Coronavirus Disease 2019 and Cardiometabolic Disease

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Abstract: Cardiometabolic disease describes a combination of metabolic abnormalities that increases the risk of type 2 diabetes and cardiovascular diseases, including pathological changes such as insulin resistance, hyperglycemia, dyslipidemia, abdominal obesity, and hypertension, and environmental risk factors such as smoking, sedentary lifestyle, poor diet, and poverty. As the number of coronavirus disease 2019 (COVID-19) patients continues to rise, type 2 diabetes, cardiovascular disease, hypertension, and obesity, all components of, or sequelae of cardiometabolic disease, were identified among others as key risk factors associated with increased mortality in these patients. Numerous studies have been done to further elucidate this relationship between COVID-19 and cardiometabolic disease. Cardiometabolic disease is associated with both increased susceptibility to COVID-19 and worse outcomes of COVID-19, including intensive care, mechanical ventilation, and death. The proinflammatory state of cardiometabolic disease specifically obesity, has been associated with a worse prognosis in COVID-19 patients. There has been no evidence to suggest that antihypertensives and antidiabetic medications should be discontinued in COVID-19 patients but these patients should be closely monitored to ensure that their blood pressure and blood glucose levels are stable. Assessment of vaccination efficacy in cardiometabolic disease patients is also discussed.

Key Words: cardiometabolic disease, cardiovascular diseases, coronavirus disease 2019, diabetes, hypertension, obesity

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Cardiometabolic disease describes a combination of metabolic abnormalities that increases the risk of type 2 diabetes (T2DM) and cardiovascular diseases (CVDs), including pathological changes such as insulin resistance, hyperglycemia, dyslipidemia, abdominal obesity, and hypertension (HTN), and environmental risk factors such as smoking, sedentary lifestyle, poor diet, and poverty.[1–3] It can also be understood as a spectrum of interconnected pathophysiological changes to the cardiovascular system and associated metabolic organs resulting in significantly increased risk of T2DM and CVD. It is a multidimensional disease involving genetic, behavioral, and environmental factors, with increasing evidence that lifestyle changes and patient education can significantly reduce the risk of this disease.[4,5] On the spectrum of disease progression to T2DM and CVD is metabolic syndrome, which describes a common co-occurrence of previously mentioned metabolic risk factors for T2DM and CVD.[6–8] Currently, according to the Cardiometabolic Disease Staging (CDMS) system and the National Cholesterol Education Program's Adult Treatment Panel III, metabolic syndrome is diagnosed as patients having any 3 of the following 5 traits: (1) abdominal obesity measured as waist circumference ≥40 inches in men and ≥35 inches in women, (2) serum triglycerides ≥150 mg/dL or drug treatment for elevated triglyceride, (3) serum high-density lipoprotein (HDL) <40 mg/dL in men and <50 mg/dL in women or drug treatment for low HDL, (4) blood pressure ≥130/85 mm Hg or drug treatment for HTN, and (5) fasting plasma glucose ≥100 mg/dL or drug treatment for hyperglycemia.[5,8–10] While it is unclear whether cardiometabolic disease has a unique pathophysiology or is simply a collection of the risk factors of its individual components, cardiometabolic disease and its components are important risk factors of atherosclerotic CVD and T2DM and, therefore, must be identified and managed throughout a patient's life. Thus, to reduce the chances of complications in at-risk patients, physicians must identify the signs of cardiometabolic disease and prescribe aggressive lifestyle changes centered around healthy nutrition, physical activity, and weight loss.

