Metabolic Syndrome and COVID 19: Endocrine-Immune-Vascular Interactions Shapes Clinical Course

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Abstract

The ongoing coronavirus disease 2019 (COVID-19) pandemic is caused by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Individuals with metabolic syndrome are at increased risk for poor disease outcomes and mortality from COVID-19. The pathophysiologic mechanisms for these observations have not been fully elucidated. A critical interaction between SARS-CoV-2 and the angiotensin-converting enzyme 2 (ACE2) facilitates viral entry into the host cell. ACE2 is expressed in pancreatic islets, vascular endothelium, and adipose tissue, and the SARS-CoV-2-ACE2 interaction in these tissues, along with other factors, govern the spectrum and severity of clinical manifestations among COVID-19 patients with metabolic syndrome. Moreover, the pro-inflammatory milieu observed in patients with metabolic syndrome may contribute towards COVID-19-mediated host immune dysregulation, including sub-optimal immune responses, hyper-inflammation, microvascular dysfunction, and thrombosis. This review describes the spectrum of clinical features, the likely pathophysiologic mechanisms and potential implications for the management of metabolic syndrome in COVID-19 patients.
The coronavirus disease 2019 (COVID-19) pandemic due to the global spread of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has unleashed an unparalleled economic and health crisis. Lacking effective pharmacological treatments or a vaccine, community mitigation strategies have been adopted across the world to reduce the spread and burden of COVID-19. Human SARS-CoV-2 infection leads to a spectrum of manifestations that include the asymptomatic carrier status, acute respiratory disease (ARD), and pneumonia. In general, in most immunocompetent individuals, COVID-19 is mild or asymptomatic. However, a proportion of symptomatic individuals require hospitalization, a risk that increases with age. Overall infection fatality rate (IFR) is around 1.4% but is many-fold higher in older individuals (1). Metabolic syndrome is a constellation of cardiovascular risk factors that include abdominal obesity, elevated blood pressure, dysglycemia, atherogenic dyslipidemia, pro-thrombotic state, and pro-inflammatory state (2). Clinically, metabolic syndrome is defined as the presence of three or more of the following factors: increased waist circumference (population and country-specific cutoff), hypertriglyceridemia (>150 mg/dL or on treatment for hypertriglyceridemia), elevated blood pressure (systolic ≥ 130 and/or diastolic ≥ 85 mm Hg or with a history of hypertension on treatment), reduced high-density lipoprotein cholesterol (<40 mg/dL in males; <50 mg/dL in females), and dysglycemia (≥100 mg/dL or on treatment for hyperglycemia) (2). Components of metabolic syndrome such as hypertension, type 2 diabetes mellitus (T2DM), and obesity are highly prevalent and significantly increase the risk of hospitalization and mortality in COVID-19 patients (3). To explicate the mechanisms that mediate this accentuated risk, the global scientific community has responded vigorously and rapidly with the publication of numerous studies in peer-reviewed journals and preprint servers. In this mini-review, we first examine the prevalence and relationships between metabolic syndrome and COVID-19. Next, we delineate the interactions between endocrine, immune, and vascular systems that underlie the pathogenesis and clinical course of COVID-19. Finally, we briefly discuss current therapeutic approaches in treating metabolic syndrome in the context of COVID-19, ongoing and prospective clinical trials, and the need for multidisciplinary collaboration to address the pandemic.

1. Risk associations between metabolic syndrome and COVID-19

1.1 Diabetes and COVID-19

Metabolic syndrome is emerging as a significant risk factor for worse outcomes in people with COVID-19 (3-14). T2DM is a significant factor for severe COVID-19 and its complications. Current data suggests that patients with T2DM are not at an increased risk for developing COVID-19. However, many studies have shown worse outcomes in patients with pre-existing diabetes. In a meta-analysis among a total of 44,672 patients with SARS-CoV-2 infection in China, COVID-19 patients with T2DM had 4.4 times the risk of death compared to non-diabetic patients (unadjusted relative risk, RR = 4.43, 95% CI = 3.49–
5.61)(9). In a retrospective longitudinal, multi-centered study from a cohort of 7,337 confirmed COVID-19 cases in Hubei Province, China, the fatality rate was higher in patients with T2DM relative to non-diabetic individuals (7.8% versus 2.7%). Indeed, 28-day all-cause mortality was higher in COVID-19 patients with T2DM [hazard ratio, HR: 1.70 (95% CI, 1.29–2.24)] (10). Likewise, patients with T2DM were more likely to develop complications such as acute respiratory distress syndrome (ARDS), acute kidney injury, and septic shock. It appears that hyperglycemia modulates this risk. The risk of death (1.1% versus 11.0%) was lower in the subgroup with blood glucose (<7.5 [5.2–7.5] mmol/L) compared with poorly controlled blood glucose group (> 7.6 [7.6–14.3] mmol/L) (10). In one of the largest studies to date, health data from 17.4 million adults in the UK were analyzed for risk factors associated with death from COVID-19 (14). After adjustment for other co-variates, uncontrolled DM was an independent risk for death (HR, 2.36, 95% CI 2.18-2.56). In a cohort of 5,700 COVID-19 patients in New York City, non-survivors with DM were more likely to have received invasive mechanical ventilation or ICU care compared with those who did not have diabetes (3). Similarly, in a multi-center observational study in people with diabetes hospitalized for COVID-19 (n=1317) in France, BMI was independently associated with the need for mechanical ventilation and/or death (15). These studies suggest that DM increases the risk of death and complications in COVID-19 and glycemic control is associated with lower fatality and complication rates.

