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REVIEW

The Dual Pandemics of COVID-19 and Obesity: Bidirectional Impact

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the COVID-19 pandemic, has been shown to disrupt many organ systems in the human body. Though several medical disorders have been affected by this infection, a few illnesses in addition may also play a role in determining the outcome of COVID-19. Obesity is one such disease which is not only affected by the occurrence of COVID-19 but can also result in a worse clinical outcome of COVID-19 infection. This manuscript summarizes the most recent evidence supporting the bidirectional impact of

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COVID-19 and obesity. It highlights how the presence of obesity can be detrimental to the outcome of COVID-19 in a given patient because of the mechanical limitations in lung compliance and also by the activation of several thrombo-inflammatory pathways. The sociodemographic changes brought about by the pandemic in turn have facilitated the already increasing prevalence of obesity. This manuscript highlights the importance of recognizing these pathways which may further help in policy changes that facilitate appropriate measures to prevent the further worsening of these two pandemics.

Keywords: Obesity; COVID-19; SARS-CoV-2; Syndemic; Bidirectional impact

Key Summary Points

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the COVID-19 pandemic, has been shown to disrupt many organ systems in the human body. Although several medical disorders have been affected by this infection, a few illnesses play a role in determining the outcome of COVID-19.

Obesity is one such disease, which is not only affected by the occurrence of COVID-19 but can also result in a worse clinical outcome of COVID-19 infection.

This manuscript summarizes the most recent evidence supporting the bidirectional impact of COVID-19 and obesity. It highlights how the presence of obesity can be detrimental to the outcome of COVID-19 in a given patient because of the mechanical limitations in lung compliance and by the activation of several thrombo-inflammatory pathways.

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INTRODUCTION

Medical diseases have been traditionally classified as communicable and non-communicable disorders. In the past, many of the communicable disorders have been associated with non-communicable diseases. A higher occurrence of non-alcoholic fatty liver disease (NAFLD) has been associated in those infected with human immunodeficiency virus (HIV) infection [1] and similarly a higher occurrence of metabolic bone disorders has shown to be associated with hepatitis B infection [2]. Following the emergence of the COVID-19 pandemic, the intersection between COVID-19 and other non-communicable diseases has been researched by many clinician scientists [3].

Several metabolic disorders like diabetes, hypertension, and obesity have been linked with the severity and prognosis of COVID-19 [4]. There have also been reports about how COVID-19 infection can predispose to the development and worsening of these disorders [5–7]. In this scoping review the authors describe the bidirectional association of COVID-19 and obesity and propose methods to improve the outcomes of those affected by both of these pandemics.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

PROBLEM STATEMENT OF COVID-19 AND OBESITY

Obesity has reached pandemic proportions globally, and though initially considered to be a disease more prevalent in developed countries, it is rapidly affecting those in developing countries. Most recent data from a global meta-analysis involving 13.2 million subjects, it was noted that the overall prevalence of central obesity is about 42% [8]. Data from The National Health and Nutrition Examination Survey (NHANES) database suggested that about 35% of the American population is affected with obesity [9]. Even recently published data from developing countries like India based on the national family health survey found that about 38% of the Indian adult population are overweight or have obesity [10].

With the onset of the COVID-19 pandemic since December 2019, there has been a drastic change in the physical activity behaviors, screen time, and dietary practices of individuals [11]. This has led to a rapid increase in the prevalence of obesity not only in adults but also in children [12, 13] In a longitudinal analysis, the prevalence of obesity in adolescents (11–-16 years) from China showed a significant increase in the percentage who are obese (14.2–15.4%) after onset of the pandemic. The

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average body mass index in this cohort increased from 20.3 to 21.2 kg/m^2 [14].