In the current coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, according to the December 29, 2020, epidemiological update by World Health Organization, the global cumulative number is over 79 million cases reported and over 1.7 million deaths globally, with 4 million new cases reported in the last week alone.[11–13] Additionally, the United States has over 20 million reported cases and over 300,000 deaths. While the overall mortality rate remains low from 1.4% to 2.3%, there has been strong evidence that the risk of mortality is significantly higher in patients with comorbidities such as T2DM, HTN, CVD, cancer, chronic kidney disease, congestive heart failure, obesity, and smoking.[14–17]

Obesity, T2DM, HTN, and CVD are all either components of or associated sequelae of cardiometabolic disease, and previous studies have established that they are all associated with increased severity of SARS-CoV-2 infection, requiring hospitalization due to infection, intensive care, intubation, or death. To date, there has been a significant number of papers that have reviewed components of cardiometabolic disease and their relationship to COVID-19 patients whether from an epidemiologic, risk factor, prognostic, or management point of view. This paper will consolidate these studies and focus on 4 main topics in regards to cardiometabolic disease: (1) susceptibility to SARS-CoV-2 infection, (2) severity of SARS-CoV-2 infection, (3) specific pathophysiology of SARS-CoV-2 in regards to obesity and a proinflammatory state, and (4) considerations for management of SARS-CoV-2 in these more vulnerable patients.

CARDIOMETABOLIC DISEASE AND SUSCEPTIBILITY TO SARS-COV-2 INFECTION

Many studies have provided information about patients with cardiometabolic disease and their susceptibility to the SARS-CoV-2 infection. In a retrospective, multicenter cohort study of confirmed COVID-19 patients in Wuhan, China, between December 2019 and January 2020, Zhou et al[18] found that 48% of patients had at least 1 comorbidity: 30% with HTN, 19% with T2DM, and 8% with CVD. Two additional studies in Wuhan also showed similar baseline characteristics of people who were infected with SARS-CoV-2, with T2DM, HTN, and CVD as the most common comorbidities.[19,20] This prevalence of comorbidities related to cardiometabolic disease has also been reported in other countries struck by the pandemic. In Italy, with a staggering overall case-fatality rate of 7.2% in March 2020, a review of deceased COVID-19 patients showed that 30%

had ischemic heart disease, 24.5% had atrial fibrillation, and 35.5% had T2DM.[21] Likewise, a prospective observational cohort study of 16,749 COVID-19 patients in 166 UK hospital reported that of the listed comorbidities, the 2 most common were chronic heart disease (29%) and uncomplicated T2DM (19%).[22] Unsurprisingly, this prevalence is also present in US samples, and as of May 2020, the most common underlying comorbidities in COVID-19 cases were CVD (32%) and T2DM (30%).[23] The common limitation among all these studies is that reported frequencies of individual symptoms and underlying health conditions, in addition to asymptomatic cases not captured in case surveillances, likely underestimate the true prevalence of COVID-19 patients and limit the ability to effectively estimate the risk of SARS-CoV-2 infection in cardiometabolic disease patients.

In addition to HTN, CVD, and T2DM, obesity is also associated with increased susceptibility to SARS-CoV-2 infection. In a study of hospitalized COVID-19 patients in the New York City area between March 2020 and April 2020, 41.7% of patients were overweight (body mass index [BMI] ≥25 kg/m²) or obese (BMI ≥30 kg/m²).[24] A study of COVID-19 patients' BMI provided further insight by reporting a positive correlation between the number of COVID-19 cases and the prevalence of patients with obesity and mean BMI.[25] A review of a commercial database aggregating the electronic health records of 26 major healthcare systems throughout the United States showed that a past diagnosis of metabolic syndrome was associated with 7 times increased odds of SARS-CoV-2 infection.[26] Regarding the components of cardiometabolic disease, the study also showed increased adjusted odds ratios (aORs) of COVID-19 with underlying diagnoses of HTN (aOR, 2.53), obesity (aOR, 2.20), T2DM (aOR, 1.41), and dyslipidemia (aOR, 1.70). Finally, a study of cardiometabolic profiles in 9005 COVID-19 patients in the UK Biobank showed that T2DM and obesity were associated with significantly increased odds of SARS-CoV-2 infection, while elevated levels of HDL and apolipoprotein A were associated with significantly decreased odds of infection.[27] Interestingly, in this final study, after controlling for HDL, the effects of BMI, T2DM, and hemoglobin A1c lost significance, suggesting that HDL may be a major mediator providing protection against COVID-19. The exact mechanism by which obesity predisposes patients to SARS-CoV-2 infection remains unclear; however, there are some key parameters to consider. Obesity and its complications can cause underlying cardiovascular, respiratory, metabolic, and thrombotic implications, all of which impair the body's ability to cope with the initial infection and also develop a sufficient immune response to it.[26,28,29] For example, obesity can reduce the cardiorespiratory reserve (such as decreased functional residual capacity and expiratory reserve volume) which in turn decreases cardiorespiratory fitness and increases susceptibility to immune-driven vascular and thrombotic effects.[29] Studies of obesity and increased risk of other infections including the influenza virus have previously documented this increased risk of infection in patients with obesity, supporting the findings of the current COVID-19 studies.[28–31]