1.2 Obesity and COVID-19

Higher COVID-19 complications in obese individuals is a significant concern due to the high prevalence of obesity (~42%) in the US (16). Although anthropometric data for understanding the role of obesity in COVID-19 patients are scarce and not reported in earlier studies from China and Italy, recent studies suggest that increased body mass index (BMI) is linked with poor prognosis. Cai et al. analyzed data from COVID-19 patients (n=383) in Shenzhen. They concluded that obese and overweight patients showed 2.4-fold greater and 86% higher odds, respectively, for developing severe pneumonia compared to normal-weight patients (17). Another study (n=124) in France reported that obesity (BMI >35 kg/m²) independently increased the risk for invasive ventilation (odds ratio, OR = 7.4, 95% CI = 1.6-33.1) (12). Furthermore, a study of COVID-19 patients (n=4103) in New York City showed that severe obesity (BMI >40 kg/m²) was a strong independent risk factor for predicting hospitalization (OR = 6.2, 95% CI = 4.2-9.3) (18). In a prospective observational cohort study using survey data from hospitalized patients (n = 16,749), obesity increased fatality risk (adjusted for age and gender) (HR = 1.37, 95% CI = 1.16-1.63) (13). Similarly, a large study from the UK, obesity was an independent risk factor for death with a strong BMI gradient (HR = 1.27 in BMI 30-34.9 kg/m²; 1.56 in BMI 35-39.9 kg/m²; and 2.27 in BMI > 40 kg/m²) (14). These studies suggest that obesity is a significant risk factor for severe COVID-19 and death.
1.3 Hypertension and COVID-19

Earlier studies have established that systemic hypertension is a risk factor for worse outcomes in patients with pneumonia and ARDS (19,20). It is plausible that the coexistence of hypertension in COVID-19 could enhance the risk of unfavorable outcomes. An early study from China did not find any association between hypertension and COVID-19 (21). However, in a pooled analysis of studies in China, Lippi et al. found that hypertension was associated with a ~2.5-fold increased risk of severe COVID-19 and mortality (22). Nevertheless, all the studies reported so far do not account for potential confounding factors such as age and other cardiovascular diseases in the estimation of any causal role of hypertension. Also, in more diverse populations as in the US and UK, hypertension is frequently present in COVID-19 (3,14). In a large study from the UK, accounting for age and sex, hypertension increases the risk of in-hospital death (HR = 1.22, 95% CI =1.15-1.30). However, after adjusting for other confounders, the presence of hypertension increased the risk slightly (HR =1.07, 95% CI = 1.00-1.15) (14). Although the magnitude of the risk varies among the studies, it appears that hypertension contributes to severity and death associated with COVID-19.

Age (> 60 yr, RR~2-8 times), male sex (RR~2), and components of the metabolic syndrome each independently increase the risk of death (RR = 1.5-2.5). Thus, a 62-year-old white male with a BMI of 32 kg/m² and T2DM has ~ 15-fold higher risk when compared with a 50-year-old white male with no co-morbidities. Compared to whites, blacks and Asians have a higher risk for death (~1.7 fold) due to COVID-19 (14). The data is clear that metabolic syndrome accentuates the risk of COVID-19 complications, including death. However, the pathophysiological mechanisms that underlie this increased risk are unclear and are a topic of investigation.

2. Pathophysiology of COVID-19

2.1 Clinical Course and Manifestations

The clinical manifestations of COVID-19 vary and include the asymptomatic carrier status, mild respiratory illness, pneumonia, and ARDS and multiorgan failure (5,23). The most commonly reported age group for COVID-19 patients is 45–60 years with an average median age of 47 years, the mean incubation period is ~5 days, and 98% of those who develop symptoms will do so within 12 days (5,23-27). The prevalence of asymptomatic cases varies (20-86% of all infections) and is a significant contributor to the rapid spread (6,28-31). The virus is contagious and spreads through contact and airborne transmission (32). There is substantial transmission even among asymptomatic carriers (30,33). In addition to a laboratory-confirmed SARS-CoV-2 infection, patients with ARD manifest with fever, fatigue, respiratory (cough, dyspnea) or gastrointestinal (loss of taste, nausea, diarrhea, vomiting)
symptoms, and no significant abnormalities on chest imaging (7, 23, 34). Patients with pneumonia have respiratory symptoms and positive findings on chest imaging. Severe pneumonia can present as ARDS leading to severe hypoxia, respiratory failure, multiorgan failure, shock, and death (7, 23, 35). Myocarditis, ischemic myocardial infarction, cardiac arrhythmias, and acute neurological stroke are part of COVID-19 (36, 37). The clinical course and severity of COVID-19 depend on the viral load, timing and magnitude of the host response to virus, age and sex of the individual, and presence of underlying co-morbidities (Figure 1).