Furthermore, obesity has also been shown to predispose persons to severe COVID-19 infection. Though in the initial reports several comorbidities like diabetes, hypertension, cardiovascular disease, and cancer were associated with high risk of developing COVID-19-related complications, obesity was added later to the list. In a study by Docherty et al., among 20,133 hospitalized patients with SARS-CoV-2 infection in 208 hospitals across the UK, about 10% of patients were found to have obesity. Obesity was also found to be a strong predictor of mortality (HR 1.33; 95% CI 1.19–1.49) after adjusting for other comorbidities [15]. In another study at the New York University Langone Medical Center involving 5279 subjects with COVID-19, in a multivariate regression severe obesity (body mass index, BMI > 40 kg/m^2) emerged as an independent risk factor for both hospital admission (OR 2.5; 95% CI 1.8–3.4) and intensive care unit (ICU) requirement (OR 2.5; 95% CI 1.8–3.4) [16]. In a Mexican cohort, out of 51,633 SARS-CoV-2-positive cases, 5332 deaths (10.3%) were reported. Patients with obesity were found to have a higher rate of mortality (13.5% vs 9.4%), need for critical care support (5.0% vs 3.3%), and ventilator requirement (5.2% vs 3.3%) as compared to those without obesity [17].

These data highlight the impact of COVID on the prevalence of obesity and also underscore the importance of recognizing obesity as an important risk factor for poor outcomes associated with COVID-19 infection. Each of these amplifies its deleterious effect on the another, in a bidirectional manner. The data on mortality associated with SARS-COV2 infection is summarized in Table 1.

Table 1 Impact of obesity on mortality associated with COVID-19

Authors	Country	Number	Odds of mortality	95% CI
Peng et al. [18]	China	244	8.59	4.18, 17.63
Rottoli et al. [19]	Italy	482	12.10	3.25, 45.1
Palaiodimos et al. [20]	USA	200	3.78	1.45, 9.83
Giacomelli et al. [21]	Italy	233	3.04	1.42, 6.49
Docherty et al. [22]	UK	20,133	1.33	1.19, 1.49
Pettit et al. [23]	USA	238	1.7	1.10, 2.80

FACTORS RELATED TO OBESITY THAT PREDISPOSE FOR DEVELOPING COVID-19 AND ITS RELATED COMPLICATIONS

People living with obesity have about a 46% higher chance of contracting SARS-COV2 infection as compared to those with normal weight. Moreover, the risk of an ICU admission and need for mechanical ventilation is also increased by 73% and 69%, respectively [24]. Several mechanisms of how people with obesity get predisposed to severe infection are outlined in Fig. 1. These are detailed below.

Enhanced Inflammatory Response

Acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) are two of the key reasons for heightened morbidity and mortality among individuals who are infected with SARS-CoV-2. These are predominantly driven by excessive production of pro-inflammatory cytokines which in turn leads to extensive pulmonary damage, hypoxemic respiratory failure, and pulmonary edema. People living with obesity have a higher chance of developing ARDS and requiring mechanical ventilation [25].

Excessive adiposity is also linked to altered intracellular signaling. Enlarged adipocytes are hyperresponsive to tumor necrosis factor alpha (TNFα) with increased expression of nuclear factor kappa beta (NF-κB), thus leading to adipocytokine overproduction [26]. Moreover,

