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Review Article

Pharmacology Section

Effect and Impact of Obesity on Outcome and Complications of COVID-19: A Narrative Review

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) is a viral disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) that triggered a global pandemic back in 2019 and was primarily found to affect the respiratory system which continues its devastating effect across nations. Obesity is already a pre-existing modern-day complication, the root causes for which are largely attributed to the contemporary lifestyle. Many severe cases of COVID-19 in obese patients were reported globally which sparked many theories relating the two as some of their clinical manifestations are closely related. This review aims at providing the possible links between the two providing an idea based on which future research could be carried out since both these diseases tend to affect multiple organs, thus producing profound detrimental effects.

Keywords: Coronavirus disease-2019, Long-term complication, Obese patients

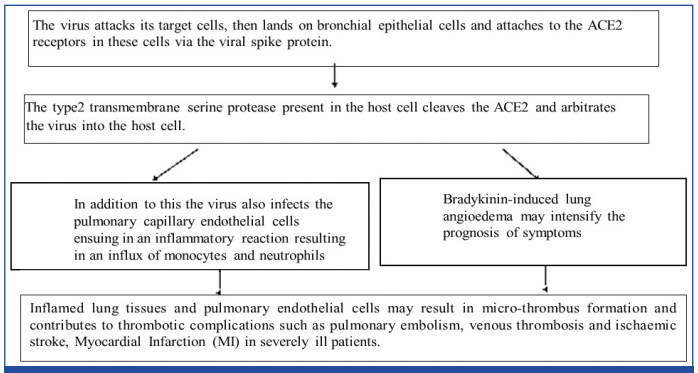
INTRODUCTION

Obesity is a complex condition that occurs when a person has an over abundance of body fat. Obesity is associated with and contributes to a shortened life span with the co-morbidities associated being type 2 diabetes mellitus, cardiovascular disease, cancers, renal disease, gout, osteoarthritis, and hepatobiliary disease, among the others [1]. The aetiology of obesity is largely attributed to genetics, environment, lifestyle, and behavioural traits; it is also closely associated with co-morbidities like hypertension and dyslipidaemia. Mehanna O et al., found a significant difference between normal weight and obese individuals with regards to their random blood glucose levels, triglycerides, lymphocyte count, Erythrocyte Sedimentation Rate (ESR), and C-Reactive Protein (CRP) in an Egyptian population [2].

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which is transmitted through airborne particles [3]. This acute respiratory disease was first reported in Wuhan in China in December 2019. The World Health Organisation (WHO) declared COVID-19 to be a global pandemic in 2020. As of December 2021, India reported over 34 million cases with nearly half a million deaths [4].

Patients with diabetes have a much more severe progression compared to normal subjects when they contract respiratory viruses and invariably the percentage of COVID-19 patients being already affected with diabetes is quite high [5]. Certain classes of medications like Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs) are assumed to increase the expression of ACE2 receptors, thus paving the way for increased viral invasion [6]. While this theory is still a topic of debate, it is worth a consideration [Table/Fig-1].

The link between obesity and COVID is interdisciplinary with effects shown on multiple organs. Majority of the damage being inflicted on the lungs, invariably affects the lung volumes and capacities and thus has a detrimental effect on the quality of life of the patient. Decreased respiratory compliance in obese patients is attributed to reduced chest wall compliance due to deposition of fat in and around the diaphragm and mainly in the abdominal region causing difficulty in breathing by causing increased airway resistance and inefficiency of airway muscles. Thus, obese patients who already



[Table/Fig-1]: Pathophysiology of COVID-19 [7,8].

tend to have a diminished and attenuated respiratory function comparatively take an increased time to recover if affected by any severe infection that affects the respiratory physiology. The link between body fat levels and pulmonary functioning was seen more profoundly in men than in women. In a study conducted by Steele RM et al., (2009) it was inferred that an average of 266 mL decrease of Forced Vital Capacity (FVC) in men and 88 mL in women was seen with an increase of 1 kg/m^2 in Body Mass Index (BMI) [9].