2.2 Pathology and Laboratory Abnormalities in COVID-19

Most patients with COVID-19 have mild symptoms that do not require hospitalization. Lymphopenia, elevated lactate dehydrogenase (LDH), neutrophilia, increased C-reactive protein (CRP), mild increases in liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)), higher levels of D-dimer, ferritin, and pro-calcitonin are often observed in these patients. Persistent lymphopenia and elevated D-dimers, CRP, lactate, and pro-calcitonin are known predictors for severe COVID-19 (38). Radiologically, bilateral multi-lobar ground-glass opacifications are typically seen in the periphery of lower lobes of the lung (35). On histopathology, diffuse alveolar damage, hyaline membranes, interstitial edema, activated pneumocytes, infiltration of mononuclear inflammatory infiltrates, capillary congestion, microvascular thrombo-emboli, thrombi in small pulmonary arteries, and endothelialitis were frequently present (39-41). Interstitial edema, thickening of membranes, microvascular and venous thrombi may contribute to impairment in oxygen diffusion and ventilation/perfusion (V/Q) mismatching that leads to profound and rapid worsening of hypoxemia observed in these patients.

2.3 Cell Entry Mechanisms of SARS-CoV-2

Efficiency of SARS-CoV-2 entry into host cells is a significant factor that influences the pathogenesis of COVID-19. Coronaviruses are enveloped, single-stranded, positive-sense, RNA viruses belonging to the family *coronaviridae* that can infect both humans and mammals (42). SARS-CoV-2, SARS-CoV, and Middle East respiratory syndrome coronavirus (MERS-CoV) belong to the genus of β coronaviruses (43). Cell entry is initiated by virus binding to a cell surface receptor, followed by entry into endosomes and finally fusion of viral and lysosomal membranes delivering RNA cargo to the cytosol. A viral surface spike protein (S) is critical for cell entry. This S glycoprotein has two subunits; S1 subunit responsible for binding to the host cell receptor through the receptor-binding domain (RBD) and S2 subunit that facilitates the fusion of the viral and cellular membranes after it is cleaved from S1 by proteases (44, 45) (Figure 2). SARS-CoV-2 virus attaches to the host cell membrane-bound angiotensin-converting enzyme 2 (ACE2) that is expressed in many cells, including the respiratory epithelial cells (type II alveolar
epithelial cells), myocardium, Leydig cells and cells in seminiferous ducts in the testes, vascular endothelial cells, proximal renal tubular cells, gastrointestinal epithelial cells, urothelial cells lining the bladder, alveolar monocytes, macrophages, and in both exocrine pancreas and pancreatic islets (43,46-48). Once the S protein engages ACE2 on the cell membrane, the target cell proteases, transmembrane serine protease 2 (TMPRSS2), and the pH-dependent cysteine protease cathepsin L in the lysosomes cleave the S-protein for cell entry. A feature unique to the SARS-CoV-2 virus is that the S glycoprotein harbors a furin cleavage site between the S1 and S2 subunits (49). Furin may pre-activate S protein and facilitate CoV-2 entry into cells that have a low expression of cellular proteases (e.g., TMPRSS2) (50). Thus, interference in the binding of spike-RBD to ACE2 (e.g., by neutralizing antibodies) or factors that modulate ACE2, TMPRSS2, and furin activity/expression are likely to affect viral infectivity.

2.4 Innate and Adaptive Immune Responses to SARS-CoV-2 Infection

Once the virus enters the cells, innate immune cells recognize the invasion of the virus by pathogen-associated molecular patterns (PAMPs) (51). Single-stranded RNA (ssRNA) bind to pattern recognition receptors (PRRs) and double-stranded RNA (dsRNA) bind to endosomal Toll-like receptors (TLRs such as TLR3 and TLR7) and cytosolic retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs) (51). These receptors subsequently stimulate signaling pathways that lead to the activation and nuclear translocation of transcription factors, nuclear factor-κB (NF-κB) and interferon regulator factors (IRFs) (Figures 2 and 3). These pathways lead to the secretion of type I interferons (IFNs) and pro-inflammatory cytokines/chemokines. Type I IFNs produced by macrophages, pneumocytes, and dendritic cells stimulate IFN-stimulated genes (ISGs) that inhibit viral entry and replication and enhance viral clearance (52-54). SARS-CoV-2-induced ISGs include IFN-induced transmembrane family (IFITM) proteins and lymphocyte antigen 6 complex locus E (LY6E), both known to inhibit viral cell entry (55,56). In addition, macrophages, monocytes, and neutrophils release cytokines such as pro-inflammatory tumor necrosis factor-alpha (TNF-α), and interleukin-1 (IL-1), IL-6, and chemokines, CXC-chemokine ligands [CXCL10, CXCL2, CXCL8, CXCL9, and CXCL16] and CC-chemokine ligands [CCL2, CCL2, CCL8] (57). These chemokines recruit T or natural killer (NK) cells (CXCL9 and CXCL16), monocytes/macrophages (CCL8 and CCL2), and neutrophils (CXCL8) (57,58) (Figure 3). These cytokines play a significant role in SARS-CoV-2 driven hyper-inflammation in the cytokine storm syndrome leading to multiorgan failure. Although not completely elucidated, the SARS-CoV-2 virus employs multiple mechanisms to evade immune mechanisms including, conformational changes in the S protein and inhibition of PRR signaling leading to attenuation in type I IFN response (50,59).