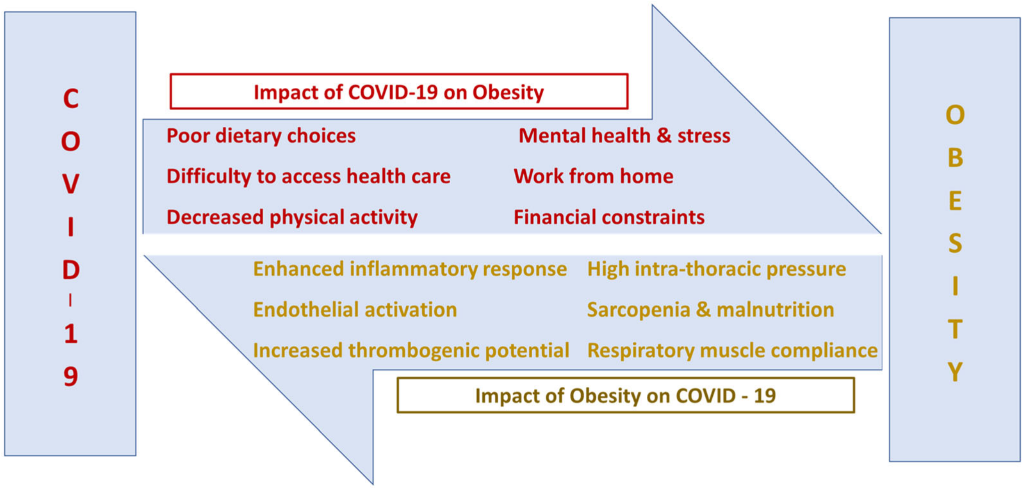

Fig. 1 Bidirectional impact of COVID-19 and obesity

higher circulating levels of monocyte chemoattractant protein 1 (MCP-1) in individuals with obesity enhance the recruitment of monocytes and macrophages into adipose tissue and the arterial wall [27]. This augmented systemic inflammatory tone is suspected to contribute to increased cardiovascular events, which have often been reported in patients with COVID-19. Furthermore, additional factors like increased oxidative stress and hypoxia also synergize with the pro-inflammatory microenvironment in patients with obesity [28].

Endothelial Activation

In addition to an altered immune response, microthrombi have been found in about 60% of patients who have died as a result of COVID-19 in different autopsy studies [29]. These microthrombi were present in the lung, kidney, liver, and the heart. The other associated histopathological findings in these patients with microthrombi included exudative alveolar damage, pulmonary embolism, and pulmonary infarction. These findings suggest that there is widespread endothelial hyperactivation during COVID-19 infection that can lead to respiratory failure by promoting deposition of intra-alveolar deposits of fibrin and activated leukocytes [30].

It has been reported that endothelial dysfunction is very closely associated with COVID-19, and that this profound alteration may led to impaired organ perfusion and generating a number of acute events such as renal failure, myocardial injury, and procoagulant state, thus resulting in thromboembolic events [31]. Some authors have highlighted the pro-thrombotic potential of monocytes, and consequently the link with the prothrombotic state associated with SARS-CoV-2 infection [32, 33]; indeed, the involvement of endothelial dysfunction in the pathogenesis of COVID-19 in patients with cardiometabolic diseases has been extensively investigated [34].

The hyperactivation of intracellular pathways secondary to endothelial dysfunction leads to excessive production of adhesion molecules, adipocytokines, and other pro-inflammatory cytokines, especially in those with obesity [35]. The enhanced adhesion, rolling, and transmigration of monocytes across the endothelium further promotes thrombosis described in the next section.

Increased Thrombogenic Potential

Further to the mechanisms related to endothelial dysfunction that promote a prothrombotic state in individuals with obesity following COVID-19 infection, other mechanisms are also described. The adipose tissue-regulated factors including thrombospondin-1 and TNFα have been shown to promote the production of plasminogen activation inhibitor 1 (PAI-1) [36]. PAI-1 has been shown to reduce fibrinolytic activity in an infected person with obesity, thus further enhancing thrombogenic potential and its associated mortality [37]. In many patients with obesity having ARDS, thrombotic complications like venous thromboembolism, thrombocytopenia, renal failure, and disseminated intravascular coagulation have been reported [38].

High Intra-Abdominal/Thoracic Pressure

Increased adiposity is known to be associated with an increases in both intra-abdominal and intra-thoracic pressures. The latter often results in a restrictive lung condition. Sugerman et al. found that the intra-abdominal pressure measured during bariatric surgery was significantly higher in those having a BMI of more than 35 kg/m^2 ($n = 84$) as compared to those without obesity ($n = 5$) (18 ± 0.7 vs 7 ± 1.6 cmH_2O, $p < 0.001$) [39]. Similarly, for the intra-thoracic pressure, in a study by Behazin et al., the airway pressure was about 1.3 cmH_2O higher in individuals with a BMI greater than 35 kg/m^2 ($n = 50$) as compared to those without obesity ($n = 10$) [40]. These elevated pressures are associated with reduced respiratory compliance in people with obesity as compared to those who are not obese.

