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REVIEW ARTICLE

Obesity and Coronavirus Disease 2019

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Obesity, which is one of the most important noncommunicable diseases, has become an epidemic. With the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, the collision of these two health risks has increased the threat of adverse events and serious threats to public health. In this review, the impact of obesity on COVID-19 severity and mortality is presented. The mechanism by which obesity increases susceptibility and severity is discussed. As a low-grade inflammatory disease, obesity provides a pro-inflammatory milieu by which adipose tissue expressing angiotensin converting enzyme 2, which is known as a receptor for severe acute respiratory syndrome coronavirus 2, works as a viral reservoir. Finally, the role of metabolic and bariatric surgeries during the COVID-19 era will be discussed.

Key Words: Coronavirus disease 2019, Obesity, Bariatric surgery, Angiotensin converting enzyme 2

INTRODUCTION

The number of coronavirus disease 2019 (COVID-19) patients has increased exponentially worldwide over the past year. According to an official report by the World Health Organization, more than 160 million people were infected as of May 15, 2021, which led to more than 3.3 million deaths. Its severity varies widely, ranging from asymptomatic to fatal, albeit the precise risk factors and pathophysiology remain elusive. Recent evidence has indicted a strong epidemiologic correlation between COVID-19 and obesity severity.

Obesity is now recognized as a representative non-communicable disease. The prevalence of obesity has increased worldwide in the past few decades regardless of the region [1]. Because obesity is a status of low-grade inflammation, it is not surprising that patients with obesity suffer from a more severe systemic immune response following COVID-19 infection. Given the explosive number of available literatures regarding the relationship between COVID-19 and obesity, the impact of obesity on COVID-19 and that of weight loss intervention on COVID-19 susceptibility and severity will be identified in the near future.

In this review, we highlight the epidemiologic factors linking obesity and COVID-19, followed by a discussion of our current understanding of the pathophysiology of obesity-mediated COVID-19. In the last section, we discuss the benefit of bariatric surgery during the COVID-19 era, which is supported by several recent literatures.

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DOES OBESITY WORSEN COVID-19 OUTCOMES?

The number of patients with obesity has increased rapidly worldwide. The proportion of adults with a body mass index (BMI) of 25 kg/m^2 or greater increased between 1980 and 2013 from 28.8% to 36.9% in men and from 29.8% to 38.0% in women [1].

An accumulating number of reports provide evidence that obesity-related conditions worsen the severity of COVID-19 infection. One of the very first reports describing the relationship between obesity and COVID-19 severity was released from China, which was one of the earliest countries affected by COVID-19. The report revealed that obesity increased the risk for developing severe pneumonia in patients with COVID-19 infection. The authors examined the association between obesity and the severity of COVID-19 infection in 383 patients with COVID-19 who were admitted to a single center. Compared with patients of normal weight, the obesity group showed 2.42-fold higher odds of developing severe pneumonia after adjusting for potential confounders. The odds ratios (ORs) for severe pneumonia in men who were overweight and obese were 1.96 (95% CI, 0.78-4.98) and 5.70 (95% CI, 1.83-17.76), respectively [2].

In France, 85 (25%) of 340 patients with severe COVID-19 had obesity compared with 15.3% in the French adult population in 2014 [3]. The prevalence of obesity was numerically higher in patients with critical COVID-19 than in intensive care unit (ICU) patients without COVID-19. Even after adjusting for age and sex, the odds for obesity-mediated severity of a cooccurring disease were significantly higher in patients with critical COVID-19 than in ICU patients without COVID-19. In another study conducted in France, obesity (BMI>30) and severe obesity (BMI>35) were present in 47.6% and 28.2% of 124 patients with COVID-19, respectively. Eventually, 68.6% of the patients required invasive mechanical ventilation (IMV). The proportion of patients who required IMV increased with BMI categories. The requirement of IMV was significantly associated with the male sex (P<0.05) and BMI (P<0.05), independent of age, diabetes, and hypertension in multivariate logistic regression. The ORs for IMV in patients with BMI >35 versus patients with BMI <25 was 7.36 (1.63-33.14; P=0.02) [4]. Similar findings were reported in patients hospitalized with COVID-19. In 5,795 patients with COVID-19 infection, the ORs for relative risk of mortality at 30 days for patients with a BMI of 25-29.9, 30-35, 35-40, and >40 were 1.41, 1.89, 2.79, and 2.55, respectively, even after correction for age, sex, and comorbidities [5]. In line with the accumulating reports, it was shown in a retrospective analysis of 140 consecutive COVID-19-related acute respiratory distress syndrome (CARDS) cases admitted to the ICU of two hospitals in Italy that the BMI was significantly higher compared with that of 247 other patients with nonCOVID-19-related ARDS (28 vs. 25 kg/m^2, P<0.0001) [6].

