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Obesity a Risk Factor for Severe COVID-19 Infection:

Multiple Potential Mechanisms

Running Title: *Sattar et al.; Mechanisms for COVID Severity in Obesity*

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The Coronavirus Disease 2019 (COVID-19) pandemic has led to worldwide research efforts to identify people at greatest risk of developing critical illness and dying. Initial data pointed towards older individuals being particularly vulnerable, as well as those with diabetes or cardiovascular (including hypertension), respiratory or kidney disease. These problems are often concentrated in certain racial groups (e.g. African Americans and Asians) which also appear to be more prone to worse COVID-19 outcomes.[1] Increasing numbers of reports have linked obesity to more severe COVID-19 illness and death.[1-3] In a French study, the risk for invasive mechanical ventilation in patients with COVID-19 infection admitted to Intensive Treatment Unit was more than seven-fold higher for those with Body Mass Index (BMI) >35 compared with BMI <25 Kg/m^2.[2] Among individuals with COVID-19 aged less than 60 years in New York City, those with a BMI between 30-34 Kg/m^2 and >35 Kg/m^2 were 1.8 times and 3.6 times more likely to be admitted to critical care, respectively, than individuals with a BMI <30 Kg/m^2.[3] We suggest obesity or excess ectopic fat deposition may be a unifying risk factor for severe COVID-19 infection, reducing both protective cardiorespiratory reserve as well as potentiating the immune dysregulation that appears, at least in part, to mediate the progression to critical illness and organ failure in a proportion of COVID-19 patients (**Figure**). Whether obesity is an independent risk factor for susceptibility to infection requires further research.

From a cardiovascular perspective, trial and genetic evidence conclusively show that obesity (and excess fat mass) are causally related to hypertension, diabetes, coronary heart disease, stroke, atrial fibrillation, renal disease and heart failure. Obesity potentiates multiple cardiovascular risk factors, the premature development of cardiovascular disease and adverse cardiorenal outcomes. There is also a metabolic concern. In individuals with diabetes, or at high risk of diabetes, obesity and excess ectopic fat lead to impairment of insulin resistance and

reduced beta-cell function. Both the latter limit ability to evoke an appropriate metabolic response upon immunologic challenge, leading some diabetes patients to require substantial amounts of insulin during severe infections. Overall, the integrated regulation of metabolism required for the complex cellular interactions, and for effective host defense, are lost, leading to functional immunologic deficit. COVID-19 virus may also directly disrupt pancreatic beta cell function through an interaction with ACE2. Furthermore, obesity enhances thrombosis, which is relevant given the association between severe COVID-19 and pro-thrombotic disseminated intravascular coagulation and high rates of venous thromboembolism.

Beyond cardiometabolic and thrombotic consequences, obesity has detrimental effects on lung function, diminishing forced expiratory volume and forced vital capacity (**Figure**). Higher relative fat mass is also linked to such adverse changes, perhaps relevant to emerging reports of greater critical illness from COVID-19 in certain ethnicities e.g. Asians.[1] Asians often display lower cardiorespiratory fitness and carry proportionally more fat tissue at lower BMIs. With extreme obesity (e.g. BMI >40Kg/m^2), care for individuals admitted to intensive therapy units is often impeded as these patients are more difficult to image, ventilate, nurse and rehabilitate. With respect to the immune response, there is a clear association between obesity and basal inflammatory status characterised by higher circulating Interleukin 6 and C-reactive protein levels. Adipose tissue in obesity is “pro-inflammatory”, with increased expression of cytokines and particularly adipokines. There is also dysregulated tissue leukocyte expression, and inflammatory macrophage (and innate lymphoid) subsets replace tissue regulatory (M2) phenotypic cells. Obesity *per se* is an independent and causal risk factor for the development of immune mediated disease e.g. psoriasis,[4] suggesting that such adipose state may have systemic immune consequence upon additional environmental provocation. In terms of host defense,

obesity impairs adaptive immune responses to influenza virus,[5] and conceivably could do so in COVID-19. Obese individuals may exhibit greater viral shedding suggesting potential for great viral exposure, especially if several family members are overweight. This may be aggravated in overcrowded multigenerational households which are more common in the socioeconomically deprived communities in which obesity is prevalent. All these observations point towards a potential for obesity to give rise to a more adverse virus versus host immune response relationship in COVID-19. Poorer nutritional status and hyperglycaemia may further aggravate the situation in some obese individuals.

While much of the focus of COVID-19 has been in older people, it is important to remember that while not necessarily obese, in the elderly weight and muscle mass start to decline at advanced age but relative fat mass increases, particularly in those with comorbid diseases such as cardiovascular and respiratory conditions. Older age is also associated with more hypertension and diabetes due to stiffer vessels and impaired metabolic efficiency, respectively. People who are older (e.g. >70 years of age), like younger obese individuals, have less cardiorespiratory reserve to cope with COVID-19 infection. Immune senescence is well recognised, as is the concept of *inflammageing*, and both may influence virus-host dynamics in the elderly, and infection outcomes.

What are implications of these emerging observations for future research and public health messaging? With respect to research, predictive instruments for those most at risk of severe outcomes should consider BMI. Mechanistic understanding of the relationship between obesity and COVID-19 may suggest therapeutic interventions (e.g. proven weight loss drugs, low calorie diets) to potentially reduce the risk of developing severe COVID-19 illness. With respect to public health, it is important to communicate risks without causing anxiety. People

worldwide should be encouraged to improve their lifestyle to lessen risk both in the current and subsequent waves of COVID-19. In addition to increasing activity levels, there should be improved messaging on better diet, focusing on simpler advice to help people adopt sustainable changes. This is particularly challenging with current stay-at-home rules limiting activity levels – the "lockdown cost of weight gain". Even more worrying, the resultant economic downturn may worsen obesity, especially in the most vulnerable, a risk that governments need to address when we come out of the current pandemic. Indeed, this pandemic has highlighted that more, not less, must be done to tackle and prevent obesity in our societies for the prevention of chronic disease and greater adverse reactions to viral pandemics.

Disclosures

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Figure Legend

Figure. Pathways potentially linking obesity / excess fat mass to more severe COVID-19 illness. This figure depicts multiple pathways by which obesity (and/or excess ectopic fat) may increase the impact of COVID-19 infection. These include underlying impairments in cardiovascular, respiratory, metabolic and thrombotic pathways in relation to obesity, all of which reduce reserve and ability to cope with COVID-19 infection and the secondary immune reaction to it. At the same time, there are several reasons why obese individuals may have amplified or dysregulated immune response, linked both to greater viral exposure, as well as the possibility that excess adipose tissue potentiates the immune response.

SES: socioeconomic status, FEV1: forced expiratory volume, FVC: forced vital capacity, BP: Blood Pressure, CV: cardiovascular, COVID-19: Coronavirus Disease 2019