Review

Reviving the mutual impact of SARS-COV-2 and obesity on patients: From morbidity to mortality

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ABSTRACT

Obesity-related metabolic dysfunction, endothelium imbalance, chronic inflammation, immune dysregulation, and its comorbidities may all have a role in systemic inflammation, leading to the pulmonary fibrosis and cytokine storm, which leads to failure of lung function, which is a hallmark of severe SARS-CoV-2 infection. Obesity may also disrupt the function of mucociliary escalators and cooperation of epithelial cell's motile cilia in the airway, limiting the clearance of the coronavirus that causes severe acute respiratory syndrome (SARS-CoV-2). Adipose tissues in obese patients have a greater number of proteases and receptors for SARS-CoV-2 admittance, proposing that they could serve as an accelerator and reservoir for this virus, boosting immunological response and systemic inflammation. Lastly, anti-inflammatory cytokines such as anti-IL-6 and the infusion of mesenchymal stem cells could be used as a modulation therapy of immunity to help COVID-19 patients. Obesity, on the other hand, is linked to the progress of COVID-19 through a variety of molecular pathways, and obese people are part of the SARS-CoV-2 susceptible individuals, necessitating more protective measures.

1. Introduction

The pandemic of COVID-19 has collided squarely with the obesity pandemic. Being overweight increases the risk of symptomatic infection, hospitalisation, and even mortality from the SARS-CoV-2 virus, according to news reports from around the world [1]. Obesity has previously been associated with a greater risk of disease severity in viral infections. Obesity leads to a reduction in total respiratory system compliance. This is due in part to a reduction in lung compliance, which may be linked to the higher pulmonary blood volume seen in obese people. COVID-19 pneumonia has the L phenotype, which is characterised by low elastance, a low ventilation/perfusion (VA/Q) ratio, and hypoxemia, according to the study [2]. Given the COVID-19 outbreak, the fact that viral diseases have a substantial impact on obese patients points to a potential factor which deserves more attention extensively. Many countries have experienced serious socioeconomic difficulties as a result of the efforts required to battle COVID-19 [1,2]. According to the financial crisis during 2007–2008, in nations with abundant market-financial prudence and a deficiency of welfare programs on harmony, socioeconomic complications habitually worsen the situation for the poor persons in the world, thereby exacerbating socioeconomic dissimilarity and divergence of population sections [3].

COVID-19's connection to the 2007–2008 financial crisis could not be grasped. During the COVID-19 epidemic, however, time-varying conditional correlations between markets were higher. The COVID-19 pandemic has had a significant impact on the intraday volatility gap between oil, gold, and stock markets from 2019 to 2022 [111].

One of the first studies to report BMI data was a descriptive study of a small sample of 24 severely ill subjects identified with SARS-CoV-2 in the Seattle area [63% of whom were men] (13 - obese, 7 - overweight, 3 - normal BMI and 1 omitted data) [4]. Despite the fact that the records are too lesser for statistical analysis, a ventilation support system was used on 85% of obese patients, and 62% of them died [4]. These proportions are higher than in patients without obesity, who required a ventilation support system (64%), and 36% of individuals died [4]. Due to its negative impact on drug pharmacokinetics and pharmacodynamic activity, as well as safety and efficacy, obesity is frequently abandoned as a cause of poor treatment in infectious diseases [2]. Obesity also alters cellular immunity, impairing the protective immune response to virus infection and immunisation, as shown with influenza. Obesity surges the risk of diabetes mellitus, high blood pressure, cardiovascular disease, and respiratory disease [1,2]. Furthermore, aberrant cytokine profiles are linked to lymphoid and myeloid responses inside the RAAS receptor signalling [5]. In relevant patients, adipose tissue can operate as a pool for larger viral dissemination, with enhanced shedding, immunological stimulation, and cytokine increment [4,5]. Obesity was also linked to a number of respiratory problems, including higher ventilation demand, increased labour of breathing, respiratory muscle inadequacy, and decreased respiratory compliance. The link between obesity and SARS-CoV-2 could be explained by a variety of processes [6]. People with obesity had higher levels of the transmembrane enzyme angiotensin-converting enzyme-2 (ACE-2) that SARS-CoV-2 exploits for cell entrance. It's unclear whether this is due to greater ACE-2 appearance in the adipocytes of obese patients or to the fact that they have more adipose tissues in common (and hence a bigger number of cells expressing ACE-2) [6]. As it has been shown with other viruses, the adipose tissue of obese patients could be a viral reservoir and possible target for SARS-CoV-2 before it blow-outs to other organs [7]. Obesity has been linked to a condition of severe inflammation and a weakened immune system, making a person more susceptible to infections [2]. As a result, being overweight may be an independent risk factor for COVID-19 disease development. Given that ARDS is one of COVID-19's most serious clinical symptoms, these opposing viewpoints cast doubt on the role of obesity in the disease's prognosis and severity [8]. Obesity has been linked to SARS-CoV-2 severity and/or fatality in a growing number of studies [1,4,7]. US Centers for Disease Control and Prevention released preliminary epidemiological data which revealed that 69% of SARS-CoV-2 infected obese patients had a BMI of 30–40 kg/m^2, with 30.1% having severe obesity (BMI $\geq$ 40 kg/m^2) [9]. In addition, after correcting for sex and age, the obesity rate among 340 critical SARS-CoV-2 patients was considerably greater than the overall adult population of France [10]. Severe obesity (BMI $\geq$ 40 kg/m^2) has been identified by the Centers for Disease Control and Prevention as a prevalent clinical risk factor for greater mortality and poorer prognosis in patients with COVID-19, based on presently accessible data and clinical expertise [9]. Furthermore, in patients with COVID-19, any obesity degree (BMI $\geq$ 30 kg/m^2) has been linked to a poorer prognosis [11,12].