Innate immune response prime cells of the adaptive immune network. PRR activation in antigen-presenting cells (APCs) present virus-derived peptides to naive CD4+ T cells and activate them (60).
Activated CD4+ T cells help B-cell antibody production and also undergo differentiation to effector T helper (Th) cells that release various cytokines such as IFN-γ, IL-4, and IL-17 (60). Activated CD8+ T cells cause apoptosis of viral-infected cells (61). Lymphopenia is a characteristic finding in moderate and severe COVID-19, specifically lower CD4+ and CD8+ T cell count when compared with patients with mild disease (62-68). The mechanisms for lymphopenia are not known, but elevated levels of IL-6 and TNF-α may cause T cell apoptosis (66,69). Interestingly, SARS-CoV-2 reactive CD4+ T cells were present in 40-60% of unexposed individuals suggesting cross-reactive T cell recognition to common circulating CoV (70). The SARS-CoV-2 virus elicits a robust B-cell response with seroconversion occurring 7-14 days post-infection, including neutralizing antibodies against the RBD sequence of the spike protein required for cellular entry of the viruses (71). Indeed RBD-specific IgG+ memory has been demonstrated in recovered COVID-19 patients (72).

Determinants of inter-individual variability of clinical manifestations following SARS-CoV-2 infection are not known. However, the temporal kinetics of type I IFN response and the presence or absence of hyperinflammation appear to underlie the pathogenesis of severe COVID-19, as observed in SARS (52,53,69,73-75). A timely and robust type I IFN response, regulated inflammation, appropriate T cell response, and a vigorous B-cell response may contribute to inhibition of viral replication in asymptomatic individuals or with mild COVID-19 (Figure 1). However, delayed type I IFN response and high viral replication may shift the balance to hyperinflammation and impaired T cell response (Figure 1 and 3) (52,53,69,73-77). Indeed, low lymphocyte count and elevated levels of CRP and LDH are significant predictors of severe COVID-19 (78,79).

2.5 SARS-CoV-2, Hyperinflammation, and Microvascular Endothelium

Elevated D-dimers, degradation products of fibrin, and presence of extensive microvascular thrombi in COVID-19 suggest a hypercoagulable state with excess formation of fibrin, reduced fibrinolysis, endothelial dysfunction, and increased vascular permeability (38-41). During an infection, the interaction between endothelium, platelets, innate immune cells, and coagulation factors leads to a thrombotic state in a process termed immune-thrombosis (Figure 3) (80). PRR activation pathway and IL-6 stimulate monocytes tissue factor (TF) expression. TF activates the extrinsic coagulation pathway. Neutrophil extracellular traps (NETs), composed of cell-free DNA, histones, and enzymes such as myeloperoxidase and neutrophil elastases are released by neutrophils and play an important role in innate immunity (81). NETs recruit platelets by binding to von Willebrand factor (vWF) and activate factor XII and TF to trigger the contact (intrinsic) and extrinsic coagulation pathways, respectively (81). NET levels were elevated in COVID-19 patients and positively related to CRP, LDH, and neutrophil counts (82). Interestingly, sera from individuals with COVID-19 triggered NET release from control neutrophils in
vitro (82). Levels of vWF, fibrinogen, and factor VIII were elevated in COVID-19 (83). The contact and extrinsic pathways converge to activate thrombin, which subsequently converts fibrinogen to fibrin. Fibrinolysis is regulated by the balance of tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) activity. Elevated PAI-1 levels favor a hypofibrinolytic state and increased fibrin formation. SARS-CoV-2 interaction with ACE2 expressed in the endothelium could potentially lead to endothelial dysfunction and a hypercoagulable state.

2.6 Angiotensin II, Angiotensin-Converting Enzyme, and SARS-CoV-2

ACE catalyzes the conversion of the prohormone, angiotensin I to the octapeptide, angiotensin II (AngII), whereas ACE2 converts AngII to angiotensin 1-7. AngII, through the activation of Ang II type 1a receptors, induces vasoconstriction and proliferation, but angiotensin 1-7 vasodilates and suppresses cell growth. In patients with ARDS, an increased ratio of pulmonary ACE/ACE2 leads to ambient increases in AngII (84). Indeed, once bound to ACE2, SARS-CoV downregulates cellular expression of ACE2, which favors increased AngII action and acute lung injury (85). Whether SARS-CoV-2 causes down-regulation of pulmonary ACE2 is unknown. However, blocking ACE or AngII receptors (AR) can be hypothesized to provide benefit in the setting of COVID-19. In a retrospective, multi-center study that included 1,128 adult patients with hypertension diagnosed with COVID-19, use of ACE inhibitors (ACEIs)/AR blockers (ARBs) was associated with lower all-cause mortality (ACEI/ARB group versus the non-ACEI/ARB group; adjusted HR = 0.42, 95% CI = 0.19-0.92) (86). However, in two large studies of COVID-19 patients, ACEI or ARB use did not affect the risk of contracting SARS-CoV-2 or COVID-19 complications, including death (87,88). Prospective randomized controlled trials (RCTs) are needed to address the role of ACEI/ARBs in COVID-19.

3. Possible Mechanisms Underlying Increased Risk of COVID-19 Complications in Metabolic Syndrome

Age, sex (male), hypertension, obesity, and T2DM independently increase the risk of complications and death due to COVID-19. The mechanisms that underlie this increased risk are unknown. Results from ongoing studies will provide us with more clarity in the future. However, based on currently available evidence and from prior studies in rodents and clinical manifestations in SARS and MERS, we propose possible mechanisms that accentuate the risk.

