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We Should Do More to Offer Evidence-Based Treatment for an Important Modifiable Risk Factor for COVID-19: Obesity

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Abstract

Observational studies, from multiple countries, repeatedly demonstrate an association between obesity and severe COVID-19, which is defined as need for hospitalization, intensive care unit admission, invasive mechanical ventilation (IMV) or death. Meta-analysis of studies from China, USA, and France show odds ratio (OR) of 2.31 (95% CI 1.3-4.1) for obesity and severe COVID-19. Other studies show OR of 12.1 (95% CI 3.25-45.1) for mortality and OR of 7.36 (95% CI 1.63-33.14) for need for IMV for patients with body mass index (BMI) $\geq 35\,kg/m^2$. Obesity is the only modifiable risk factor that is not routinely treated but treatment can lead to improvement in visceral adiposity, insulin sensitivity, and mortality risk. Increasing the awareness of the association between obesity and COVID-19 risk in the general population and medical community may serve as the impetus to make obesity identification and management a higher priority.

Keywords

obesity, BMI, weight, COVID-19, SARS-CoV-2

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The 2019 novel coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to disrupt thousands of lives every day.[1] Potential risk factors for severe COVID-19 include older age, male sex, obesity, hypertension, diabetes, cardiovascular disease, and cancer.[2] Notably, of the known risk factors, the only modifiable one that does not get routinely diagnosed or treated is obesity.[3-7] Increasing the awareness of the association between obesity and COVID-19 risk in the general population and medical community may serve as the impetus to make obesity identification and management a higher priority.

Observational studies (cross-sectional, prospective cohort, retrospective cohort, and case-control) in China, USA, France, and Italy have shown a consistent and dose-dependent relationship between higher body mass index (BMI) and severe COVID-19, defined as need for hospital admission, intensive care unit admission, invasive mechanical ventilation (IMV), and mortality.[8-15] A meta-analysis of nine observational studies with over 4000 patients in China (obesity defined as BMI $> 27\,kg/m^2$; unlike western countries where obesity is defined as BMI $> 30\,kg/m^2$), USA and France, found patients with obesity have an increased odds of severe COVID-19 (odds ratio [OR] 2.31. 95% CI 1.3-4.1).[16] Furthermore, a dose-dependent relationship appears to exist. When studies looked at class 2 and 3 obesity (BMI of $\geq 35\,kg/m^2$) to those with a normal BMI, patients with obesity had an even higher increased odds of death (OR 12.1, 95% CI 3.25-45.1) or need for IMV (OR 7.36, 95% CI 1.63-33.14).[10,15] Other evidence supporting the correlation stems from assessing differences in BMI with end organ complications. For example, Zheng et al.[17] found patients with non-alcoholic hepatic steatosis may be at even higher risk than patients with obesity without such complications. These findings support not only an association between obesity and severe COVID-19, but start to

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uncover a possible mechanistic pathway given the consistency of findings and dose-dependent relationship between BMI and poor outcomes from COVID-19.

There is biological plausibility to the observational data that suggest obesity leads to worse outcomes in COVID-19. Adipocytes, specifically visceral adipocytes, release inflammatory and coagulopathic mediators that contribute to COVID-19, including interleukins (IL-6, IL-8), C-reactive protein (CRP), tumor-necrosis-factor-alpha (TNF-alpha), angiotensinogen, plasminogen activated inhibitor-1, chemokine (C-C motif) ligand 2, D-dimer, lipoprotein lipase, compliment C5a, and lactic acid.[18-22] Patients with high adiposity may also be more susceptible to COVID-19 because levels of human angiotensin-converting enzyme 2 (ACE2), which is a binding site for the spike protein of SARS-CoV-2,[23] and may be higher in adipose tissue than lung tissue.[24]

In addition to inflammatory and coagulopathic processes, there may be mechanical reasons for poor outcomes from COVID-19 in individuals with obesity. Obesity increases perfusion mismatching, shunting related to atelectasis, alveolar hypoventilation, and increased resting oxygen consumption, the combination of which may predispose to respiratory muscle inefficiency and precipitate respiratory failure.[25-27] As BMI increases, expiratory reserve volume and functional residual capacity decrease, with the greatest decrements seen between BMI 25 to 30 kg/m^2 and BMI 30 to 35 kg/m^2, with very little additional change at higher BMIs.[28] This may explain the increased risk for invasive ventilation seen starting at a BMI of 25 kg/m^2 in patients in France, after controlling for comorbidities,[10] and the increased risk for ICU admission in young patients with a BMI starting at 30 kg/m^2[28] Male sex as a risk factor for poor outcomes from COVID-19 may be due to the that visceral adiposity rapidly accumulates at a lower BMI in men versus women.[29]