1.1. Epidemiology of covid-19 in obese patients

Even if the influence of obesity and overweight on SARS-CoV-2 consequences has yet to be fully understood, the earlier H_1N_1 influenza understanding clearly demonstrated that extreme obese patients were at a greater risk for illness advancement and death from influenza impediments; SARS-CoV-2 is no different [13]. Linking how obesity acts as a severe risk for the infection of SARS-CoV-2 is given in Fig. 1. Obesity was found in 31% of patients in a minor case chain from China, Germany, and Italy, with an extra 58% of unfavourably sick Italian patients being overweight [14]. Obesity is on the rise in the United States; 9.2% of the population exist with a great rate of obesity with a BMI greater than 40 kg/m^2 (class III) [15]. As a result, countries with high obesity rates and rapidly increasing cases of COVID-19 would face extraordinary challenges. A study from the US found that deaths due to COVID-19 were more commonly linked to obesity (95% CI: 1.5–6.6; OR 3.1), with morbid obesity exhibiting the strongest link (95% CI 2.1–27.9; OR 7.6) even in patients with no extra problems (95% CI 2.1–27.9; OR 7.6) [16].
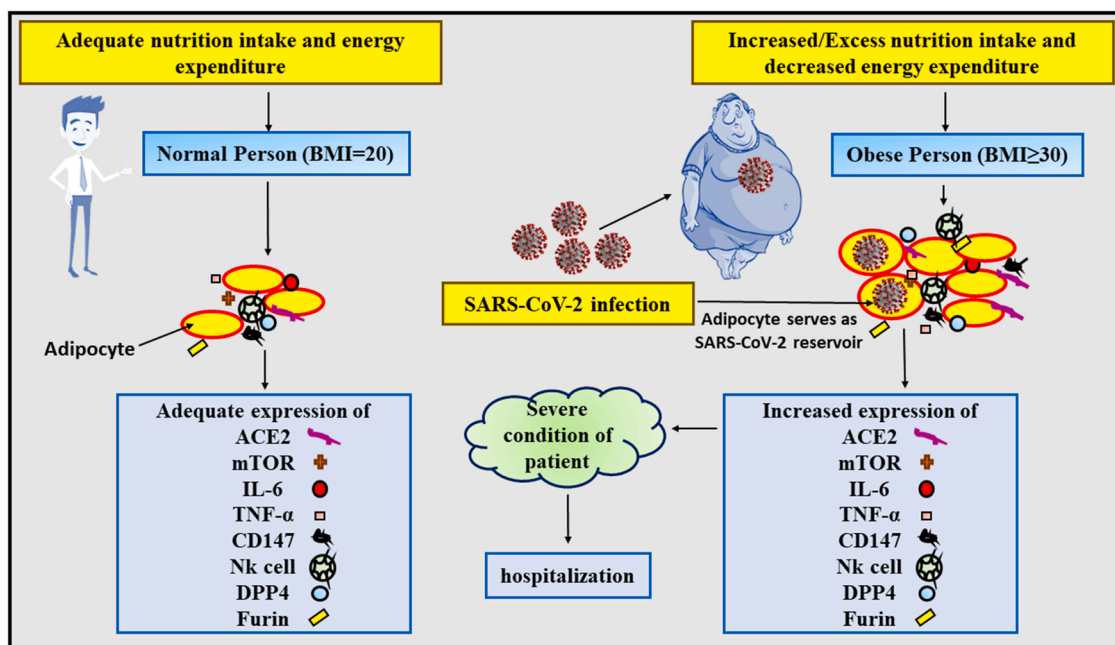
Fig. 1. Linking how obesity acts as a severe risk for SARS-CoV-2 infection. Adipocytes act as the reservoir for SARS-CoV-2, which bounds with DPP4 or ACE2. Higher DPP4 expression stimulates inflammation. mTOR increases the duration of SARS-CoV-2 shedding [2,7,10,14]. [BMI: body mass index; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; ACE2: angiotensin-converting enzyme-2; mTOR: mammalian target of rapamycin; IL-6: interleukin-6; TNF-α: tumour necrosis factor-alpha; CD147: transmembrane glycoprotein; Nk cell: natural killer cell; DPP4: dipeptidyl peptidase-4].