Airway hyperresponsiveness is also known to be greater in patients with obesity. This was studied in the Normative Aging Study wherein airway hyperresponsiveness was evaluated with methacholine challenge tests. The two groups, those who tested positive in a follow-up test as compared to those who tested negative during follow-up, were compared. Individuals in both groups tested negative at baseline. After controlling for common confounding factors including age, smoking status, etc. people with obesity were found to have a 7.5 times higher odds of having a subsequent positive methacholine challenge. Furthermore, those who had the highest increment in BMI had a higher odds of developing airway hyperresponsiveness when compared to those with minimal weight gain [41]. In another large meta-analysis covering over 300,000 subjects to assess the association of obesity with asthma, it was found that people with obesity had a 1.92 (95% CI 1.43–2.59) higher odds of having asthma [42].

Sarcopenia and Malnutrition

Sarcopenia is referred to as decreased muscle mass, function, and/or strength. Sarcopenia has been associated with an increased occurrence of pneumonia, mechanical ventilation, hospitalizations, and mortality [43, 44]. Increased body fat in the presence of low muscle mass further enhances mitochondrial dysfunction, impaired bioenergetics, and increased production of reactive oxygen species [44]. The secretion of proinflammatory myokines in this setting is known to worsen the muscle dysfunction [45]. Obesity in the setting of COVID-19 is an important predictor of a poor clinical outcome, but sarcopenic obesity is probably even a more important risk factor [46].

Poor Respiratory Muscle Function

Excessive fat deposition also increases the pressure against which the respiratory muscles need to act to produce lung expansion. It increases the effort both that is required to raise the chest wall and faces increased resistance offered by the elevated abdominal pressures, described above [47]. Moreover, the diaphragm function is also impaired, further compounding the lung expansion during respiration. These limitations result in a reduction of the total lung capacity and the functional residual capacity in individuals with obesity. It was also found that BMI has a significant effect on all of the lung volumes, and that the functional residual capacity can decrease by 3% for each unit increase in BMI [48, 49]

Long-Term Consequences of Obesity on COVID-19 Outcomes

Obesity is associated with significant morbidity and mortality from COVID-19 infection. In a recent meta-analysis by Cai et al., involving 46 studies and 625,153 study subjects, patients with obesity were found to have a significantly increased risk of infection (OR 2.73, 95% CI 1.53–4.87), hospitalization (OR 1.72, 95% CI 1.55–1.92), clinically severe disease (OR 3.81, 95% CI 1.97–7.35), mechanical ventilation (OR 1.66, 95% CI 1.42–1.94), ICU admission (OR 2.25, 95% CI 1.55–3.27), and mortality (OR 1.61, 95% CI 1.29–2.01) [50]. Not only is the number of patients with obesity admitted to the ICU higher than the non-obese individuals but also their overall outcome is poorer.

In a cohort study by Shang et al., patients with obesity had a significantly poorer clinical outcome at discharge as compared to those without obesity [51]. The clinical features and the pathological findings on computed tomography scans of patients with obesity were more serious after discharge than in those without obesity. Moreover, people with obesity had significantly worse metabolic abnormalities in terms of blood lipids, uric acid, and liver function tests. Furthermore, the antibody titer was inversely correlated with BMI in patients with obesity [51, 52].

FACTORS RELATED TO COVID-19 THAT PREDISPOSE TO OBESITY

During several phases of lockdown in the pandemic, restricted physical activity coupled with increased food intake was the most common cause cited for increases in body weight. Among the several risk factors contributing to weight gain during lockdown, factors such as female sex, younger age, previous excess weight, those living in smaller apartments, having lower level of education, and low income had a greater probability of gaining weight [53].