In single prospective cohort study in the United States, the strongest risk for hospital admission was associated with age, followed by heart failure, male sex, chronic kidney disease, and any increase in BMI (BMI>40: 2.5, 1.8-3.4). The strongest risks for critical illness besides age were associated with heart failure (1.9, 1.4-2.5), BMI>40 (1.5, 1.0-2.2), and male sex (1.5, 1.3-1.8) [7]. Additionally, in a retrospective case series study that included confirmed COVID-19 positive cases consecutively admitted at a referral hospital in the United States, 35.8% were obese and 43.4% required IMV. It is noteworthy that the number of patients who received IMV was more than 10-fold higher compared with that of China [8]. Although the exact reason remains to be elusive, it is likely that the large number of patients with obesity in the United States might have contributed to this discrepancy. Another study in the United States showed that of the symptomatic patients who tested positive for COVID-19, 21% had a BMI between 30 and 34 kg/m^2, and 16% had a BMI greater than 35 kg/m^2. Importantly, among patients younger than 60 years, those with a BMI between 30 and 34 kg/m^2 were, respectively, 2- and 1.8-fold more likely to receive acute or critical care. Likewise, among patients younger than 60 years with a BMI greater than 35 kg/m^2, patients were 2.2- and 3.6-fold more likely to receive acute or critical care, respectively [9]. Although young age is considered to be a negative risk factor for COVID-19 severity, patients with obesity with COVID-19 require

special attention, regardless of age.

The United Kingdom (UK) was one of the nations most severely impacted by COVID-19. The International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) World Health Organization (WHO) Clinical Characterisation Protocol UK (CCP-UK) study was conducted with the aim to explore risk factors associated with mortality in hospitals. A multivariate analysis of 20,133 hospitalized patients with COVID-19 clearly showed that chronic cardiac disease, nonasthmatic chronic pulmonary disease, chronic kidney disease, liver disease, and obesity, but not diabetes, were associated with increased hospital mortality (hazard ratio [HR] 1.33) [10]. In another community-based cohort study, there was an upward linear trend in the likelihood of COVID-19 hospitalization associated with increasing BMI that was evident in BMI groups categorized as overweight (OR, 1.39), obese stage I (OR, 1.70), and obese stage II (OR, 3.38) compared with the BMIs of a normal weight group [11]. A recently released study demonstrated that among 6,910,695 eligible individuals (mean BMI 26.78 kg/m^2), 13,503 (0.20%) were admitted to a hospital, 1,601 (0.02%) to an ICU, and 5,479 (0.08%) died after testing positive for COVID-19. The authors found a linear increase in the risk of severe COVID-19 leading to admission to hospital and death among patients with a BMI greater than 23 kg/m^2 and a linear increase in admission to an ICU across the whole BMI range, which was not attributable to the excess risks of related diseases. The authors concluded that the relative risk due to increasing BMI is particularly notable in people younger than 40 years and of black ethnicity [12].

Two successive studies also highlighted that obesity is a potential predictor of disease severity in young patients with COVID-19, especially who are younger than 50 years of age [13,14]. In South Korea, data from 5,628 patients with COVID-19 showed that obesity was associated with a higher HR for mortality (adjusted HR = 1.71) [15]. The impact of obesity on COVID-19 severity is briefly summarized in Table 1.

Based on the general belief that obesity predicts worse outcomes of COVID-19, the UK government advised those with a BMI of at least 40 kg/m^2 to be particularly stringent in following social distancing measures [16]. Obesity experts are expressing a concern about excessive social and medical costs that are potentially elicited by patients who are morbidly obese with COVID-19 infection.

ARE PATIENTS WITH OBESITY MORE SUSCEPTIBLE TO COVID-19 INFECTION?