These findings regarding the association of cardiometabolic disease components and the increased risk of COVID-19 are especially concerning when considering the staggering prevalence of said risk factors. In the United States from 1999 to 2018, the prevalence of obesity increased from 30.5% to 42.4%, while the prevalence of severe obesity increased from 4.7% to 9.2%.[32] In 2017, the age-adjusted prevalence of all heart diseases was 10.6%.[33] Additionally, the 2020 Diabetes Statistics Report estimated 34.2 million people to have diabetes (10% of the US population), with 88 million adults having pre-diabetes (34.5% of the adult US population).[34] With a drastically increasing number of patients who are at an increased risk of SARS-CoV-2 infection, not only is proper treatment and management of underlying risk factors crucial but prevention of exposure to the virus is fundamental as well as care for patients with cardiometabolic disease throughout the pandemic.

SEVERITY OF COVID-19 IN PATIENTS WITH CARDIOMETABOLIC DISEASE

While the global case-fatality rate of COVID-19 remains at around 2.3%, a report by the Chinese Center for Disease Control and Prevention provided a grimmer reality for patients with cardiometabolic disease. In an assessment of 44,672 confirmed cases in mainland China, the mortality rate was 10.5% for patients with CVD, 7.3% for those with diabetes, and 6% for those with HTN.[15] This finding raises concerns regarding the negative effect of cardiometabolic disease on the overall prognosis of COVID-19 patients. Numerous studies of COVID-19 patients support the increased severity of illness in patients with cardiometabolic disease. Patients who developed critical or mortal illness were significantly more likely to have underlying comorbidities such as HTN, CVD, and T2DM.[15,35–38] A deeper analysis of individual comorbidities associated with cardiometabolic disease shows that HTN and CVD were major indicators of COVID-19 severity. Data from 1590 laboratory-confirmed COVID-19 cases across China showed that after adjusting for age and smoking status, COVID-19 patients with HTN were 3 times more likely to be admitted to the intensive care unit (ICU) and to require invasive ventilation than patients without HTN.[38] This statistical significance of HTN and COVID-19 severity is reported in other smaller studies.[39,40] Similar findings of increased risk for severe illness requiring ICU care have been noted in patients with CVD as well.[35,38,40] A prospective cohort study of 5279 COVID-19 patients in New York City showed that heart failure was one of the strongest significant risks for intensive care, mechanical ventilation, discharge to hospice care, or death.[41] Overall, CVD and HTN are consistently reported as major risk factors of fatality in COVID-19 patients.