Psychological Impact of COVID-19 on Obesity

The psychological impact of obesity is well known. In a recent study conducted in southern India, it was found that about 30% of individuals attending an obesity clinic have an underlying psychological problem [54]. The prevalence of depression is about 25% higher among people with obesity, who also have a significantly higher risk of anxiety and eating disorders. In the context of COVID-19, the prevalence of psychological problems has increased significantly in the last 2 years. These psychological problems in turn translate into increased social stress, isolation, sleep deprivation, and disruption of the circadian rhythm. Ultimately they promote a sedentary lifestyle, eating disorders, increased alcohol intake, and an increase in other addictions. Moreover, the constant fear of infection for oneself and family adds to the existing mental stress. In the elderly, isolation may further worsen dementia, as they feel disconnected from their usual family environment and health monitoring. Furthermore, the stress of unemployment, lack of job security, and the consequent socioeconomic gap further contribute to an obesogenic environment [55].

Difficult to Access Healthcare

During the COVID-19 pandemic many healthcare centers were catering to only emergency healthcare in order to reserve the workforce to run the COVID services. As a result, healthcare delivery for chronic disorders was significantly affected. In addition to obesity, diseases like diabetes, hypertension, dyslipidemia, and coronary heart disease have shown a worsening trend.

For obesity, one of the major setbacks was on the bariatric surgery waiting list. Up to 50% of patients on the bariatric surgery waiting list developed a new complication of obesity while awaiting surgery, and 1.5% even died at that time [56]. Beyond the benefits that patients can gain following timely bariatric surgery, it has been reported that patients on a waiting list experienced a worse severity of illness due to COVID-19 [57].

Limited Scope of Physical Activity

With the institution of social lockdowns there was limited access to athletic facilities, and restrictions made it difficult to do outdoor physical activity outdoors; coupled with the lack of routine exercise at home, this greatly hindered the ability to maintain an active lifestyle.

Robertson et al.'s recent study investigating changes in physical activity patterns due to the COVID-19 pandemic in individuals with obesity found that there was a significant decrease in the weekly step count and decline in their weekly active minutes compared to their counterparts from the year before [58]. Decreased motivation, gym closures, and safety concerns were cited as the key barriers to physical activity.

Poor Dietary Choices While Working from Home

Weight gain was greater in the first few weeks of lockdown because of a 50% increase in purchase and consumption of high calorie products like alcoholic beverages, sweets, and snacks.

In a study from Poland involving over 1000 individuals, aimed at assessing the impact of the pandemic on nutritional and consumer habits [59], about 52% of study participants reported increased snacking, more commonly in overweight and obese individuals. Almost one-third of individuals experienced weight gain. An increase in weight was associated with less frequent consumption of vegetables, fruits, and legumes during quarantine, and higher adherence to meat, dairy, and fast food. Moreover, an increase in alcohol consumption was seen in about 15% of individuals, with a higher tendency to drink more alcohol in those already addicted.

COVID-19 and Normal Weight Obesity

With a recent increase in the number of CT scans of the chest done to assess COVID-19 severity, a lot of data has emerged about the presence of visceral adiposity in individuals with normal weight [60]. This has been previously described and studied in the South Asian region [61–63]. Emerging evidence from the study of these scans suggests a higher morbidity and mortality in individuals with normal weight obesity as compared to those without higher adiposity [64]. This further highlights the importance of the heightened inflammatory state in individuals with increased adipose tissue in the setting of COVID-19. Several authors have highlighted the importance of inflammation during SARS-CoV-2 infections, as well as the ethnic differences in the outcomes of the pandemic [65, 66].