3.1 Sex Hormones, SARS-CoV-2, and COVID-19

Men are more prone to contract the SARS-CoV-2 virus and at higher risk for severe complications and mortality (3,4 351,5-14). Similarly, men had a higher mortality rate in the SARS epidemic due to SARS-
CoV-1 in 2003 (89). This sexual dimorphism can be ascribed to differences in sex-steroid hormones and the number of X chromosome-linked genes modulating immunity (90,91). Levels of TLR7, a gene encoded on the X chromosome is higher in females than males. TLR-dependent type I IFN responses are robust in women when compared with men (91). Indeed, male mice were susceptible to death and manifested severe lung pathology compared with female mice (92). Inflammatory monocytes/macrophages were higher in male mice. However, ovariectomy or administration of estrogen receptor antagonists to SARS-CoV-1 infected mice reduced survival compared with control female mice (92). Estrogen is known to reduce viral replication and inhibit monocyte/macrophage recruitment (Figure 2) (92). Tamoxifen, an estrogen receptor agonist, inhibits SARS-CoV-2 in vitro (93). In contrast, gonadectomized mice or administration of anti-androgen, flutamide does not alter the higher mortality in male mice with SARS-CoV-1 infection (92). Expression of ACE2 located on the X chromosome and TMPRSS2, an androgen-responsive gene appears to be similar in both sexes (94). Estrogen reduces viral load, enhances type I IFN response, and inhibits recruitment and activation of monocytes/macrophages. Thus, it appears that the protective effect of estrogenic milieu may explain the sex bias in survival in COVID-19.

3.2 Diabetes Mellitus and COVID-19

Multiple mechanisms may play a role in the increased susceptibility of complications in diabetic COVID-19 patients. Increased cellular binding and infection of SARS-CoV-2 is possible due to the enhanced expression of ACE2 in the lung, kidney, heart, and pancreas, as observed in rodent models of DM (95,96). Insulin administration decreases ACE2 protein expression in the lungs of diabetic mice (96). Liraglutide, a glucagon-like peptide-1 (GLP-1) agonist, restores reduced mRNA expression in the lungs of diabetic rats (97). Rosiglitazone, a thiazolidinedione (TZD), upregulates vascular ACE2 protein expression in hypertensive rats (98). Similarily, atorvastatin and fluvastatin increases cardiac ACE2 protein expression in rats (99,100). Circulating levels of furin, a cellular protease involved in facilitating viral entry by cleaving the S1 and S2 domain of the spike protein, are elevated in patients with DM (101). Furin pre-activates the spike protein and allows SARS-CoV-2 to infect target cells with low expression of TMPRSS2 and/or lysosomal cathepsins (50). DM inhibits neutrophil chemotaxis, phagocytosis, and intracellular killing of microbes. Delay in the activation of Th1 cell-mediated immunity and a late hyper-inflammatory response is frequently observed in people with diabetes (102). Kulcsar et al. examined the effects of DM in a humanized mouse model of MERS-CoV infection on a high-fat diet (103). Following MERS-CoV infection, the disease was more severe and prolonged in diabetic male mice and was characterized by alterations in CD4+ T cell counts and abnormal cytokine responses. These findings are consistent with the immune and cytokine changes observed in COVID-19 characterized by lower
peripheral counts of CD4+ and CD8+ T cells, a higher proportion of pro-inflammatory Th17 CD4+ T cells, as well as elevated cytokine levels (7,8,73,75,104-106). Consequently, patients with DM may likely have blunted anti-viral IFN responses, and delayed activation of Th1 may contribute to the heightened inflammatory response. Microvascular endothelial dysfunction is a frequent manifestation in patients with metabolic syndrome (107). Hypo-fibrinolysis, elevated PAI-1 and complement levels, and increased platelet aggregation favors microthrombi formation (108,109). Furthermore, NETs in patients with established T2DM were higher compared to healthy individuals (110,111). These findings suggest that dysregulated immune response and microvascular dysfunction in T2DM may contribute to the poor outcomes in COVID-19.

3.3 Obesity and COVID-19

Various hypotheses have been proposed to contribute to the unfavorable prognosis in obese COVID-19 patients. Obese individuals have low-grade inflammatory state altering innate and adaptive immunity. Obese patients have a higher concentration of circulating pro-inflammatory cytokines like TNF-α, MCP-1, and IL-6, mainly produced by visceral and subcutaneous adipose tissue leading to a dysregulated pro-inflammatory response (112). Further, alterations in the metabolic profile of T cells in obesity may also impair the adaptive immune response (113). Patients with obesity often have compromised respiratory function characterized by decreased lung volumes, decreased diaphragmatic strength, increased airway resistance, and impaired gas exchange (114). Adipose tissue is known to be a reservoir for influenza A and the duration of viral shedding is protracted in obese individuals (115,116). ACE2 expression in adipose tissue is higher than that in the lung tissue and this shared viral tropism for both tissues may favor prolonged SARS-CoV-2 shedding in obese individuals (117). It is known that thrombosis is enhanced in obesity and given the increased frequency of pro-thrombotic events in severe COVID-19, it can be one of the mediators of higher morbidity. Lastly, microvascular endothelial dysfunction is present across different vascular beds (107), and is likely exacerbated due to SARS-CoV-2 infection.

3.4 Hypertension and COVID-19

Systemic hypertension is associated with the activation of the renin-angiotensin-aldosterone system (RAAS). The vascular effects of Ang II are mediated by the activation of the Ang II type 1 receptor (AT1R) and type 2 (AT2R) receptor. AT1R mediates the vasoconstrictive, hypertensive, proliferative, and inflammatory actions of Ang II, while AT2R activation counteracts these effects. Relative proportions of AT1R and AT2R in the endothelium determines the ultimate vascular effects of Ang II (118). The balance in ACE/ACE2 activity in the lungs determines the effects of Ang II (119). Estradiol decreases, while testosterone increases ACE activity in the lung (120). ACE, Ang II, and aldosterone are known to
modulate innate immunity (121-124). Activation of RAAS favors a pro-inflammatory and procoagulant state that may predispose to SARS-CoV-2-induced multiorgan failure. The precise role of RAAS in COVID-19 is a subject of intense investigation.

