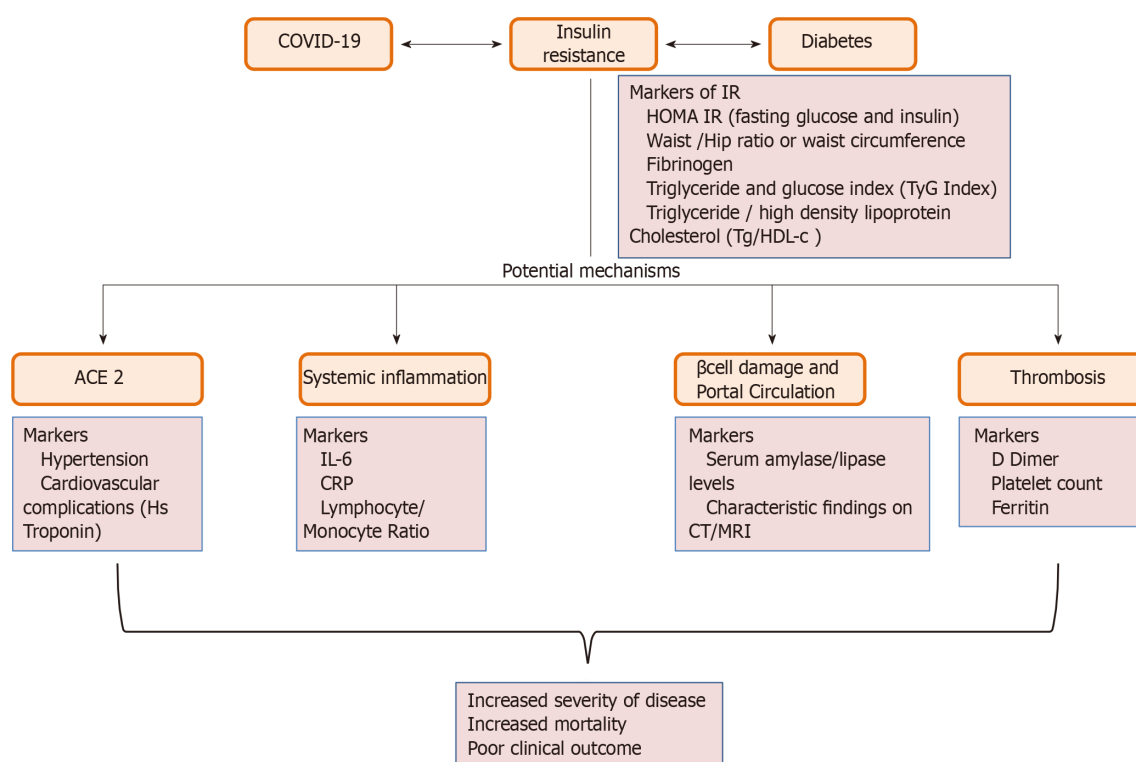


Figure 1 Insulin resistance may act as a bridging link between coronavirus disease 2019 and diabetes. The potential mechanism by which insulin resistance mediates coronavirus disease 2019 (COVID-19) severity is through angiotensin converting enzyme 2 protein, systemic inflammation, pancreatic β cell damage, and thrombosis. The potential markers of insulin resistance for evaluating diabetes status in patients with COVID-19 are also mentioned. CRP: C-reactive protein; CT: Computed tomography; IL-6: Interleukin-6; IR: Insulin receptor; MRI: Magnetic resonance imaging; T2DM: Type 2 diabetes mellitus.

glucose levels (HOMA), such as dynamic response to oral glucose loading, would also be impractical to perform in acutely unwell patients[54]. Alternatively, careful evaluation of biomarkers of inflammation (IL-6, CRP, fibrinogen, lymphocyte to monocyte ratio), thrombosis (d-Dimer, platelet number), and cardiovascular complications (Hs troponin), along with other parameters (fasting insulin and glucose) may serve as helpful prognostic tools in case of COVID-19 in the presence of diabetes. Furthermore, non-invasive strategies to assess the long-term consequences of insulin and PBF dynamics (contrast-enhanced ultrasound measurement) may also be helpful predict clinical progression[55,56].