Several review articles have provided insight into how obesity increases COVID-19 susceptibility [17]. Indeed, in South Korea, a comparison of 2,231 patients with confirmed COVID-19 and 10-fold-matched negative test controls by a propensity score-matched case-control study showed that overweight and class 1 obesity had significantly increased COVID-19 risk, whereas class 2 and 3 obesity (BMI≥30 kg/m^2) showed a similar but nonsignificant trend [18]. Another nationwide case-control study included 3,788 case patients with COVID-19 and 15,152 age- and sex-matched controls who underwent National Health Insurance Service health examinations in 2015-2017. In multivariable logistic regression models, there was a graded association between higher BMI levels and a higher risk of COVID-19 infection; compared to normal weight individuals, the adjusted ORs in the individuals who were overweight and obese were 1.13 (95% CI, 1.03-1.25) and 1.26 (95% CI, 1.15-1.39), respectively [19].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) gains cellular entry via angiotensin converting enzyme 2 (ACE2) [20]. ACE2 is an enzyme of the renin-angiotensin system that degrades angiotensin II, thereby promoting vasodilation and increased water excretion. Although ACE2 generally plays a beneficial role in COVID-19 infection, increased ACE2 expression in lung epithelium theoretically promotes viral entry. A recent study compared bronchial epithelial ACE2 gene expression in patients with chronic obstructive pulmonary disease (COPD) according to BMI (BMI<24.9 [n=14] and BMI>24.9 [n=23]) [21]. Increased ACE2 expression was observed in patients who were overweight with COPD (mean BMI, 29 kg/m^2) compared with nonoverweight patients with COPD (mean BMI, 21 kg/m^2). Nevertheless,

Table 1. Summary of recent literatures showing the impact of obesity on coronavirus disease 2019 severity

Country	Number of Patients & Prevalence of Obesity	Major Findings	References
China	Total no. of patients: 383, BMI 28 kg/m^2: 41 (10.7%)	Increased risk for developing severe pneumonia in BMI 28 kg/m^2 (OR, 1.84; 95% CI, 0.99–3.43)	Cai et al. (2020) [2]
France	Total no. of patients: 291, BMI 35 kg/m^2: 85 (25%)	Higher prevalence of obesity in ICU in COVID-19 compared without COVID-19 (OR, 1.69; 95% CI, 1.10–2.56)	Caussy et al. (2020) [3]
France	Total no. of patients: 124, BMI 30 kg/m^2: 47.6% BMI 35 kg/m^2: 28.2%	Higher requirement for IMV in higher BMI (P< 0.05), greatest in BMI>35 kg/m^2 (OR, 7.36; 95% CI, 1.63–33.14)	Simonnet et al. (2020) [4]
France	Total no. of patients: 5,795, BMI 30–35; M=318; F=474 BMI 35–40; M=170; F=126 BMI>40; M=104; F=72	Higher mortality in BMI of 25–29.9, 30–35, 35–40, and >40 (OR, 1.41, 1.89, 2.79, and 2.55 respectively, even after correction for age, sex, and comorbidities)	Czernichow et al. (2020) [5]
Italy	Total no. of patients: 140, BMI 30–35 kg/m^2 18 (25%), BMI 35–40 kg/m^2 9 (13%), BMI>40 kg/m^2 2 (3%)	Higher percentage for ICU care, requiring mechanical ventilation and severe ARDS in patients with BMI 30 kg/m^2 (OR, 3.42; 95% CI, 1.79–6.52)	Chiumello et al. (2020) [6]
United States	Total no. of patients: 5,279, BMI 25–29; 1,760 (33.5%), BMI 30–39; 1,554 (29.4%), BMI>40 kg/m^2 311 (5.9%)	Higher risk for hospital admission for BMI >40 kg/m^2: OR, 2.5; 95% CI, 1.8–3.4) and critical illness for BMI >40 kg/m^2 (OR, 1.51;95% CI, 1.0 to 2.2)	Petrilli et al. (2020) [7]
United States	Total no. of patients: 393, BMI 30 kg/m^2: 136 (35.8%),	Obesity was a risk factor for respiratory failure leading to invasive mechanical ventilation: obese patients in IMV group; 56/129 (43.4%) vs. in non-IMV group 80/251 (31.9%)	Goyal et al. (2020) [8]
United States	Total no. of patients: 3,615 Age<60y: BMI 30–35 kg/m^2: 171 (29%) BMI 35 kg/m^2: 134 (22%)	Higher risk for acute and critical care for BMI 35 kg/m^2 (OR, 2.0; 95% CI, 1.6–2.6) and critical illness for BMI >40 kg/m^2 (OR, 1.51; 95% CI, 1.0 to 2.2), compared to BMI < 30 kg/m^2 in patient aged < 60 years.	Lighter et al. (2020) [9]
United Kingdom	Total no. of patients: 20,133 Obesity: 1,685 (10.5%)	Higher mortality in obese patients (HR, 1.33; 95% CI, 1.19–1.49)	Docherty et al. (2020) [10]
United Kingdom	Total no. of patients: 502,655 Overweight: 19.1 per 10,000 BMI 30–35: 23.3 per 10,00 BMI >35: 42.7 per 10,000	Linear trend of COVID-19 hospitalization with increasing BMI: Overweight (OR, 1.39; 95% CI, 1.13–1.71), BMI 30–35 kg/m^2 (1.70;1.34–2.16), BMI >35 kg/m^2 (3.38;2.60–4.40)	Hamer et al. (2020) [11]
United Kingdom	Total no. of patients: 6.9milion (6,910,695) BMI 30 kg/m^2: 15.5% BMI 35 kg/m^2: 8.8%	J-shaped associations between BMI and admission to hospital due to COVID-19 (HR, from the nadir at BMI of 23 kg/m^2 of 1.05; 95% CI, 1.05–1.05) and death (HR, 1.04; 95% CI, 1.04–1.05),	Gao et al. (2021) [12]
China	Total no. of patients: 65 (age: 18–40) divided by COVID-19 severity; Moderate (n=53) vs. Severe (n=12)	Higher BMI (29.23 kg/m^2) in the patients with severe/critical group compared moderate group (22.79 kg/m^2)	Deng et al. (2020) [13]
United States	Total no. of patients: 3,406, Survivor vs. non-survivors; BMI 40 kg/m^2, Age 50: 69 (13.5%) vs. 19 (31.7%)	Higher mortality with BMI40 both in the younger population, (OR, 5.1; 95% CI, 2.3–11.1) and older population (OR 1.6; 95% CI, 1.2–2.3).	Klang et al. (2020) [14]
South Korea	Total no. of patients: 5,628, BMI 30 kg/m^2: 47.6%, BMI 35 kg/m^2: 28.2%	Higher HR of mortality (HR, 1.71; 95% CI, 1.10–2.66)	Kim et al. (2020) [15]