Furthermore, in addition to the increased severity of SARS-CoV-2 infection, patients with T2DM without other comorbidities had a significantly higher risk of critical issues such as uncontrolled inflammatory response, hypercoagulable state, and severe pneumonia, further raising the concern for the complexity of care for these patients.[42,43] Additionally, a retrospective, multicentered study of 7337 COVID-19 patients in Hubei Province, China, reported that the patients with preexisting T2DM required significantly more intensive care compared with patients without diabetes.[44] These additional intensive care measures for T2DM patients with COVID-19 included more antibiotics, antifungals, systemic corticosteroids, immunoglobins, vasoactive drugs, metformin, insulin, oxygen supplementation, and noninvasive and invasive ventilation, in addition to a significantly increased risk of mortality. Finally, a study of 10,926 COVID-19 deaths in the United Kingdom similarly observed increased risk of mortality with both obesity and T2DM, further emphasizing the worse prognosis for COVID-19 patients with cardiometabolic disease.[45]

Other studies also support the finding that obesity and patient BMI are major prognostic factors for severe COVID-19. Multiple reviews of patients from China showed that severe illness of COVID-19 was independently associated with increased BMI, with overweight patients 1.84-fold and patients with obesity 3.4-fold more likely to develop severe disease compared with normal-weight patients.[46–48] Studies of patients from France similarly reported that obesity and BMI were independently associated with an increased need for tracheal intubation and invasive mechanical ventilation.[49,50] A retrospective study of 3615 patients in New York City further reported that individuals with BMI ≥35 kg/m² were 2.2-fold and 3.6-fold more likely to be admitted to acute and critical care than those with BMI <30 kg/m².[51] There is substantial evidence that patients with obesity are at an increased risk even compared with overweight patients, and

this finding has important practical implications in the United States, where >40% of the adult population is obese.

Throughout the literature published during this pandemic, cardiometabolic disease and its components have been repeatedly reported as increasing the risk of severe illness in patients with COVID-19. For this reason, it is important that patients with such comorbidities should be considered without hesitation for intensive surveillance or treatment if necessary. Such interventions are key to protecting this vulnerable population and simultaneously attempting to mitigate the notable strain that severe COVID-19 and associated respiratory disorders place on critical care resources in the hospitals.

COVID-19, OBESITY, INFLAMMATION, AND IMMUNE RESPONSE

As obesity and increased BMI are associated with increased susceptibility to and severity of SARS-CoV-2 infection and its complications, an analysis of the current research available regarding the relationship between obesity and COVID-19 patients and specifically, proinflammatory state as a mediator, is important to consider. Past studies have shown that patients with cardiometabolic disease have increased levels of proinflammatory markers indicative of a dysregulation of the immune system, ultimately resulting in suboptimal immune responses.[52,53] Cardiometabolic disease components such as excess adipose mass is known to upregulate the levels of key immune factors such as C-reactive protein, tumor necrosis factor alpha, interleukin-6 (IL-6), and many other adipokines that are involved in chronic inflammatory conditions.[52,53]

Specifically, there have been numerous reports studying the relationship between IL-6 levels in patients with obesity and T2DM with COVID-19. One of the pathophysiological hallmarks of COVID-19 is the hyperactivation of the immune system with a prominent IL-6 response, resulting in severe inflammation and a chemokine storm, consequently causing systemic damage.[54,55] In an analysis of COVID-19 patients from China, serum IL-6 levels were significantly elevated in critically ill groups, with even higher serum levels for patients who eventually died.[54] This finding is further supported by other meta-analyses that similarly reported increased IL-6 levels in patients with severe COVID-19.[56,57] Other inflammation-related biomarkers such as C-reactive protein, serum ferritin, and D-dimer have also been recorded at significantly higher levels in patients with diabetes, indicating the susceptibility of such patients to rapid deterioration following a SARS-CoV-2 infection.[43] Numerous other inflammatory biomarkers have also been shown to be strong predictors of COVID-19 severity, including, cardiac troponin, procalcitonin, tumor necrosis factor alpha, ILs 2, 4, 8, 10, and interferon-gamma.[58,59] Ultimately, the elevation of inflammatory cytokines and other proinflammatory factors that already exist in patients with obesity and diabetes further increases their risk of severe COVID-19 infections due to the underlying hyperinflammatory state and a chemokine storm. However, the findings that support the association of these biomarkers with COVID-19 severity also suggest that said markers could be helpful for early detection and identification of patients who are at an increased risk.