4. Management of Metabolic Syndrome in COVID-19:

Cardiometabolic syndrome is a risk factor for worse outcomes in COVID-19. Epidemiologic data from over 72,000 patients in mainland China demonstrated that the overall case fatality rate from COVID-19 was 2.3%, but the case fatality rate was higher with cardiovascular disease (10.5%), diabetes (7.3%), and hypertension (6%) (125). As per the reports from the National Health Commission of China, among the patients who died from COVID-19, those without any history of cardiac disease developed significant myocardial damage, underscoring the importance of cardio-protection in COVID-19 (126). Moreover, long-term sequelae of dysregulated metabolism have been identified in patients 12 years after infection with the 2003-2004 SARS-CoV-1 (127). A summary of treatment considerations in patients with cardiometabolic syndrome is summarized in Figure 4.

Patients with T2DM and without other co-morbidities who contract COVID-19 are at a higher risk for severe pneumonia, uncontrolled inflammatory response, and hypercoagulability (128). In addition, experiences of physicians from around the globe have identified that insulin requirements are disproportionately high among patients with severe COVID-19, suggestive of increased insulin resistance, when compared with non-COVID-19 critical illnesses (129,130). Therefore, early and optimal management of hyperglycemia is crucial among patients with DM (131). Although robust data on DM management in COVID-19 is currently lacking, approach towards managing hyperglycemia in COVID-19 patients with DM can be pursued using tailored therapeutic strategies guided by the established guidelines, and individualizing treatment based on the type of DM, presence of risk factors and co-morbidities, and the setting of the treatment: outpatient vs. inpatient (129,132-135).

The primary objective of outpatient management of COVID-19 patients with DM is to ensure optimal glycemic control and prevention of hospitalization. COVID-19 has already disrupted routine outpatient DM care, and due to the socioeconomic afflictions that come along with the pandemic, optimal dietary habits and physical activity will likely be hampered and will continue to take a hit for months after the pandemic resolves (136). Apart from encouragement on following the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), the national, and the state government guidelines on handwashing and social distancing, maximal utilization of telemedicine services should be promoted in order to support self-containment (129). In China, several online resources, including e-books and educational videos were utilized to cater to the diabetic population to minimize transmission of
infection during the COVID-19 outbreak (135). The decision to continue or stop an oral antidiabetic agent requires thoughtful judgment by weighing in the patient’s general condition and the risk for progression to severe respiratory disease (137). Metformin carries the risk of acute kidney injury and lactic acidosis. However, metformin has demonstrated anti-inflammatory effects in pre-clinical study, and in patients with T2DM, metformin reduces circulating inflammation biomarkers (138). Sodium-glucose cotransporter-2 (SGLT-2) inhibitors could also have to propensity to increase the risk for dehydration and euglycemic diabetic ketoacidosis (DKA). Patients on metformin or sodium-glucose transporter-2 (SGLT-2) inhibitors must be closely monitored and must be encouraged to maintain adequate fluid intake. Patients previously not on SGLT-2 inhibitors should not be started on this treatment during their COVID-19 illness (129). Glucagon-like peptide-1 (GLP-1) agonists have been previously shown to reduce the levels of systemic inflammation markers among individuals with T2DM and obesity (138). GLP-1 agonists could be continued if they are well-tolerated by the patients. Due to the risk of nausea and dehydration, patients who do not tolerate these medications should be closely monitored (129), and GLP-1 agonist naïve patients should not be started on this therapy. Emphasis must be placed on maintaining adequate hydration and regular intake of meals (129). DPP-4 inhibitors can be safely continued if the patient has been tolerating the medication well (129,139). Sulfonylureas can be continued during COVID-19 illness, but the patients need to be cautioned about the risk of hypoglycemia in case of reduced appetite and reduced oral intake. Patients who administer insulin at home must be encouraged to continue with insulin therapy, and adjust the dose based on the blood glucose levels (129). Frequent self-monitoring of blood glucose (every 4 hours) should be advised, and patients on continuous glucose monitoring (CGM) should continue to keep a close track of their glycemic control (129,136). Patients with T1DM should be advised to check for urinary ketones if they notice worsening of glycemic control during the illness (140). Patients with newly diagnosed T1DM can also be successfully managed through telemedicine by adequate education on insulin injection use and provision of CGM supplies, preferably free-of-cost when feasible, in order to avoid the barriers between patients and insurance companies (141). Another substantial at-risk population includes healthcare professionals (142). Healthcare workers with DM should preferably be given an option to defer deployment to COVID-19 centers and wards, and access to adequate amounts of high quality personal protective equipment should be ensured (129).