EVALUATION OF OBESITY IN THE SETTING OF COVID-19

The evaluation of a patient with obesity in COVID-19 times is no different than in prepandemic times. It is important to assess the comorbidities associated with obesity as individually addressing them is essential to improve the overall outcome of COVID-19 [5–7]. The Edmonton obesity staging system (EOSS), which was recently endorsed by the Canadian obesity guidelines, is one of the most practical and effective ways of assessing obesity in a given individual [67]. It assesses the functional status of the patient with obesity and also is able to predict mortality in patients with obesity. In a recent study from Mexico, the EOSS was used in the evaluation of obesity during the COVID epidemic. In this study the mortality risk was increased in EOSS stages 2 and 4 as compared to EOSS stages 0 and 1 [68].

Management of Obesity During the COVID-19 Pandemic

Management of obesity during the COVID -19 pandemic is challenging and a large body of evidence has linked obesity to the most severe forms of COVID-19 disease and related mortality [69, 70]. As a result of limited numbers of appointments, short consultation time, and limited number of bariatric surgeries, the treatment of obesity during the pandemic was compromised. To combat some of these limitations, telemedicine facilities helped to bridge the gap to some extent. In a recent review on the utility of telemedicine for the management of obesity during the COVID-19 pandemic, certain patient-specific and healthcare-specific barriers were identified [71]. Though overall telemedicine has helped to facilitate the management of obesity, certain barriers including the acceptance of the healthcare provider, delay in reimbursement, and following local, regional, and national regulatory guidelines are often required.

In another review, telehealth and tele-exercise were found to be helpful in promoting self-monitoring and behavioral changes, including adherence to exercise training programs in children and adolescents [72]. Moreover, these platforms and applications also allowed flexible scheduling, thereby limiting the infection risks. The importance of telemedicine was emphasized early during the pandemic, and it soon became clear that only the experience can guide future management, in order to implement the most successful digital tools for better care of our patients [73].

Over the past few months, the role of bariatric surgery has also become clearer in the setting of COVID-19. Obesity is now considered a reversible risk factor for preventing or mitigating the impact of the pandemic. It is now suggested to consider metabolic surgery as a medically necessary procedure, as suggested by the American Society for Metabolic and Bariatric Surgery. Moreover, the recent guidelines and consensus statements guide hospitals in resuming bariatric surgery in the COVID-19 era. These guidelines highlight the importance of providing improved access to bariatric surgery in patients with need during the COVID-19 pandemic [19].

BIDIRECTIONAL IMPACT OF COVID-19 AND DIABETES

Patients with diabetes require now, during this long and difficult COVID-19 pandemic, closer management more then ever, since we have observed a bidirectional relationship between COVID-19 and diabetes. Indeed, diabetes is associated with an increased risk for the most severe forms of COVID-19 and its related mortality [74, 75], but, at the same time, patients with COVID-19 have shown new onset of diabetes [76] as well as different forms of damage in the heart and vessels.

Yet, patients with diabetes have been exposed to a significant higher risk of complications for many concomitant reasons, such as altered eating behaviors, reduced physical activity, and lack of access to healthcare facilities for regular control visits. As a result of this, excess mortality and higher numbers of cardiometabolic complications have been noticed early during the pandemic, particularly in patients with diabetes [77–79].

Therefore, careful and proper management of patients with diabetes is mandatory during the COVID-19 era, to minimize the deleterious effects of the pandemic on this category of high-risk subjects, and to promote the use of existing antidiabetic medications with proven cardiometabolic benefits [80–83].

CONCLUSION

There is a bidirectional impact of obesity and COVID-19 on each other, and we have emphasized the importance of a novel multidisciplinary syndemic approach for better management of subjects with obesity during the COVID era [84, 85]. In this review we provide a comprehensive review on the recent evidence that supports the impact of obesity on COVID-19 outcomes. Furthermore, the effects of COVID-19 on obesity and its related comorbidities have also been discussed. This review highlights the urgent need for policy makers to emphasize the importance of lifestyle interventions to improve the lifestyle of individuals in order to reduce risks both in the current and subsequent waves of COVID-19.

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