In the New York (NY) City area, it was found that COVID-19 patients hospitalised with BMI > 35 (severe obesity) have been established as a substantial risk factor for SARS-CoV-2 infection. A total of 5700 subjects were involved in another NY study (median age 63 years). Diabetes (41.7%), obesity (41.7%), and hypertension (56.6%) were the most frequent comorbidities; diabetics were more expected to have ventilation support systems or intensive care unit care (ICU) [17]. During their stay in the hospital, 3.2% of patients had kidney replacement, 12.2% of patients were on a ventilation support system, and 21% died [17]. The death rate for those who needed a ventilation support system was 88.1% [17]. In intensive care unit requirements and SARS-CoV-2 infection severity, overweight acts as a key risk factor according to a huge New York's retrospective case series [17].

Patients with "ARDS" in Germany were more likely to be obese (83%) as compared to an ordinary BMI (42%) [18]. Waist circumference and BMI were autonomously related to COVID-19 (lab-confirmed) in a dose-dependent manner in a huge prospective cohort study in the United Kingdom on 502,543 middle-aged people [19]. The results were unaffected by adjusting for possible confounders. In comparison to individuals of normal weight, the corrected odds ratios for severely obese, obese, and overweight patients were 1.57 (95% CI: 1.14–2.17), 1.55 (1.19–2.02), and 1.31 (1.05–1.62), respectively [19]. The number of patients requiring IMV rose with BMI groups in retrospective French cohort report (chi-square test for trend, p < 0.01), and it was highest in subjects (85.7%) with BMI greater than 35 kg/m^2 [20]. Liberated from hypertension, diabetes, and age, the requirement for IMV was strongly linked with BMI (p < 0.05) and male sex (p < 0.05) in multivariate logistic regression. IMV in subjects odds ratio with BMI < 25 kg/m^2 vs. subjects with BMI > 35 kg/m^2 was 7.36 (p = 0.02, 11.63–33.14) [20]. In Mexico, obesity is the biggest predictor of COVID-19 as per the case-control report, followed by chronic renal failure in females exclusively and hypertension & diabetes in both sexes [21]. Obesity with BMI greater than 40 had a risk ratio of 1.92 (95% CI 1.72–2.13) in a study of 10,926 fatalities linked to COVID-19 in England [22]. Comorbidity with obesity was 11%, type 2 diabetes was 30%, and hypertension was 67% who died (80 years' median age) with COVID-19 in Italy [23]. COVID-19 severe illness was independently linked with a BMI $\geq$ 28 kg/m^2 in 221 patients- Chinese case series (95% CI, 1.595–21.621; p = 0.008; OR, 5.872) [24]. Overweight/obese patients in China were hospitalised for a longer duration as compared to an ordinary BMI patient. Obesity was found to be strongly linked with illness severity in a study of children and adolescents hospitalised with COVID-19 in the US [25]. Being overweight is evolving as a risk for SARS-CoV-2 consequences irrespective of age or comorbidities, implying that even young persons who have a greater BMI are at risk of catastrophic disease. Obesity, thus, might be linked to SARS-CoV-2 sickness and death, irrespective of age or the existence of comorbidities [10,15,16]. Being overweight was the record essential factor leading to the death of young Chinese patients due to COVID-19, according to a retrospective case-control study [26]. Obesity would cause hyperinsulinism first, followed by insulin resistance and type 2 diabetes mellitus [27]. Increases in blood pressure are one of the major medium-term repercussions of being overweight, which is regarded as the major risk that predisposes to cardiovascular problems in middle age [28]. The role of diabetes, hypertension and cardiovascular disease cannot be reduced when taking the prospective role of being overweight as a risk factor for sickness and mortality due to SARS-CoV-2 infection [27,28]. Specified that overweight is an intimate link to the sickness, and all together are linked to COVID-19 severe cases.