Due to the difficulties associated with breathing in obese patients, the body tends to compensate for this by disproportionately allocating a large proportion of inhaled oxygen for respiration, eventually resulting in a reduction in functional residual capacity and expiratory volume. Thus, a compromise in the ventilation or perfusion of lungs leads to various pulmonary disorders and in severe cases can even lead to pulmonary failure [10]. To add up to the gripe, obese individuals are at an increased risk for developing pulmonary embolism and aspiration pneumonia [11].

Obesity and Blood Coagulation

The coagulation system gets affected due to the alterations in the levels of cytokines and inflammatory mediators in the blood circulation. Blood coagulation is also directly affected by the release of procoagulant and proinflammatory cytokines which can lead to the formation of thrombo-embolic states that affect pulmonary, cardiovascular, and cerebrovascular tissues [12]. There is an increased incidence of thromboembolic complications in COVID-affected individuals with pre-existing obesity amplifying this

condition. Elevated D-dimer levels and fibrin degradation products were found in patients with COVID-19, the reason for it being the inflammatory responses. COVID-19 can also accentuate Metabolic Dysfunction Associated with Fatty Liver Disease (MAFLD) [13].

Obesity and Immune Response

Increased adiposity in obese and overweight individuals results in a substantial rise in the release of inflammatory mediators like cytokines resulting in hyperactive immune response furthermore piling up on the pulmonary damage. Basal state obese individuals generally tend to have higher concentrations of various pro-inflammatory cytokines like Tumour Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6), mainly being synthesised by subcutaneous adipose tissue leading to defect in innate immunity. The initial immune response to the invasion of a novel strain of virus is given by our innate immunity. The accumulation of pro-inflammatory cells in an individual cause an imbalance in the immune system resulting in an inadequate initial response [14]. Leptin is a pleiotropic protein that has long been recognised to play an important role in the regulation of energy homeostasis, metabolism, etc., The core function of leptin is metabolic homeostasis and it delivers information regarding the total body fat mass to the hypothalamus which in turn alters the Central Nervous System (CNS) function and regulates glucocorticoids, insulin hormone, food intake and energy balance [15]. Concurrently, leptin is also found to be a critical regulator of immunity and functions as a pro-inflammatory cytokine-like IL-1, IL-8, IL-18,TNF-α, and its deficiency increases susceptibility to infections [16]. Obesity does promote certain cellular processes that attenuate leptin signalling (resulting in leptin resistance) and amplify the extent of weight gain by environmental and genetic factors. Hence, one can interpret that reduced leptin levels in obese patients could result in impaired immune response upon encountering an infection thus worsening the prognosis of the infection [17].

Obesity and COVID-19

Acute Respiratory Distress Syndrome (ARDS) is a common early manifestation of COVID-19 which could result in lung epithelial cell damage resulting in pulmonary oedema. There are two major phenotypes of COVID-19 that alter the respiratory physiology in our body. These are the L (low) phenotype and the H (high) phenotype. In the L phenotype, the lung requires a reduced air pressure for its inflation and has normal pulmonary compliance, low ventilation-perfusion ratio and low lung recruit ability but due to impaired regulation of perfusion and loss of hypoxic vasoconstriction hypoxemia occurs in this condition. Whereas in the H phenotype, increased lung elastance and low lung compliance were found. Thus, impaired ventilation affects pulmonary function in this case [18].

Various studies indicate that the SARS-CoV-2 uses the ACE2 as a co-receptor to gain intercellular entry into the lung and brain. ACE2 is a membrane-bound peptidase enzyme with its catalytic site oriented externally. It is expressed in many tissues, although it shows increased activity in the kidney, ileum, adipose tissue, heart, and lungs [19]. The viral coat expresses a spike protein that contains a Receptor-Binding Domain (RBD) and attaches itself to the ACE2 receptor with exemplary affinity. The spike protein cleaves along with the dibasic arginine sites present in it by the host enzyme TMPRSS2 resulting in the formation of S1 and S2 subunits. The S2 subunit now invades the pulmonary epithelium by fusing with ACE2 expressed in that region, resulting in viral internalisation by endocytosis. The extent of expression of ACE2 in obese and normal individuals is found to be the same, however, since obese individuals have an increased adipose tissue content in their body they have an increased number of ACE2 receptors in their body. Thus, obese individuals have increased susceptibility to getting infected with SARS-CoV-2. Obesity can also predispose to a greater viral shedding, resulting in increased viral exposure and also obesity-related co- morbidities, which are commonly found in COVID-19 patients. Hence, it accounts for an additional risk factor.

