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COVID-19 and Severe Obesity: A Big Problem?

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On 11 March 2020, the World Health Organization declared coronavirus disease 2019 (COVID-19) a pandemic. The disease, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has now infected nearly 20 million persons worldwide, with a global mortality rate of 3.7%. It is unusual in that symptoms range from none to severe respiratory failure with diffuse lung damage and death. Given these diverse effects, understanding the risks for developing the most severe manifestations was particularly important from the start. Early reports from China and Italy, where the pandemic first took hold, identified a broad range of factors—old age, autoimmune disease, hypertension, and coronary artery disease—as risks for worse outcomes. However, as the pandemic reached the United States, another factor appeared that was particularly common in severely affected patients: obesity. The United States has a 20% rate of severe obesity (body mass index [BMI] >35 kg/m^2) and a 10% rate of morbid obesity (BMI >40 kg/m^2)—the highest rates in the industrialized world. More than 40% of Americans are considered obese (BMI >30 kg/m^2). One possibility was that given this high prevalence, one would expect to find obesity more often in patients with COVID-19 as well. Yet, by early April, research was countering this hypothesis, showing that patients with COVID-19 in the intensive care unit were more likely to be obese than historical ICU patients without COVID-19 (1), and that obese persons who had COVID-19 were more likely to require hospitalization and intensive care unit treatment (2). In contrast to other known risk factors, obesity was very common even in persons younger than 50

years, and this high prevalence predicted a shift in severe COVID-19 disease to younger populations (3).

During the past few months, nearly 300 articles have reported an association between severe obesity and increased morbidity and mortality from COVID-19. Most of the focus is on hospitalized patients and ranges from small single-center studies to large retrospective analyses of thousands of patients (4). They generally cover the period from March 2020, when the pandemic first exploded in New York City, to May 2020, when it had spread to the rest of the United States. The findings are consistent: There is a dose-dependent association of obesity with worse COVID-19 morbidity requiring hospitalization and intensive care and with mortality. This particularly applies to patients younger than 50 to 60 years (5).

In their article, Tartof and colleagues (6) provide an analysis for a large community population: patients in the Kaiser Permanente Southern California system. They retrospectively examined records from 5652 persons with SARS-CoV-2, with the primary outcome being death within 3 weeks of diagnosis. Two thirds of patients were hospitalized, and 43% were ventilated. Patients with BMIs greater than 40 kg/m^2 had higher death rates overall, and those with BMIs greater than 45 kg/m^2 had a risk ratio of 4.18. Most strikingly, however, those younger than 60 years had increased risk ratios of 12 to 17 versus 1 to 3 if they were older; high BMI increased risk in men more than in women. More important, the obesity risk was adjusted for common comorbidities, including diabetes, hypertension, heart failure, myocardial infarction, and chronic lung or renal disease. The study also took into account when SARS-CoV-2 was detected. Interestingly, with each ensuing week, mortality risk declined substantially. This may

reflect the growing social awareness with evolving policies to reduce spread and improve medical practice.

This study follows 2 recent reports in *Annals* examining a similar question but solely in hospitalized patients. Goyal and colleagues (7) reported on 1687 hospitalized patients in 2 New York City hospitals, finding that those with BMIs greater than 40 kg/m^2 were at higher risk for respiratory failure but not death. However, 69% of their cohort had a BMI less than 30 kg/m^2, and only 5% had a BMI greater than 40 kg/m^2. In a second study, Anderson and colleagues (8) reported on 2466 patients with COVID-19 that had at least 47 days of hospital observation. They found that those younger than 65 years with a BMI greater than 40 kg/m^2 had a 2-fold higher risk for intubation; however, BMI was no longer a significant risk factor in older patients.

The consistency of this new study and prior research should put to rest the contention that obesity is common in severe COVID-19 because it is common in the population. Obesity is an important independent risk factor for serious COVID-19 disease. That the risks are higher in younger patients is probably not because obesity is particularly damaging in this age group; it is more likely that other serious comorbidities that evolve later in life take over as dominant risk factors. That males are particularly affected may reflect their greater visceral adiposity over females, given that this fat is notably proinflammatory and contributes to metabolic and vascular disease. As a cardiologist who studies heart failure, I am struck by how many of the mechanisms that are mentioned in reviews of obesity risk and heart disease (9, 10) are also mentioned in reviews of obesity and COVID-19 (9). The top mechanisms include restrictive pulmonary physiology and sleep apnea, diabetes and dyslipidemia, immune dysfunction with depressed anti-inflammatory signaling (for example, adiponectin) and increased proinflammatory signaling (for example, leptin,

interleukin-6, and tumor necrosis factor-α), endothelial dysfunction, and renin–angiotensin stimulation that stimulates hypertension and worsens lung inflammation and alveolar damage. Fat deposited in skeletal muscle may be sought after by top-end steakhouses but, in vivo, it compromises muscle metabolic efficiency, nutrient uptake, and performance. Then, there is Newton's second law: force = mass × acceleration. It requires more muscle force to displace the diaphragm downward when a substantial fat mass lies below it. Abdominal obesity also makes it more difficult to breathe in a prone position that is favored to improve ventilation in patients with COVID-19. Among more specific mechanisms is expression of angiotensin-converting enzyme 2 protein in adipose tissue. This is the docking protein for SARS-CoV-2 to enter a cell, and fat has higher levels than the lungs and so may serve as a viral refuge and replication site, prolonging virus shedding.

Arguably the hardest question to answer is: What is to be done? Severe and morbid obesity is sufficiently common in the United States to have become part of our social fabric. That makes messaging about its health risks difficult but does not change the fact that they are real. The data consistently show major risks at BMIs greater than 35 kg/m^2, and at that level, weight reduction is difficult and certainly is not achieved rapidly. Therefore, social distancing; altering behaviors to reduce viral exposure and transmission, such as wearing masks; and instituting policies and health care approaches that recognize the potential effects of obesity should be implemented. These actions should help and are certainly doable.

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