Obesity and COVID-19 outcomes: a risk factor that needs attention

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Obesity, a comorbidity not well documented in the COVID-19 pandemic, is now being identified as a risk factor for severe COVID-19 infection, including in those less than 60 years of age. We discuss parallels of increased severity, prolonged viral shedding of influenza A (H1N1) which are relevant, and the mechanisms which link obesity to inflammation and severity of infections. We suggest that weights and heights be recorded in all case-record forms and epidemiologic surveillance tools to assess the associations of body mass index with infection status and disease outcomes. Obese individuals should be closely monitored in view of the risk of increased severity of COVID-19 infection.

The current expanding pandemic of coronavirus disease-19 (COVID-19) has resulted in more than one million infections worldwide, and considerable levels of morbidity and mortality.

Mortality in COVID-19 infection has been related to age and the presence of comorbidities, among which hypertension, cardiovascular disease and diabetes are the most common. A recent meta-analysis showed that the pooled prevalence of hypertension, cardiovascular disease and diabetes was 16.3%, 12.1% and 7.8% respectively, in hospitalized patients[1]. Obesity is one of the commonest underlying comorbidities worldwide. However, none of the studies in the systematic review mention the prevalence of obesity in the COVID-19 cases. Obesity is a potential confounder of the association between hypertension, diabetes and outcomes in COVID-19 infection, and should therefore be assessed.

The previous pandemic due to an acute viral respiratory infection that the world witnessed in 2009 was that of influenza A (H1N1). The presence of chronic underlying illness was also identified as a risk factor for hospitalization, acute respiratory distress syndrome (ARDS) and the need for mechanical ventilation, and mortality during the pandemic. Obesity was identified as a novel risk factor for increased disease severity and mortality reported in the influenza A (H1N1) pandemic[2,3]. In a global pooled analysis of more than 70,000 laboratory-confirmed influenza A cases, obesity defined as a body mass index (BMI) >30 kg/m^2 was found to have an odds ratio of 2.9 (95% CI, 1.3–6.6) for death[4] and this risk was particularly high in those with morbid obesity[5]. It is pertinent to note that obesity is also a risk factor for the severity of other viral infections like dengue fever in children[6]. Now evidence is emerging on the association of obesity with severe COVID-19 infection. The proportion of patients requiring invasive mechanical ventilation in a study from France increased with increasing BMI and reached 90% in those with a BMI > 35 kg/m^2 (ref. 7). The associations of age, diabetes and hypertension were not significant when adjusted for obesity[7]. Importantly in a recent study, BMI > 30 kg/m^2 was identified as a risk factor for hospital admission in patients younger than 60 years, an age group previously not considered as 'high risk'[8]. Patients aged <60 years with BMI between 30 and 34 were 2.0 (95% CI, 1.6–2.6; $P < 0.0001$) and 1.8 (95% CI, 1.2–2.7; $P = 0.006$) times more likely to be admitted to acute and critical care respectively, compared to individuals with BMI < 30 (ref. 8).

In the case of influenza A (H1N1) infection, later work highlighted several other implications of obesity which might be relevant to COVID-19 infection. Obesity has been associated with greater susceptibility to infection with influenza A, increased viral load in exhaled breath and 43% more prolonged viral shedding and decreased responsiveness to influenza A vaccines[9–11].

Moreover, it was also found that in asymptomatic or minimally symptomatic persons with influenza A, obesity prolonged the duration of shedding 104% longer (adjusted event time ratio of 2.04; 95% CI, 1.35–3.09), and this has implications for influenza transmission in the community[11]. It would be worth noting if there is any similar association of obesity with susceptibility, prolonged viral shedding of SARS-CoV-2 and the potential influence on efficacy of any future vaccines. The analysis of mortality rates due to COVID-19 infection across countries may also examine BMI as one of the predictors. It would also be important to examine whether lower prevalence of obesity in countries like India is linked to lower mortality due to COVID-19 infection.