Inpatient management of hyperglycemia in COVID-19 patients with DM is critical, and several studies have consistently shown worse outcomes among hospitalized patients with DM and COVID-19 (128,143,144). Conversely, optimal glycemic control during hospitalization is associated with improved outcomes (10,131). In a large-sample retrospective cohort study from China, COVID-19 patients with well-controlled blood glucose levels (≤ 10 mmol/L or ≤ 180 mg/dL) were found to have lower levels of IL-6, CRP, and lactate dehydrogenase. They had higher lymphocyte counts and lower neutrophil counts
when compared to patients with poorly-controlled blood glucose levels (≥ 10 mmol/L or ≥ 180 mg/dL) (10). The HR for all-cause mortality was significantly lower in the well-controlled glycemia group when compared to the poorly-controlled group [0.13, 95% CI = 0.04–0.44; p < 0.001]) even after adjusting for age, sex, COVID-19 severity, co-morbidities and site effect (10). Furthermore, the well-controlled glycemia group exhibited lower frequencies of occurrence of ARDS, septic shock, disseminated intravascular coagulation, acute cardiac dysfunction, and acute kidney injury. These findings highlight the importance of achieving optimal glycemic control among patients hospitalized for COVID-19. Oral antidiabetic agents should be discontinued, and insulin should be used to achieve glycemic control in an inpatient setting (130,137,140,145). Severely ill DM patients with COVID-19 admitted to monitored units could develop high degrees of insulin resistance and are preferably managed using insulin infusion (129,146). Monitoring for hypoglycemia is crucial, especially among patients with ARDS who may need to be prone for ventilation, which may interrupt feeding (136). Patients with T2DM and obesity with underlying fatty liver disease may be at a higher propensity to experience a cytokine storm, and close monitoring of hepatic transaminases, ferritin, prothrombin time, fibrinogen, erythrocyte sedimentation rate, c-reactive protein, IL-6, and D-dimer is recommended in these patients (129,147-149). Precipitation of DKA by COVID-19 is being increasingly recognized, not only in patients with pre-existing DM, but also in previously healthy individuals (150,151). Treatment of DKA must be promptly initiated with frequent monitoring of blood glucose and anion gap. Intravenous hydration, correction of electrolyte abnormalities (hypokalemia, hypomagnesemia, hypophosphatemia), and insulin administration must be undertaken as per institutional DKA-management protocols and established guidelines (134). Due to the high prevalence of thromboembolic complications associated with COVID-19, pharmacologic prophylaxis should be instituted in all patients in the absence of contraindications (152). Following discharge from the hospital, close telehealth follow-up should be provided to ensure continued optimization of glycemic control.

An observational study from New York found no significant increase in risk for COVID-19 among patients taking five major classes of anti-hypertensives (thiazides, calcium channel blockers, ACEIs, ARBs, and beta-blockers) (87). A position statement from the European Society of Cardiology and the Heart Failure Society of America, the American College of Cardiology, and the American Heart Association recommended the continuation of ACE inhibitors/ARBs in patients with COVID-19 (153). Similarly, statins have been shown to upregulate ACE2 levels in rat models (154). However, due to the long-term cardiovascular benefits, in vitro evidence of suppression of IL-6-induced CRP expression by statins, and the emerging epidemiologic data on lower odds of mortality from COVID-19 among statin users, therapy with statins can be continued during COVID-19 illness (129,155).
5. Ongoing clinical trials

As of April 27th, 2020, a search for the term “COVID-19” on Clinicaltrials.gov yielded a total of 945 studies, with 27 completed studies and 417 actively recruiting studies. The potential effects of DPP-4 inhibitors on diabetes are going to be evaluated in a phase 3 (using sitagliptin; ClinicalTrials.gov Identifier: NCT04365517), and a phase 4 (using linagliptin; ClinicalTrials.gov Identifier: NCT04341935) randomized controlled trial (RCT). The aldose reductase inhibitor, AT-001 is being studied in a phase 2 single-center open-label clinical trial to evaluate its effects on cardiometabolic profile in hospitalized COVID-19 patients (ClinicalTrials.gov Identifier: NCT04365699). The renin-angiotensin system (RAS) is one of the key pathways that need further investigation among COVID-19 patients, especially given the conflicting opinions on the use of ACEIs/ARBs (129). An RCT based in Denmark plans on evaluating the effects of ACEI/ARB therapy on RAS, interferon and T cell signatures (ClinicalTrials.gov Identifier: NCT04351581). Similarly, the effects of RAS-modifying medications in COVID-19 are being investigated in several other clinical trials and observational studies (ClinicalTrials.gov Identifiers: NCT04364984, NCT04331574, NCT04330300). Other studies are investigating the effects of COVID-19 on complications of cardiometabolic syndrome, such as acute coronary syndrome, myocarditis, and venous thromboembolism (ClinicalTrials.gov Identifier: NCT04335162). To investigate the anti-inflammatory effects of statins, a phase 2 RCT is evaluating a combination of the Janus kinase (JAK) inhibitor, ruxolitinib and simvastatin in the prevention and treatment of respiratory failure in COVID-19 (ClinicalTrials.gov Identifier: NCT04348695).

6. Future Research and Directions

As clinical and pre-clinical data continue to amass rapidly, more insights into the biology of SARS-CoV-2 and the pathophysiology of COVID-19 are being unveiled. However, several questions remain unanswered. From the broader questions of why cardiometabolic syndrome places an individual at a higher risk for severe COVID-19, to more specific issues such as pathophysiology of development of extreme forms of insulin resistance, precipitation of DKA, increased risk for myocardial injury, severe inflammatory response and hypercoagulability, and alterations in the immune system constitute topics for future research. Furthermore, data on ethnic and geographic variations in susceptibility to SARS-CoV-2 infection may shed light on mechanisms that link dysregulated metabolism and clinical severity of COVID-19. Finally, ongoing studies aimed at exploring genetic determinants of risk and severity of COVID-19 will offer additional insights (156).
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Figure Legends

Figure 1. Clinical course and innate immunity in COVID-19

Time course of clinical presentation and course, type I interferon (IFN) response (green), and inflammatory monocyte/macrophage recruitment and cytokine production (red). Timely and robust type I IFN response and regulated inflammatory monocyte/macrophage and cytokine levels limits viral replication in patients with mild/moderate COVID-19. High viral load with delayed and suboptimal type I IFN response, exaggerated inflammatory monocyte/macrophage recruitment, and cytokine storm is characteristic of severe COVID-19. Neutrophilia, lymphopenia, elevated LDH, and high c-reactive protein levels predict severe COVID-19.