Another important consideration that has been investigated regarding cardiometabolic disease patients with COVID-19 is the relationship between obesity and reduced vaccine efficacy. Past studies of diet-induced obese mice receiving vaccines for influenza and H1N1 have found evidence that prophylactic immune response is severely compromised.[60,61] Obese mice were shown to have reduced neutralizing antibody and memory T cell production after the vaccination due to the underlying hyperinflammatory state. This was worsened by an increased viral pathogenicity in the obese mice which further worsened the clinical presentation in these mice. This decreased production of T cells has similarly been documented in

individuals with obesity and T2DM and in COVID-19 patients, thus raising concerns for the care of these patients with a weakened adaptive immune response.[40,62,63] The impairment of B and T cell responses in patients with cardiometabolic disease is suspected to both delay the resolution of viral infection and decrease efficacy of vaccination. In a recent study of 248 healthcare workers who received the 2-dose regimen of the Pfizer COVID-19 vaccine, patients with under- and normal-weight (BMI $<25\,kg/m^2$) had a significantly higher antibody titer level than patients with preobesity and obesity (BMI $\geq30\,kg/m^2$), further providing evidence of a possible decrease in the efficacy of vaccination; however, whether this significant decrease in titer level will significantly affect the risk of infection is currently too early to be determined.[64] Therefore, despite the advent of a COVID-19 vaccine, physicians must remain aware of this increased risk in a large percentage of the US adult population and as more Americans receive the vaccine, it is imperative that these susceptible patients are closely monitored for both the onset of COVID-19 symptoms and the management of underlying cardiometabolic disease symptoms.

CONSIDERATIONS FOR MANAGEMENT OF COVID-19 PATIENTS WITH CARDIOMETABOLIC DISEASE

Due to the heightened susceptibility of patients with cardiometabolic disease and its associated components to SARS-CoV-2 infection, it is necessary to explore the multiple variables that must be effectively managed in such patients. An important topic of study has been angiotensin-converting enzyme 2 (ACE2) and its role in COVID-19 management. ACE2 in humans has been identified as the point of host cell entry by SARS-CoV-2, and infection occurs via the coronavirus spike proteins, which are activated into a receptor-binding domain and a membrane-fusion domain following cleavage by host cell proteases.[65,66] Because ACE2 is the receptor for SARS-CoV-2, a natural possibility is that cells with the greatest expression of ACE2 are the most vulnerable to infection. Thus, in the human body, the areas that are among the most at risk are the lung, heart, gastrointestinal tract, and kidney.[67,68] Furthermore, ACE2 expression is increased in adipocytes of those with obesity and T2DM, and this may be one of the variables responsible for the susceptibility of patients with cardiometabolic disease to COVID-19.[67,68]

To explore the relationship between ACE2 expression and COVID-19, studies have assessed the outcomes of patients taking antihypertensive medications. These medications that affect the renin-angiotensin-aldosterone system, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin 2 receptor blockers (ARBs), are known to increase the expression of ACE2.[69] Then, as previously discussed, because patients with HTN have been shown to be at an increased risk of severe COVID-19, it is important to explore whether antihypertensive medications added to the risk of SARS-CoV-2 susceptibility and disease severity due to an increase in ACE2 expression. Thus far, studies have not shown any significant association between ACEIs and ARBs and the odds of SARS-CoV-2 infection or developing severe COVID-19 symptoms, and this finding is consistent with a meta-analysis of PubMed, Google Scholar, EMBASE, and various preprint servers of COVID-19 clinical outcomes that similarly showed no increased risks of using antihypertensive medications during the management of COVID-19.[69–72] While the risk of COVID-19 susceptibility is elevated in patients with HTN, treatment with ACEIs and ARBs should not be discontinued as of this point. However, further investigation with larger randomized control trials regarding the expression of ACE2 and susceptibility to SARS-CoV-2 is still required.