In case of infections, increased serum glucose levels can impair immune response by the generation of oxidants and glycation products which would damage the pancreatic cells. One may wonder why the virus might reach the pancreas of the host? The pancreas is also found to shelter a few ACE2 receptors resulting in the viral invasion [20].

In a study (Busetto L et al.,) regarding the prevalence of COVID-19 in obese and overweight subjects in Veneto, Italy, had shown a high prevalence among obese patients with overweight patients accounting for 33.7% and obese patients for 31.5%, they also observed that obese patients were younger compared to normal-weight patients and they required aided respiratory support beyond normal oxygen support like Invasive Mechanical Ventilation (IMV) and Non invasive Ventilation (NIV) [21].

An epidemiological study in Brazil (Goncalves DA et al.,) revealed that obese individuals were twice as more likely to get admitted into acute care and critical care units compared to normal subjects with a BMI of <30 kg/m^2. Also, this study indicated that women with obesity have a significantly higher median age compared to men [10]. A study conducted by South AM et al., had shown results indicating that overweight individuals had a 44% more chance to get infected with COVID-19 along with increased severity of the illness [22].

Long-term and Post COVID-19 Complications in Obesity

These long-term symptoms of COVID-19 can also be termed as long COVID-19 or postCOVID condition. Individuals with higher inflammatory markers, and longer hospitalisation, have fibrotic changes suggesting persisting interstitial diseases. Also, some patients are found with a risk of developing pulmonary fibrosis. Bronchial wall thickening and bronchiectasis in around 15% of patients with COVID-19 [20]. Many shreds of evidence show that lung fibrosis can last upto six months postdischarge. Pulmonary fibrosis is the scarring of the lung mainly due to inflammatory mediators like chemokines, Transforming Growth Factor-beta (TGF-β), and modulating matrix. Evidence has revealed links between diet-induced obesity and pulmonary fibrosis due to collagen or hydroxyproline deposition, resulting in lung remodelling in animal models, primarily in ApoE deficient mice [23]. Transgenic mice are test organisms whose genome is manipulated by genetic engineering techniques according to experimental needs. Links could be correlated between vitamin D deficiency and lung fibrosis upon evaluating it in obese and TGF-β 1 triple transgenic mice [24]. Obese patients in some scenarios also present with reduced vitamin-D levels, which otherwise could play a key role in reducing cytokine storm and induce cathelicidins and defencins which can modulate the immune response and lower viral replication rate [25]. Thus, obesity can be thought to be an element that increases the hyper-responsiveness of the lungs to any potent stimuli like environmental pollutants or pathogenic infections. In this scenario the stimulant is SARS-CoV-2, which progresses to fibrotic condition. All the above mentioned complications could even occur in normal individuals but the mechanisms that cause these effects are bronchiectasis, bronchial wall thickening increased levels of inflammatory mediators and fibrosis which could be accelerated in patients with obesity which plays a key role in the pathological mechanisms which manifests its effects by the following mechanisms.

1. Rupture of atherosclerotic plaque in type 1 Myocardial Infarction (MI)
2. Imbalance in the oxygen supply-demand ratio in type1 MI
3. Generalised infection
4. Increased troponin levels and severe physiological stress [26]

Patients undergoing cancer treatment are highly susceptible to chemotherapeutic cardiotoxicity if infected with COVID-19 [27].

Renal complications: Since SARS-CoV-2 downregulates ACE2 receptor, an increase in activity of ACE and a shift to overproduction of angiotensin 2 occurs, eventually leading to a pro-inflammatory state of the kidney and leading to a prolonged pro-fibrotic state of the kidney. COVID-19 can also cause Acute Kidney Injury (AKI) which can be attributed to haemostatic and infectious factors. The viral replication in the renal cells could be due to the prevalence of ACE2 receptors, which can result in the formation of lesions and glomerular fibrin thrombi even after the viral infection was resolved. Upon prolonged thrombi formation it could eventually result in renal tropism in the long-run [28].