BMI = body mass index, O = odds ratio, CI = confidence interval, ICU = intensive care unit, COVID-19 = coronavirus disease 2019; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), IMV = invasive mechanical ventilation, M = male, F = female, ARDS = acute respiratory distress syndrome, HR = hazard ratio.

transmembrane protease serine 2 (TMPRSS2) bronchial expressions between the two groups did not differ. In addition, the serum ACE2 level was higher among patients with obesity and/or type 2 diabetes in a single center population-based study of 5,457 Icelanders [22], which supports the deleterious effect of obesity on COVID-19

susceptibility.

The 2009 influenza pandemic showed that obesity was an independent risk factor for severe influenza morbidity and mortality, which is a lesson that may be extrapolated to infectious diseases. Of the influenza patients studied, 51% had a BMI ≥30, which is 2.2 times the prevalence of obesity among California adults (23%), thus, suggesting that obesity enhances susceptibility to influenza. A similar result was drawn from a study of Middle East respiratory syndrome coronavirus (MERS-CoV) 2012, which exhibited a higher prevalence among individuals with obesity [23]. Data from a recently released metaanalysis support the role of obesity in COVID-19 susceptibility. The pooled obesity prevalence rates from 19 studies were 0.32 (95% CI: 0.24-0.41) in hospitalized patients, which was higher than the general prevalence of obesity [24]. Considered together, it is highly likely that obesity not only exacerbates severity and/or mortality of COVID-19 but also contributes to susceptibility.

POSSIBLE UNDERLYING MECHANISM OF INCREASED COVID-19 SUSCEPTIBILITY AND SEVERITY MEDIATED BY OBESITY

Although it remains unclear, there are diverse mechanisms by which obesity promotes the severity and infectivity of COVID-19 [17,25]. Recent findings of a correlation between obesity and COVID-19 severity are recapitulations of old lesions from the 1918 Spanish influenza pandemic and the 2009 influenza A virus H1N1 pandemic, which universally demonstrate the contribution of obesity to the severity of infectious diseases. In particular, viral shedding is prolonged in patients with obesity [26]. Symptomatic obese adults shed influenza A virus 42% longer, with predicted mean shedding times of 5.23 days versus 3.68 days in lean subjects, which potentially causes long-term transmission. Even among paucisymptomatic and asymptomatic adults, obesity increased the influenza A shedding duration by 104%. Likewise, in a small cohort of 100 consecutive patients with COVID-19, a longer time (19±8 days) to SARS-CoV-2 negativity was reported compared to that of nonobese patients with COVID-19 (13±7 days) [27]. Considered together, it is logical to assume that obesity contributes to delayed clearance or enhanced replication of the virus.