The management of COVID-19 patients with diabetes is another important topic of consideration. In a recently published list of practical recommendations for the care of COVID-19 patients

with T2DM, an emphasis was placed on a continuous and reliable control of blood glucose level in treating COVID-19 patients.[73] Studies have shown that in individuals with T2DM, poorly controlled blood glucose (glycemic variability >10 mmol/L) yielded a markedly higher mortality rate compared with well-controlled blood glucose.[44,50] Additionally, levels of previously discussed biomarkers for severe COVID-19 illness, such as IL-6 and D-dimer, have been shown to be significantly elevated in hyperglycemic patients, further emphasizing the importance of proper management of insulin and monitoring of blood glucose.[74] Currently, insulin is the mainstay of glycemic control in COVID-19 patients, with basal or intermediate-acting insulin given daily, along with pre-prandial doses of short-acting insulin, and studies have shown that insulin-mediated blood glucose control with continuous glucose monitoring significantly improves the prognosis for hospitalized patients with COVID-19 and hyperglycemia.[73–75] For critically ill patients in the ICU, continuous intravenous insulin infusion is recommended with a target blood glucose of 140–180 mg/dL. It is also important to note that insulin requirement has been observed to increase drastically in patients with critical COVID-19.[73] The exact pathophysiology of this increase and its relevance to the treatment of COVID-19 remains unclear; however, one consideration is the current use of steroids in the management of severe COVID-19, which can induce hyperglycemia in these patients.[73]

Lastly, in the management of COVID-19 patients with T2DM, special attention should also be paid to several noninsulin therapies. Sodium-glucose transporter 2 inhibitors, which are known to exert both cardio- and reno-protective effects in patients, have been hypothesized to prevent cardiovascular and renal complications in COVID-19 patients with T2DM; however, the current recommendation is to withhold use in acute illness due to increased risk of dehydration and euglycemic ketoacidosis.[75–77] Dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists may be continued in noncritically ill patients. Metformin may be discontinued in patients with acute illness and dehydration due to risk of lactic acidosis, and pioglitazone should be stopped in critically severe COVID-19 cases. Ultimately, there is still much to be learned about the management of COVID-19 alongside cardiometabolic disease; however, treatment guidelines shared by experts emphasize the key importance of effective glycemic control.

CONCLUSIONS

Since the beginning of the current COVID-19 pandemic, there has been a significant amount of literature on the clinical relationship between cardiometabolic disease and COVID-19. Based on the research data available so far, the key findings are as follows. Cardiometabolic disease increases the susceptibility to SARS-CoV-2 infection, with a statistically significant increased odds of contracting the infection in patients with HTN, T2DM, obesity, and dyslipidemia. Patients with cardiometabolic disease are more likely to develop severe illness requiring ICU care, mechanical ventilation, discharge to hospice care, or death. Furthermore, CVD, HTN, T2DM, and elevated BMI were consistently reported as major risk factors of fatality in COVID-19 patients. There has been strong evidence that the underlying proinflammatory state of cardiometabolic disease, especially in patients with obesity, is strongly associated with worsening the hyperactivation of the immune system in COVID-19 patients, resulting in severe disease. Additionally, as vaccines become more available, it is important to closely monitor patients with cardiometabolic disease for an adequate adaptive immune response to the vaccine. Lastly, in terms of continuing current care for patients with cardiometabolic disease diagnosed with COVID-19, there is no evidence that continuing ACEis and ARBs for HTN management is associated with worsening of COVID-19 symptoms and as such, treatment

with these medications should not be discontinued. Similarly, there should be very close monitoring of blood glucose level in patients with T2DM with COVID-19 as poorly controlled blood glucose has been associated with a significantly elevated mortality rate. As the number of COVID-19 cases continues to rise, it is imperative that high-risk populations such as patients with cardiometabolic disease are closely monitored to check for early warning signs of COVID-19 so that the illness can be promptly managed.

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