The autopsies of some of the COVID-19 affected patients revealed the presence of Acute Renal Failure (ARF) and the immune histochemistry showed the accumulation of SARS-CoV-2 Nucleoprotein (NP) antigen in the renal tubules alongside CD68+ macrophages and C5b-9 deposition which could lead to tubular necrosis [29].

As a rare case scenario Sharma Y et al., found two patients with collapsing glomerulopathy and AKI with the predisposition of Apolipoprotein L1 (APOL1) high-risk genotype, and surprisingly both the patients were African Americans. Obese patients were 1.3 times more likely to be present with the APOL1 risk variants and few variants of this APOL1 confer higher risk and faster rates of progression of Chronic Kidney Disease (CKD) [30]. Thus, we could correlate the links between obesity COVID-19 collapsing glomerulopathy via the APOL1 gene.

Neurological complications: COVID-19 infection in some patients may present certain neurological defects which may be perceived or hidden. There is a wide range of neurological complications in the patients with the symptoms ranging from a normal condition to the condition of a brain fog which might result in demyelination and neurodegeneration. As a sequel of the infection, some individuals have been found with elevated antibody response, and increased levels of IL-6 and IL-4, the latter being important in restoring homeostasis in the brain and counteracting against other pro-inflammatory cytokines [14].

Human brain autopsies and neuronal cultures confirm the neurotropism due to COVID-19 notably damaged the brainstem's cardiorespiratory centre, and since neurons regenerate in rare cases this could cause a prolonged cardiopulmonary dysfunction [31]. Stroke in COVID-19 is quite rare though its chances of occurrence can be favoured due to the thromboembolic event which is a characteristic feature of this disease. Plasminogen Activator Inhibitor 1 (PAI-1) which is abundantly present in the human adipose tissue, distorts the activation of tissue plasminogen activator thus worsening the dissolving of the cerebrovascular clot formed. Invariably adipose tissue mass is higher in overweight patients compared to normal subjects hence they are at a higher risk for contracting this disadvantage [32].

Few patients have also been reported with Guillain Barre Syndrome (GBS) caused due to a hyperactive immune response that attacks neurons demyelinating it mainly show pins and needles sensation in the palms and manifests as ascending muscle weakness. The data from cohorts conducted in Massachusetts (Ding M et al.,) provided insights regarding the risk of GBS in the obese population which pipe the above said manifestations in the patients [33], thus we can infer that the occurrence of GBS is associated with both obesity and COVID-19. The electrolyte abnormalities, liver inflammation, hyper inflammation, and isolation from people have psychologically affected people, especially some of the geriatric population into delirium. Viral-induced immune reactions and the following autoimmune disorders pave the way for the virus to elicit CNS effects like infiltration of the Blood-Brain Barrier (BBB) by immune cells and CNS tissue damage [34].

Gastrointestinal complications: Gut dysbiosis has been observed in COVID-19 patients persisting for up to 30 days after resolution of infection, this gut microbiome disruption can be correlated with increased severity of the COVID-19 infection and this prolongs the faecal shedding of SARS-CoV-2 [31]. This alteration in the gut microbiota could also end up in reduced secretion of Short-Chain Fatty Acids (SCFA) like butyric acid, and valeric acid in the gut. SCFA stimulates the GPR 43 (G-protein coupled receptor 43) and GPR 41 (G-protein coupled receptor 41) human adipose tissue helping in reducing weight and inhibiting the chronic inflammatory states induced by obesity [35]. Thus, deficiency of SCFA could even be speculated to lead to increased adverse effects due to inflammation in obese COVID-19 patients.

