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The Obesity Paradox in Infections and Implications for COVID-19

See also page 550

Obesity has reached epidemic levels in the United States and much of the Western world.[1,2] Recent statistics suggest that 75% of the US population is either overweight or obese, and 42% of Americans meet the current body mass index (BMI) criteria (BMI $\geq$30 kg/m^2) for obesity. Even more concerning is that 9% of US adults currently meet criteria for severe, class III, or morbid obesity (BMI $\geq$40 kg/m^2). Obesity places a "heavy" toll on the overall health of the population and on the health care system, with a particularly adverse impact on cardiovascular health. Obesity worsens almost all cardiovascular disease (CVD) risk factors, exacerbating hypertension and dyslipidemia and increasing insulin resistance. Obesity thus leads to metabolic syndrome and diabetes mellitus and can cause chronic, low-grade systemic inflammation. Not surprisingly, the development of almost all CVD is increased with obesity, including hypertension, coronary heart disease, heart failure (HF), and atrial fibrillation. In our current pandemic, patients with obesity who are infected with COVID-19 have endured increased respiratory symptoms, renal injury, coagulopathy, and thromboembolism, including pulmonary embolism (PE).[3] In addition, obese individuals have many musculoskeletal abnormalities and have premature disabilities.[4]

Ironically, despite the increased health risks associated with obesity, patients with obesity and CVD have better short- and medium-term prognoses than do leaner patients with the same degree of CVD.[2,3,5] Termed the obesity paradox, these prognostic benefits have also been seen in end-stage renal disease[6] and respiratory diseases, including chronic obstructive pulmonary disease (COPD),[7] as well as in PE.[8]

In this issue of the *Mayo Clinic Proceedings,* Gribsholt et al[9] report the mortality of patients who were hospitalized between January 1, 2011, and September 30, 2015, for non–COVID-related infections of varied sources: sepsis, pulmonary, urinary, and skin. Data were drawn from the Central Denmark Region Clinical Information System, a comprehensive registry, of which 76,044 patients were admitted for infection and 35,406 also had height and weight data recorded within 30 days of hospitalization. In this subpopulation of patients with recent BMI, 25% were admitted with pneumonia, 12.5% with urinary tract infection, and 11.2% with sepsis, with less than 10% admitted for skin infection and less than 5% with gastrointestinal infection.

For this study, the authors compared the risk of death in patients with a normal weight range (BMI 18.5-25 kg/m^2) with that in patients who were underweight (BMI $<$18.5 kg/m^2), overweight (BMI 25-30 kg/m^2), and obese (BMI $\geq$30 kg/m^2). The authors reported an obesity paradox, with lower mortality in hospitalized infected patients with obesity compared with normal weight individuals. Underweight patients, however, had the highest overall mortality rate (adjusted 90-day mortality: adjusted hazard ratio, 1.75; CI, 1.58-1.94). Compared with the US population, this Danish population exhibited a higher prevalence of smoking and had a much lower prevalence of obesity, thus also making the prevalence of moderate and severe obesity less likely, although this was not listed. The finding of considerably higher mortality in the underweight is not a major surprise as this is seen in many other disease processes, probably because of comorbidities like cancer or severe COPD and less "reserve" to fight acute illnesses. However, compared with the normal weight patients, those who were overweight and obese had 36% and 45% lower mortality, respectively.

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The reasons for the obesity paradox in many conditions, including CVD, remain uncertain. Certainly, advanced HF is often associated with a state of cachexia and frailty,[10] so having higher weight and more muscle mass could itself be protective or an associative marker of maintained vigor, but this would not explain the obesity paradox seen in less severe HF and even stable coronary heart disease. As mentioned before, an obesity paradox has been noted in other conditions, including end-stage renal disease, COPD, and PE, among other conditions,[6-8] and the results of Gribsholt et al[9] are consistent with some other reports in hospitalized patients with pneumonia and other infections. It is crucial that future work evaluate potential medical management—based contributions to the obesity paradox, such as management of nutrition and fluid balance. Furthermore, interrogation of glycemic parameters in the obese vs nonobese is mandated as current intermediate glucose goals (eg, 130-180 mg/dL [to convert to mmol/L, multiply by 0.0555]) approximate the baseline glucose level of many patients with diabetes but reflect a "glycemic gap" in those without, which may contribute to negative outcomes.[11]

For patients suffering in recent pandemics, including COVID-19 and H1N1, however, the obesity paradox has not applied.[12] Instead, the majority of data have suggested that obesity takes a particularly heavy toll on the prognosis in COVID-19 infection, including several reports from thousands of patients,[13-15] such as those published in *Mayo Clinic Proceedings*.[3,16] COVID-19—infected patients with obesity exhibit more severe disease and are admitted to the intensive care unit more frequently, with increased need for intubation and mechanical ventilation and a higher mortality. The reasons for the increased risk in obesity with COVID-19, as we reviewed previously,[3] include multiple comorbidities, especially higher presence of CVD, but also that the adipocytes in the obese individual abundantly express angiotensin-converting enzyme 2 (ACE2) receptors. The number of ACE2 receptors in the adipose tissue of the obese is even greater than in lung tissue, the site of coronavirus entry, thereby making fat a potential reservoir for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

There are several other implications of interest regarding obesity in COVID-19. First, low serum 25-hydroxyvitamin D levels on hospital admission have been correlated with COVID-19 disease severity and mortality,[17] and obese patients are known to have lower levels of vitamin D.[18] Vitamin D is essential to a host of immune functions, control of inflammation, and modulation of the coagulation cascade. Vitamin D may be involved in decreasing the replication and survival of the SARS-CoV-2 through the induction of cathelicidins and defensins, major host antimicrobial defense proteins. Vitamin D is associated with maintenance of favorable ACE2 levels and limitation of dysregulation in the renin-angiotensin system, both of which limit viral entry and subsequent acute lung injury.[19] Furthermore, with the recent release of various COVID-19 vaccines, there is concern that obese individuals may require larger doses or a third injection; this is based on the fact that influenza vaccinated obese adults are twice as likely as healthy weight adults to develop influenza and influenza-like illness, despite similar levels of immune response to the influenza vaccine.[20] Because the COVID-19 vaccines potentially could be less effective in adults with obesity, especially moderate and severe obesity, careful post-vaccination surveillance is needed. Thankfully, early data on COVID-19 vaccines suggest equal efficacy in patients with obesity, but longer follow-up is required.[12]

Finally, a study in the *Proceedings* of 247 patients showed that higher levels of cardiorespiratory fitness (CRF) are associated with lower hospitalization rates in those infected with COVID-19.[21,22] This same study suggested that fitness is more important than adiposity in determining the risk for COVID-19 hospitalizations.[23,24] Because physical activity and CRF may play a role in immunity against infections,[22] more studies are needed to assess phenotypic variation in these characteristics and the associated risk of negative outcomes, such as hospitalizations, intensive care unit admissions, need for mechanical

ventilation, and mortality after infections, including COVID-19. Addressing the impact of physical activity and CRF in obese individuals would also be of interest in evaluating their response to COVID-19 vaccinations.

Clearly, obesity places a heavy toll on overall health and health care resource utilization, including in obese patients infected with SARS-CoV-2. For other infections, added concern should be directed at more vigorous treatment of individuals in the normal weight range and, even more so, of the underweight, for whom mortality is the highest.

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