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COVID-19 & OBESITY: BEYOND BMI

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ABSTRACT

The pandemic of novel coronavirus disease 2019 (COVID-19) has triggered an international crisis resulting in excess morbidity and mortality with adverse societal, economic, and geopolitical consequences. Like other disease states, there are patient characteristics that impact clinical risk and determine the spectrum of severity. Obesity, or adiposity-based chronic disease, has emerged as an important risk factor for morbidity and mortality due to COVID-19. It is imperative to further stratify risk in patients with obesity to determine optimal mitigation and perhaps therapeutic preparedness strategies. We suspect that insulin resistance is an important pathophysiologic cause of poor outcomes in patients with obesity and COVID-19 independent of body mass index. This explains the association of type 2 diabetes mellitus (T2DM), hypertension (HTN), and cardiovascular disease with poor outcomes since insulin resistance is the main driver of both dysglycemia-based chronic disease and cardiometabolic-based chronic disease towards end-stage disease manifestations. Staging the severity of adiposity-related disease in a "complication-centric" manner (HTN, dyslipidemia, metabolic syndrome, T2DM, obstructive sleep apnea, etc.) among different ethnic groups in patients with COVID-19 should help predict the adverse risk of adiposity on patient health in a pragmatic and actionable manner during this pandemic. **(Endocr Pract. 2020;26:923-925)**

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The pandemic of Severe Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), or novel coronavirus disease 2019 (COVID-19), has triggered an international crisis resulting in excess morbidity and mortality with adverse societal, economic, and geopolitical consequences. The clinical sequelae from COVID-19 infection range broadly from asymptomatic, to respiratory failure, and death. Like other disease states, there are patient characteristics that impact clinical risk and determine the spectrum of severity. Gathering and interpreting data on individual demographics, comorbidities or risk factors, and outcomes of patients with COVID-19 will help physicians and public health officials develop prevention and mitigation strategies.

The largest case series in the United States, recently published by Dr. Richardson and colleagues (1), described significant characteristics correlating with poor outcomes of hospitalized patients with COVID-19 in the New York City (NYC) area. Consistent with previously reported patient data, the most common medical comorbidities included hypertension (HTN; 56.6%), obesity (body mass index [BMI] ≥30 kg/m^2; 41.7%), and type 2 diabetes mellitus (T2DM; 33.8%).

Obesity, per se, has also emerged as an important risk factor for morbidity and mortality due to COVID-19. In a retrospective analysis of 3,615 symptomatic individuals presenting to a large academic Emergency Department in NYC diagnosed with COVID-19, BMI as stratified by age was strongly correlated with poor outcomes for those 49% of patients admitted to hospital, of which 12% were either

directly admitted to or transferred to the intensive care unit (ICU) (2). This study found that for patients <60 years of age, rates of admission to acute and critical care beds were 2-fold and 1.8-fold higher with a BMI between 30 and 34 kg/m^2 compared with a BMI <30 kg/m^2, respectively. Patients with a BMI ≥35 kg/m^2 and aged <60 years were 2.2 (95% confidence interval [CI], 1.7 to 2.9; *P*<.0001) and 3.6 (95% CI, 2.5 to 5.3; *P*<.0001) times more likely to be admitted for acute and critical care compared to patients of similar age and a BMI <30 kg/m^2. Another retrospective case series from two Manhattan hospitals noted that among 393 adults (median age 62 years), 35.8% had a BMI ≥30 kg/m^2 and were more likely to require invasive mechanical ventilation (IMV) (3). Patients requiring IMV also had a higher rate of T2DM, HTN, and coronary artery disease. Similarly, a retrospective cohort study of 124 COVID-19 patients admitted to a single French ICU showed the percent of patients with obesity needing IMV (68.6%) increased with adiposity (greater with BMI >35 kg/m^2 [85.7%] versus BMI >30 kg/m^2) and was independent of age, T2DM, and HTN (4). A recently published retrospective cohort of 103 consecutive patients with COVID-19 admitted to three Rhode Island hospitals also reported increasing adiposity (BMI ≥30 kg/m^2) independently associated with use of IMV, with BMI ≥35 kg/m^2 associated with increased frequency of ICU admission (adjusted odds ratio, 5.39) (5).

It is imperative, however, to further stratify risk in patients with obesity to determine optimal mitigation and perhaps therapeutic preparedness strategies. For example, to what degree are poor outcomes due to the biomechanical versus the cardiometabolic complications of obesity? Certainly, biomechanical complications such as obstructive sleep apnea and decrements in thoracic compliance, functional residual capacity, and ventilatory volume could increase the need for ICU care and IMV. Alternatively, other identified risk factors associated with poor outcomes, such as T2DM, HTN, and cardiovascular disease (CVD) constitute obesity-related cardiometabolic complications and central to the progression of cardiometabolic disease is insulin resistance. This brings us to a recently conceptualized diagnostic term for obesity, "adiposity-based chronic disease" (ABCD) (6), and to what degree abnormalities in adipose tissue mass (biomechanical) or in adipose distribution and function (cardiometabolic) contribute to poor COVID-19 outcomes. What is difficult to ascertain from current data is whether patients with increased adiposity without insulin resistance or cardiometabolic manifestations, so-called "metabolically healthy obesity" (MHO) (7), have similar or lower COVID-19 morbidity/mortality compared to patients with obesity, insulin resistance, and cardiometabolic disease. MHO is a controversial concept and term due to lack of clear definition or criteria and rare instances when it is even correct semantically as it appears to be a transient state if it exists at all.