Indeed, an adipocentric view of severe COVID-19 risk in obesity has been well described in previous literatures [17,28,29]. ACE2 is also highly expressed in the adipose tissue [30], which suggests that adipocytes are potentially infected by SARS-CoV-2. Increased expression of ACE2 in adipose tissue has been linked to worse clinical outcomes of COVID-19. Therefore, a plausible mechanism for obesity-mediated SARS-CoV-2 severity is related to a viral tropism toward adipose tissue and that adipose tissue might serve as a reservoir for SARS-CoV-2.

Another critical feature of obesity is that it can be accompanied by obstructive sleep apnea and/or ventilation disorders, which further exacerbates hypoxemia by viral pneumonia. Patients with obesity exhibit respiratory dysfunction due to a variety of factors [31], including impaired respiratory function, increased airway resistance, impaired gas exchange, low lung volume, and low muscle strength [31]. Indeed, patients with obesity tend to be mildly hypoxemic, possibly due to ventilation-perfusion mismatching at the base of the lungs [32]. Importantly, among patients with COVID-19, a BMI ≥30 kg/m^2 was associated with the risk of hypoxemia upon hospital admission [33].

Obesity accompanies noncommunicable diseases, such as diabetes mellitus, cancers, and nonalcoholic fatty liver disease. Each comorbidity is considered to increase the severity of COVID-19 [34]. Therefore, it is highly likely that a cluster of these diseases might further aggravate the prognosis of infection. Furthermore, obesity represents the status of chronic low-grade inflammation and proinflammatory cells such as macrophages, dendritic cells, Th1 cells, and cytotoxic T cells that accumulate in the adipose tissue of patients with obesity. In turn, recruited immune cells further aggravate insulin resistance and chronic inflammation [35]. Considered together, combined adipose tissue-mediated immune and metabolic dysfunctions negatively impact COVID-19 prognosis [36].

Growing evidence shows that COVID-19-related hypercoagulopathy is a prerequisite for cytokine release

syndrome and is a main cause of death [37]. Given that obesity provides prothrombotic milieu [36], and more specifically, obese subjects have higher plasma concentrations of all prothrombotic factors (plasminogen activator inhibitor-1, fibrinogen, vWF Ag, and factor VII) compared with nonobese controls, it is highly likely that obesity aggravates thrombotic tendency or endothelial dysfunction. We have summarized the pathophysiological impact of obesity on COVID-19 severity in Fig. 1.

THE ROLE OF BARIATRIC AND METABOLIC SURGERIES DURING THE COVID-19 ERA

In Italy, a retrospective analysis of 2,145 patients who had previously undergone bariatric or metabolic surgery showed that only 0.6% of patients tested positive for COVID-19 and only 0.1% needed ICU admission, which suggests that previous bariatric or metabolic surgery might be a safe preventative measure against COVID-19. In this analysis, the mean presurgical BMI was 44.5±6.8 kg/m^2, whereas the mean BMI after surgery was 29.3±5.5 kg/m^2 ($P<0.05$) [38]. Moreover, the systematic review yielded three retrospective studies on 9,022 patients. The risk of mortality in patients without previous bariatric surgery was 133 per 1,000 cases, and the risk of mortality in patients with previous bariatric surgery was 33 per 1,000 (OR 0.22). In the pooled analysis, the hospitalization rate in patients without previous bariatric surgery was 412 per 1,000 cases, and the hospitalization rate in patients with previous bariatric surgery was 164 per 1,000 (OR 0.28) [39]. In another U.S. study that conducted a multivariate analysis, a prior history of metabolic surgery was associated with a lower hospital admission rate compared with control patients with obesity. Intriguingly, it is noted