Weight bias associated with obesity also contributes to poor outcomes: many healthcare providers (HCP) hold negative attitudes and stereotypes toward patients with obesity which impact their clinical decision making.[30-34] For example, many patients with obesity experience stress while seeking care which lead them to avoid or delay seeking care and have poor adherence to treatment due to mistrust of healthcare providers.[35,36] Moreover, persons with obesity face structural stigma in healthcare settings in that many medical devices do not fit them. Additionally, moving individuals with high BMI's sometimes requires additional staff and specialized equipment and sometimes changing infrastructure such as wider doors and hallways; basic vital signs such as blood pressure may be inaccurate; obtaining diagnostic testing such as lab draws are harder and CT/MRI scanners may have size/weight limits and X-ray and ultrasound may be harder to interpret; even performing invasive procedures are harder because normal body landmarks are altered or harder to visualize; drug dosing and metabolism is altered.[37]

Given the strong association noted with obesity and worse COVID-19 outcomes (and already known association of obesity with other chronic diseases such as hypertension, diabetes, coronary artery disease, cerebrovascular disease, and various types of cancer) and a biological mechanism for such outcomes, it is important to treat obesity as a serious disease. Obesity was defined as a disease by the American Medical Association in 2013, and this was an important first step in acknowledging it for what it is: a complex dysregulation of the body's energy regulatory systems, and not a person's behavioral faults.[38] We briefly outline the (overlapping) factors that lead to dysregulation in the body's energy regulatory system, most of which is outside of any individual's control:[39]

1. Orexigenic signaling by second-order neurons is affected by epigenetic influences on intrauterine environment, including maternal BMI and stress; genetic influences; early life stress; early patterning and imprinting around food, including parental use of food as reward, punishment.
2. Anorexigenic signaling by first-order neurons is affected by modern macroenvironmental influences, including built environment, social structure, and cues.
3. Satiety signaling between the gut and limbic system and higher cortical centers are influenced by microenvironmental factors including sleep, circadian rhythm, stress, activity, nutrition.[40]
4. Anorexigenic signaling by the limbic system is affected by gut microbiome, influenced by type of birth and early life antibiotic exposure.

Obesity Medicine is an emerging field of patient care.[41] While professional guidelines differ on whether obesity should be treated in the absence of common obesity-related comorbidities,[42,43] COVID-19 may shift this paradigm, as persons with obesity are at the highest risk of IMV or death.[8-16] In patients with obesity, just a 5% total body weight loss is associated with improved insulin sensitivity in adipose tissue, muscle, liver, improved pancreatic beta cell function, decrease visceral adiposity, as well as healthful changes in adipose tissue such as reduction in reactive oxygen species.[44] For patients with obesity, weight loss in adulthood may lead to 54% reduction in mortality (HR 0.46, 95% CI 0.27-0.22) compared to those who do not lose weight.[45] Evidence-based effective treatment of obesity include behavior change approaches to dietary pattern and physical activity, self-monitoring, improved sleep quality and quantity, anti-obesity pharmacotherapy, reduction of weight-gain promoting medications, endoscopic procedures, and bariatric surgery.[43,46] Experienced obesity

medicine clinicians often combine lifestyle approaches and several anti-obesity medications, and good follow-up, in the same patient, thus achieving far greater weight losses than are shown in any of the RCT's assessing any single anti-obesity medication. Patients can access evidence-based obesity treatment in every state, and can expect to lose a significant amount of weight in the first 6 to 12 months of engaging in treatment, which may improve outcomes if infected with the SARS-CoV-2 virus.[6,41,47-49]

HCPs can use the 5As framework (Assess, Advise, Agree, Assist, and Arrange) to assess patient's current thoughts on considering weight loss.[50] Ideally, HCPs can build and coordinate a multidisciplinary team that can help patients achieve their healthy weight goals.[51] The societal stigma associated with obesity can be tackled with increased education among HCPs about biology, chronicity, and overall health impact of obesity.[52] HCPs should be encouraged to schedule follow-up visits focusing specifically on obesity and frequent follow-up visits for obesity are reimbursed.[7] Clinics, hospitals, and emergency medical services should ensure that there is infrastructure and equipment in place to be able to provide the same quality of care to patients with obesity as those without. For practicing HCPs interested in gaining additional training and certification in obesity, there is a relatively easy pathway through the American Board of Obesity Medicine.[53] Last but not the least, there is a critical need for improved education in caring for patients with obesity in medical school and residency.[54] The COVID-19 pandemic has made it clear that patients with obesity deserve treatment of this condition, even in the absence of other comorbidities, and the challenge for HCPs and health systems is to do this in a sensitive, patient-centered, and evidence-based way.

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