Psychiatric complications: Most of the psychological complications of COVID-19 are due to the traumatic experience of the disease and its symptoms in affected individuals. In a meta-analysis by Rogers JP et al., conducted in many countries like China, Hong Kong, Japan, and Singapore, the common psychiatric symptoms among patients admitted for COVID-19 were found to be confusion, depressed mood, anxiety, brain fog, and insomnia, whereas steroid-induced mania and psychosis were reported in few cases [36]. In severe cases of COVID-19, prolonged cognitive impairment as sequelae to delirium is found to occur roughly in 30% of hospitalised patients [31].

Repercussions of COVID-19 on the Reproductive System of Obese Patients

Patients recovering from COVID-19 were found with significant reduction in the sperm concentration, sperm motility and sperm morphology along with increased seminal IL-6, TNF-α and monocyte chemoattractant protein-1 etc. The presence of increased amounts of inflammatory mediators is being attributed to increased ACE2 enzyme activity in the seminal plasma. Since this cascade is linked with ACE2 receptors we can hypothesise that obesity can accelerate this process since obese patients have increased levels of adipose tissue in our body which house ACE2 receptors. The overexpression of these receptors could dampen vasoconstriction and sodium retention which could result in erectile dysfunction [37]. The expression of ACE2 and TMPRSS2 in female reproductive system is proven, which again serve as entry points for viral invasion. Evidences linking COVID-19 and female reproductive system is mostly indirect, being elicited through mechanisms like cytokine storm, psychological disorder and obesity [38].

Insulin Resistance and COVID-19 in Obesity

Insulin resistance is the resistance to the hormone insulin, resulting in increased blood sugar levels. Middle East Respiratory Syndrome (MERS) animal models suggested that hyperglycaemia and insulin resistance alter the cytokine profile and aggravates a malfunctioning immune response and worsens lung pathology. This influx of immune cells develops insulin resistance and chronic inflammation, further augmenting the symptoms [39]. This in turn indicates the severity and poor prognosis of COVID-19 in obese and insulin-resistant individuals.

The expression of several insulin signalling molecules is reduced in skeletal muscle in case of obesity and the major factor contributing to the impaired insulin-stimulated glucose transport in adipocytes is the down-regulation of the GLUT 4 transporter [40]. Thus, COVID-19 and obesity both could be thought of as accelerating factors for insulin resistance, thus leading to diabetes and further ensuing complications. The Triglyceride-Glucose (TyG) index is a product of triglycerides and glucose and is used as an authentic and reliable marker of insulin resistance. TyG index is associated with an increased risk of diabetes, and thromboembolic disorders and might even predict the occurrence of cardiovascular complications [41].

COVID-19 Vaccine Considerations in Obese Individuals

Traditionally, it is believed that patients with obesity tend to have an impaired immune response. Independent of the BMI of the subject, obesity is associated with lower antibody titres which are attributed to multiple factors like metabolic derangements due to increased visceral adiposity paired with immune dysfunction associated with obesity. The results obtained by Italian healthcare workers while evaluating the antibody titre of COVID-19 vaccines point us in the same direction that humoural immune response was more efficient in under and normal-weight subjects versus pre-obesity or obese subjects [42]. Furthermore, reliable and larger studies in this regard were not performed and the available information is scanty, hence a deep study regarding this is required [1].

CONCLUSION(S)

Obesity is a lifestyle-based risk factor that critically alerts the extent of manifestation of SARS-CoV-2 as other factors like age and certain underlying disease conditions. COVID-19 majorly affects the respiratory mechanism alongside affecting other systems like renal, gastrointestinal, reproductive, and neurological. This provides a distinguished microenvironment for pathogenesis of disease resulting in increased susceptibility to severe disease in obese host. The entry of the virus into the cell is via the ACE2 receptors into the body and every organ lodging the receptors is susceptible to viral invasion. This review provides insights on the similarities between the symptoms and complications of obesity and COVID-19. The respiratory system, immune system, renal system and the nervous systems are the victims of the infection. The possible links between obesity and COVID is a little scarce and could be potential lead for future research and the drug related alterations required in COVID affected obese patients is yet to be explored. Any variation in response to vaccines in obese COVID patients is yet to be studied which is worth a consideration, keeping in mind the increased incidence of obesity in recent times.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
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