Dysfunctional adipose tissue (especially visceral and ectopic adipose tissue) in patients with insulin resistance is associated with adipose tissue macrophages recruited by adipokines, abnormalities in innate immunity, systemic inflammation via cytokines like interleukins (i.e., IL-6 and TNF-α), endothelial dysfunction, adipocyte-derived PAI-1 perhaps contributing to coagulopathy, and increased angiotensin-converting enzyme 2 expression in both adipocytes and lung lipofibroblasts. These processes could enhance SARS-CoV-2 binding and cell uptake and drive the hyper-immune response causing pulmonary fibrosis and multi-organ system failure (8-10). Deng et al (11) noted computed tomography imaging evidence that fatty liver and epicardial adipose tissue are likely implicated in severity of illness in patients under 40 years old infected with COVID-19. We suspect that insulin resistance in ABCD is an important pathophysiologic cause of poor outcomes in patients with obesity and SARS-CoV-2 independent of BMI. Further, this explains the association of T2DM, HTN, and CVD with poor outcomes since insulin resistance is the main driver of both dysglycemia-based chronic disease and cardiometabolic-based chronic disease (CMBCD) (12,13) towards these end-stage disease manifestations.

Early data from the Chinese Center for Disease Control and Prevention, where the outbreak started, provided clues that ABCD and CMBCD were implicated as evident by elevated case fatality rates in those with HTN (6%), T2DM (7.3), and CVD (10.5%) (14). Even so, there is evidence that BMI can have adverse consequences independent of cardiometabolic disease. More recent data from Shenzhen, China, reported 1.84-fold and 3.4-fold odds of developing severe disease in patients with BMI 24.0 to 27.9 kg/m^2 and ≥28 kg/m^2, respectively, after adjusting for HTN, T2DM, and CVD (15). This risk was greatly exaggerated in men with a BMI ≥28 kg/m^2 compared to a BMI 18.5 to 23.9 kg/m^2 (odds ratio, 5.66). Outcomes from three Chinese hospitals reported by Gao et al (16) investigated the association of BMI with COVID-19 severity by comparing 75 case subjects with a BMI ≥25 kg/m^2 (mean 27.7 kg/m^2) each randomly matched to a control subject (mean BMI 21.8 kg/m^2) by sex and age. COVID-19 severity was categorized as mild, moderate, severe, or critical. Subjects with a BMI ≥25 kg/m^2 were more likely to have T2DM (24.0% vs. 14.7%), early indications of inflammation and altered immunity (higher C-reactive protein and lower lymphocyte count), longer hospital stay, and significant dose-effect correlation between BMI and proportion of those categorized with severe COVID-19. The association between BMI and COVID-19 severity was significant after adjusting for age, sex, smoking status, HTN, T2DM, and dyslipidemia via logistic regression analysis. Studies are needed that assess the contribution of insulin resistance to poor COVID-19 outcomes independent of BMI. A key observation by Gao et al (16) was that 14.7% of lean patients (defined by BMI) with COVID-19 had T2DM, which is higher than the over-

all diabetes rates, suggesting a role for insulin resistance per se.

BMI remains a valuable measure to screen and classify obesity, especially for population analysis, but continues to fall short for stratifying individual risk of ABCD and remains suboptimal for predicting risk of COVID-19 clinical severity, despite remaining the best pragmatic anthropometric measurement. BMI has variable correlations to adiposity and ABCD among different populations, making it difficult to compare in the context of COVID-19 globally. Analyzing these data to demarcate pre–COVID-19 insulin-sensitive "MHO" or stage 0 obesity from advanced ABCD with insulin resistance and abnormalities in adipose tissue function & distribution, consistent with the American Association of Clinical Endocrinologists guidelines (17), may inform and improve individual and public health recommendations. Staging the severity of adiposity-related disease in a "complication-centric" manner (HTN, dyslipidemia, metabolic syndrome, T2DM, obstructive sleep apnea, etc.) among different ethnic groups in patients with COVID-19 should help predict the adverse risk of adiposity on patient health in a pragmatic and actionable manner during this pandemic, as it is imperative to match the intensity of therapy or preventive measures to the severity of obesity-related cardiometabolic disease. Caveats to consider include the context of current literature being limited to observational and retrospective studies performed on acutely ill patients with incomplete data and the variable populations with different clinical phenotypes making up the current body of data.

DISCLOSURE

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