Figure 2. Cellular entry of SARS-CoV-2 and initial innate immune mechanisms

The initial step in cellular entry of the virus is the binding of SARS-CoV-2 spike protein to cell surface angiotensin-converting enzyme 2 (ACE2). Cellular proteases such as TMPRSS2 and furin are involved in priming of the S protein, which involves cleavage at the S1/S2 domains. This allows the fusion of the virus to the cell surface. Once inside the cell, SARS-CoV-2 viral sensing involves activation of the toll-like receptor (TLR7) to stimulate the production of type I interferons. There is also activation of inflammatory monocytes/macrophages and the production of cytokines/chemokines. ACE catalyzes the conversion of angiotensin I to the octapeptide, angiotensin II (AngII), whereas ACE2 converts Ang II to angiotensin 1–7. Ang II, through the activation of Ang II type 1a receptors, induces vasoconstriction and proliferation, but angiotensin 1–7 stimulates vasodilatation and suppresses cell growth. TMPRSS2, transmembrane protease, serine 2; GLP-1 agonist, glucagon-like peptide-1; and TZD, thiazolidinedione.

Figure 3. Immune and endothelial interactions in COVID-19

SARS-CoV-2 infection of cells stimulates type I IFN response and recruitment of inflammatory monocyte and macrophages. Activated monocytes/macrophages release cytokines/chemokines such as IL-6, TNF-α, IL-8, CCL-2, CCL-4, and CCL-14 leading to hyperinflammation. Infection of endothelial cells and activation by inflammatory cells and cytokines trigger coagulation pathways, stimulates platelet aggregation, induces microvascular dysfunction, and generates microthrombi formation. IFN, interferon; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin 6; IL-8, interleukin 8; IFNγ, interferon-gamma; CCL2, chemokine (C-C motif) ligand 2; CCL4, chemokine ligand 4; CCL14, chemokine ligand 14; and SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Figure 4. Management of metabolic syndrome in COVID-19
Figure 2
MANAGEMENT OF METABOLIC SYNDROME IN COVID-19

**Outpatient management:**
- Encourage regular hand washing and social distancing as per WHO and CDC guidelines.
- Maximize utilization of telehealth visits and facilitate easy remote healthcare provider access to patients.
- Oral anti-diabetic drugs can be continued in consultation with a primary care or endocrinologist.
- Potential risks with oral anti-diabetic agents:
  - Metformin: acute kidney injury, lactic acidosis.
  - SGLT-2 inhibitors: dehydration, euglycemic ketoadiposis.
  - GLP-1 agonists: nausea, dehydration, reduced carbohydrate intake.
- Sulfonlureas and meglitinides: hypoglycemia.
- Encourage adequate fluid intake and consumption of regular and nutritious diet.
- Patients on insulin should continue their current regimen.
- Blood glucose should be closely monitored (every 4 hours, including pre-meal and bedtime), and insulin dosage should be adjusted accordingly.
- Provide remote ancillary services to assist with obtaining diabetic testing strips, glucose monitors, and access to optimal nutrition.
- Encourage to continue at least moderate physical activity.
- Patients with T1DM must be encouraged to check urine ketones if changes are noted in their glycemic control.
- ACEIs/ARBs should be continued as per home regimen.
- Statins should be continued as per home regimen.

**Inpatient management:**
- Oral anti-diabetic agents should be discontinued.
- Weight-based basal and prandial insulin regimen should be initiated. Frequent monitoring of blood glucose is crucial.
- Severe insulin resistance, especially among patients admitted to monitored units, can be managed by intravenous insulin infusion.
- Patients with T1DM should be regularly monitored for urine ketones.
- Severely ill patients with T2DM with underlying fatty liver disease may be at risk for cytokine storm. Close monitoring of liver function tests, ferritin, IL-6, D dimer, ESR, and CRP should be performed.
- Patients with diabetic ketoacidosis should be managed as per institutional protocols and established guidelines. Intravenous hydration and replenishment of electrolytes (hypokalemia, hypomagnesemia, hypophosphatemia, and insulin infusion should be promptly initiated.
- ACEIs/ARBs can be continued in the absence of contraindications.
- Statins can be continued in the absence of contraindications.
- Pharmacologic prophylaxis for deep venous thrombosis should be administered to all patients with cardiometabolic syndrome in the absence of contraindications.

**Abbreviations:**
- T1DM: type 1 diabetes mellitus
- T2DM: type 2 diabetes mellitus
- SGLT-2: sodium glucose transporter-2
- GLP-1: glucagon-like peptide-1
- ARB: angiotensin receptor blocker
- IL-6: interleukin-6
- ESR: erythrocyte sedimentation rate
- CRP: C-reactive protein
- ACEi: angiotensin converting enzyme inhibitor