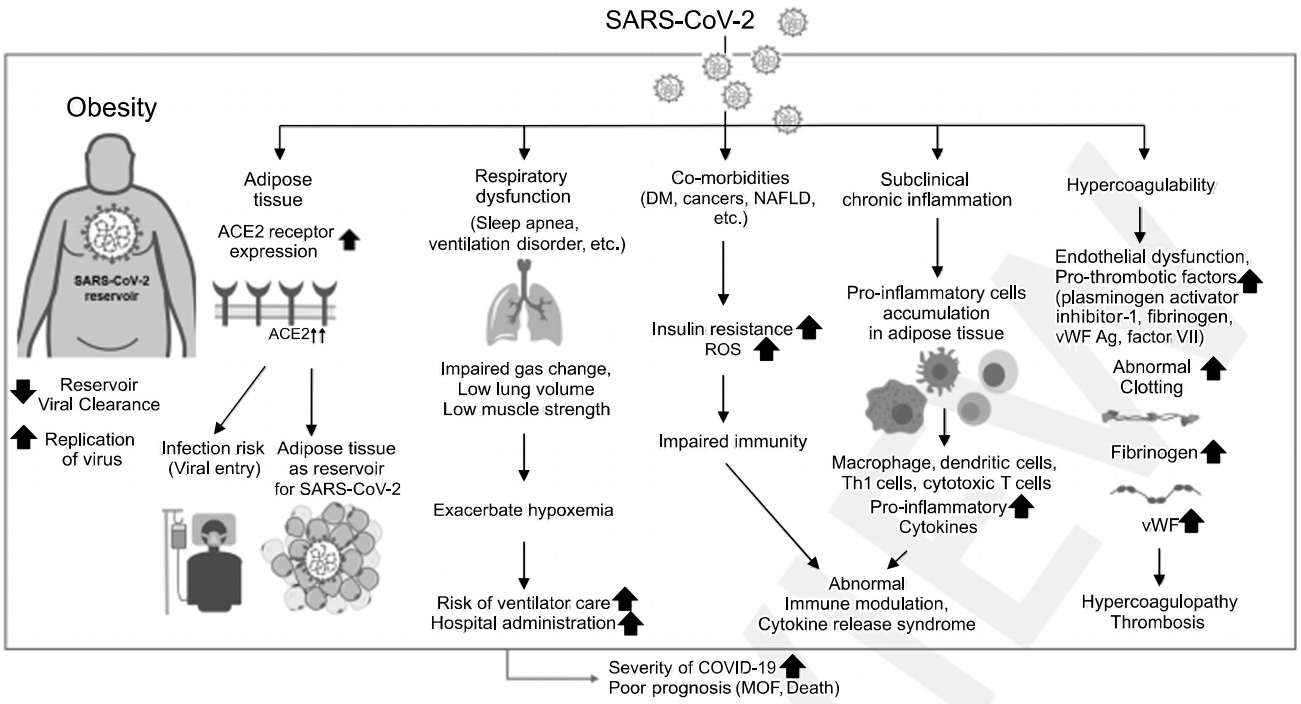

Fig. 1. Potential mechanism of increased COVID-19 susceptibility and severity by obesity. Obesity leads to delayed clearance or enhanced replication of virus. ACE2 is highly expressed in adipose tissue therefore adipose tissue might play as reservoir for SARS-CoV-2. Obesity often accompanies obstructive sleep apnea as well as ventilation disorder that further exacerbates hypoxemia by viral pneumonia. Obesity as well as co-morbidities such as diabetes mellitus, cancers and non-alcoholic fatty liver disease represents the status of chronic low grade inflammation and pro-inflammatory cells are accumulated in the adipose tissue of patients with obesity. Recruited immune cells, in turn, further aggravate insulin resistance and chronic inflammation. Obesity causes hypercoagulopathy and obese subjects has higher plasma concentrations of all pro-thrombotic factors as compared to non-obese controls. These factors aggravate endothelial dysfunction which is another hallmark of COVID-19 infection.

that Roux-en-Y gastric bypass downregulates ACE2 gene expression in subcutaneous adipose tissue [40], which might act as a protective mechanism against COVID-19 infection.

Although bariatric surgery is being postponed due to COVID-19, the American Society for Metabolic and Bariatric Surgery (ASMBS) recently released a statement regarding metabolic and bariatric surgery during the COVID-19 pandemic. The society claims that metabolic and bariatric surgeries should be resumed when it is safe, and it disagrees with the concept that the surgery should be postponed until the pandemic is over. Whether this policy can be applied to other countries needs further investigation.

CONCLUSION

Accumulating evidence shows the detrimental effect of obesity on COVID-19 prognosis. While adipose tissue inflammation and its effects on the immune system aggravate the disease course, obesity perturbs efficient ventilation and induces hypoxemia under COVID-19 infection. Furthermore, it is likely that adipose tissue expresses ACE2, thereby acting as a reservoir for SARS-CoV-2, which might possibly explain the longer viral shedding and delayed viral clearance that occur in obese patients. Patients who were previously obese who had undergone bariatric surgery generally tolerated and stayed safe from COVID-19 infection. Following the ASMBS' recommendation, it is time to consider resuming elective bariatric and metabolic surgeries.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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