Several explanations have been proposed for the susceptibility and progression of viral illnesses like influenza A in obese patients. Traditionally, adipose tissue has received a lot of attention for its influence on metabolism and insulin resistance. Adipose tissue is now recognized as an endocrine organ that secretes a host of adipokines that affect inflammatory cell and immune function, and obesity may be associated with a chronic inflammatory state[12]. The key mediators of this chronic inflammatory state may be adiponectin which normally suppresses macrophages and pro-inflammatory cytokine production and is low in obese individuals[13], and leptin which is a pro-inflammatory cytokine whose levels correlate with body fat stores[14]. Obesity may lead to a sensitized innate immune system which may show hyper-responsiveness to infections like influenza A with increased production of pro-inflammatory cytokines like IL-6 and TNF-α. Adipose tissue also harbours resident macrophages which have been noted in experimental studies to be the source of IL-6 and TNF-α[15]. Recent studies have highlighted the potential role of increased levels of cytokines, including IL-6, IL-10 and TNF-α in the cytokine storm seen in the progression of COVID-19 infection[16], and an antagonist of IL-6, tocilizumab has been used for the treatment of severe COVID-19 infection[17]. IL-6 is an adipokine whose levels have been correlated with the total and abdominal adiposity and BMI[18], and increasing BMI may predispose to severe manifestations of COVID-19 infection. IL-6 levels were also higher in obese patients with dengue and were implicated

in its severe manifestations[19]. In experimental animals it has been shown that obesity and infections can activate the same inflammatory pathways, and this additive effect of obesity can induce a cytokine storm involving IL-6 and TNF-α in the presence of infections[20]. There are other potential explanations for the association of obesity with severe COVID-19 infection. Adipose tissue also expresses ACE2 enzyme which is the putative receptor for entry of SARS-CoV-2 (ref. 21). There is currently no evidence of infection of adipose tissue by SARS-CoV-2, but this has been demonstrated for infections like influenza A[15] as well as HIV, where adipose tissue may act as a reservoir for the virus[22]. Finally obesity is associated with a higher risk of thromboembolism[23], and severe COVID-19 infection is marked by a prothrombotic state in the lungs which contributes to mortality[24]. The emerging links between obesity, and risk and outcomes of pandemic viral infections, and the underlying pathways should be important new areas of research.

Measurement of nutritional status is a vital sign in clinical practice and requires only height and weight measurements. In the case of sick patients, self-reported weight and height can be used, apart from proxy indicators of height like ulna length and of BMI like the mid-upper arm circumference. It will be important to document BMI in patients with suspected COVID-19 infection visiting healthcare facilities, in those undergoing hospitalization, and those in intensive care units to determine the potential effect of obesity on hospitalization, the occurrence of ARDS and death. Currently, anthropometric data are missing as a variable in the WHO case record surveillance form for COVID-19 infection[25], and its population-based, age-stratified sero-epidemiological investigation protocol[26]; these should be revised to incorporate weight and height.

In conclusion we suggest that obesity is an important emerging risk factor for severe COVID-19 infection that deserves attention of individuals, physicians and public health professionals during the present pandemic. The database of patients with COVID-19 infection in India and other countries should have information on BMI. This will confirm the initial observations of obesity as a risk factor for severe COVID-19 infection in a larger number of patients. It will also reveal whether a low BMI (<18.5 kg/m^2) confers risk or protection against adverse outcomes in COVID-19 infection. Obese individuals should be more careful about preventive measures during the pandemic. Physicians should consider obesity (especially severe obesity) as an important comorbidity and risk factor for adverse outcome even in those below 60 years of age, and these patients may require closer monitoring for progression to severe COVID-19 infection.

Lessons related to a novel risk factor in an earlier viral pandemic due to a novel virus are unfolding in another pandemic due to another novel pathogen, and should not be missed.

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