CONCLUSION

Preliminary studies from various countries including United Kingdom and China

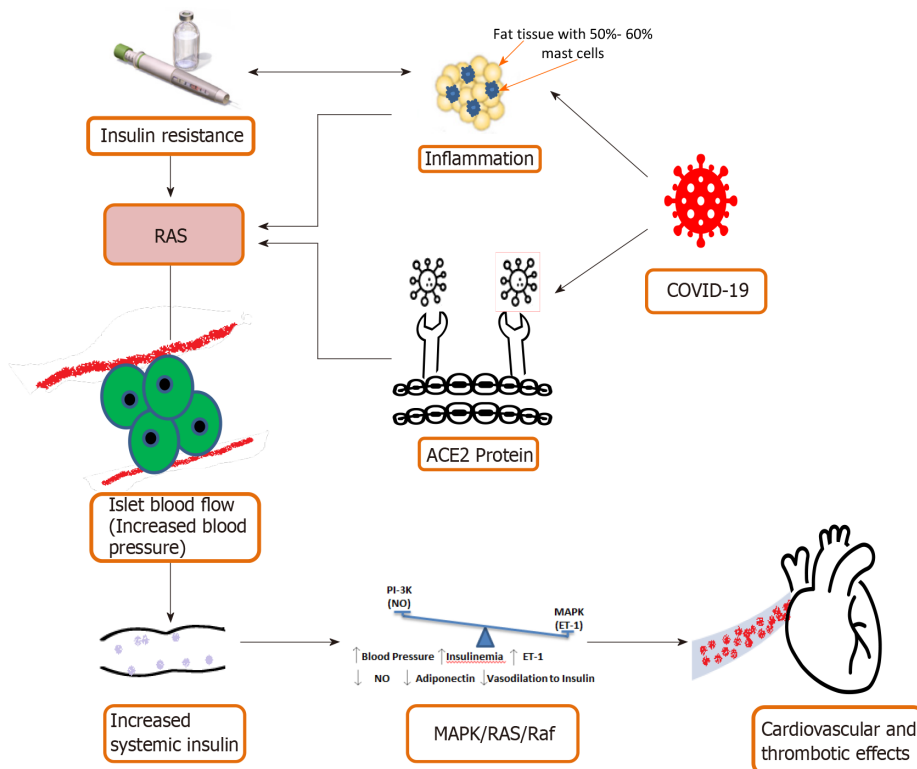


Figure 2 Inflammation linked to elevated insulin concentrations *via* portal circulation is one hypothesis that may help explain why patients with diabetes likely than others to develop extreme types of coronavirus disease 2019 diabetic patients[31,56]. The angiotensin converting enzyme (ACE) Protein is used by the severe acute respiratory syndrome coronavirus 2 to enter the host. The pathogenesis of diabetes is linked to hyperactivity of the renin-angiotensin system (RAS) pathway caused by increased reactive oxygen species (ROS). In order to maintain insulin secretion, ACE2 can modulate blood flow and morphology in the islets. A higher level of circulating insulin changes the balance from vasodilator to vasoconstrictor effects, disrupting cardiovascular homeostasis and increasing the risk of thromboembolism and multiple organ failure. COVID-19: Coronavirus disease 2019; MAPK: Mitogen activated protein kinase. Citation: Shah P, Lueschen N, Ardestani A, Oberholzer J, Olerud J, Carlsson PO, Maedler K. Angiopoietin-2 Signals Do Not Mediate the Hypervascularization of Islets in Type 2 Diabetes. *PLoS One* 2016; 11: e0161834. Copyright© The Authors 2016. Published by Open Access Article. Muniyappa R, Montagnani M, Koh KK, Quon MJ. Cardiovascular actions of insulin. *Endocr Rev* 2007; 28: 463-491. Copyright© The Authors 2007. Published by Oxford University Press.

suggest that COVID-19 is associated with increased severity and mortality in patients with diabetes. Insulin resistance-mediated metabolic and inflammatory processes are likely to be contributory factors. Patients with diabetes mellitus are also prone to significant dysglycaemia secondary to acute COVID-19, which in itself is detrimental and associated with poorer outcomes. Severe inflammation, either due to underlying metabolic syndromes or COVID-19 disease, can further worsen insulin resistance, which in turn would worsen dysglycaemia in diabetes mellitus, exacerbating the severity of COVID-19. We propose that surrogate markers of insulin resistance be evaluated for their prognostic value in predicting disease severity associated with COVID-19 amongst patients with diabetes. Since clinical and biochemical markers of insulin resistance are not routinely measured in COVID-19 patients, no real-world study has explicitly looked at the association between insulin resistance and disease severity. In addition, the expression of ACE2 in the pancreas is debated, and the role of ACE2 expression in the development of insulin resistance is also less explored.

The extent to which insulin resistance contributes to COVID-19 disease severity is not well known and may potentially be substantial. Population-based approaches to track individuals with insulin resistance and follow preventative treatment protocols could be a valuable method in the future to mitigate the impact of such pandemics.

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