1.2. Immunopathology of obesity

Obesity is a condition marked by the buildup of body fat, which increases the risk of cardiovascular disease, depression, airway disease, fatty liver, respiratory problems, type 2 diabetes, hypertension, and some cancers [2,27,28]. Furthermore, to their quality-of-life and psychosocial effects, these comorbidities are linked to a shorter life expectancy and premature death (WHO 2016) [29]. Adipokine production, anatomical changes in the kidneys, hyperinsulinemia, renin-angiotensin system (RAS) activation, and an increased sympathetic tone are all thought to have a role in blood pressure changes in obesity [30]. In classic inflammation, the inflammatory response attempts to cure the damage at the site of infection or injury [31]. When the overall mortality rate of ordinary individuals was compared, then results reported 200% increase in the sickness of obese patients and 20% increase in the mortality of obese patients [24,26,32].

Extreme nutrient feeding, combined with insufficient energy expense, reduces the size and number of metabolic cells like adipocytes, triggering the inflammatory reaction [33]. A chronic inflammatory state is observed in obesity, which is tempted by the metabolic surplus (different mechanism) [33]. Inflammation resolution is hampered by the metabolically excess induced inflammatory state, resulting in the formation of enduring inflammation [33,34]. As a result, low-grade inflammation in overweight people is influenced in part by dietary factors. In a high-fat diet (HFD) induced obesity model, increased infiltration of immune cell - inflammatory macrophages (type M1) - in adipose tissues, which is linked to an increase in inflammatory cytokines [35]. After the three weeks of HFD treatment onwards, an increase in macrophage-related genes was detected, and after the sixteen weeks ahead, the increase became more pronounced, culminating in the commencement of insulin resistance [35,36].

1.3. Impact of obesity on COVID-19

The clinical impact of obesity and obesity-related co-morbidities on SARS-CoV-2 infection has been illustrated in Fig. 2. COVID-19 can cause serious respiratory infections, septic shock, respiratory dysfunction, and, in the most severe condition, ARDS in individuals with comorbidities [34,37]. Being overweight can also raise the risk factors for various illnesses, which might have negative repercussions. Obesity, which is the most common underlying illness in SARS-CoV-2 patients below the age of 64, may cause COVID-19 risk to be shifted to younger ages [38]. COVID-19 has a broad clinical range, and most COVID-19 patients experience non-specific symptoms such as myalgia or fatigue (44%), cough (76%), and fever (98%) [39]. With around 70% of COVID-19 hospitalised cases being over 45 years old, older age is one of the supreme critical determinants in the hospitalisation rate [40].

Obesity, like renal disease, has been linked to endothelial dysfunction, which could lead to an increased risk of endothelial cell infection, as detailed below. Endothelial dysfunction induced by obesity is caused by a variety of processes, including the vasculature itself or the perivascular adipose tissue produced low-grade inflammation [41]. Inequity in the production of vasoconstricting and vasodilatory substances causes endothelial dysfunction. SARS-CoV-2 developed in December 2019 and quickly spread over the world, putting human health at risk. COVID-19 causes a wide range of symptoms that can progress to more serious manifestations such as pneumonia and non-respiratory consequences. Diabetes, hypertension, cardiovascular disorders, and, more recently, obesity have all been connected to increased vulnerability to COVID-19 hospitalisation and mortality [41,42]. Diabetes, hypertension, and obesity were the utmost allied problems with critical infection cases in a meta-analysis assessing dengue infection among 47 studies when compared to other viruses in the West Nile virus, the Flaviviridae family, where the prevalence of cardiovascular problems, diabetes, and hypertension was greater, with overweight, not actuality comorbidity linked with the severity of the disease [41,43]. Obesity is becoming progressively common as a risk factor in developed nations like the US, owing to amplified consumption of the traditional western diet, which is heavy in carbohydrates, sweets, antioxidants, essential fats (unsaturated), and low fibre saturated fat [42,44]. Through increased oxidative stress, this type of diet activates the innate immunity while inhibiting the adaptive immunity (inhibition of B and T lymphocytes action) [44,45].
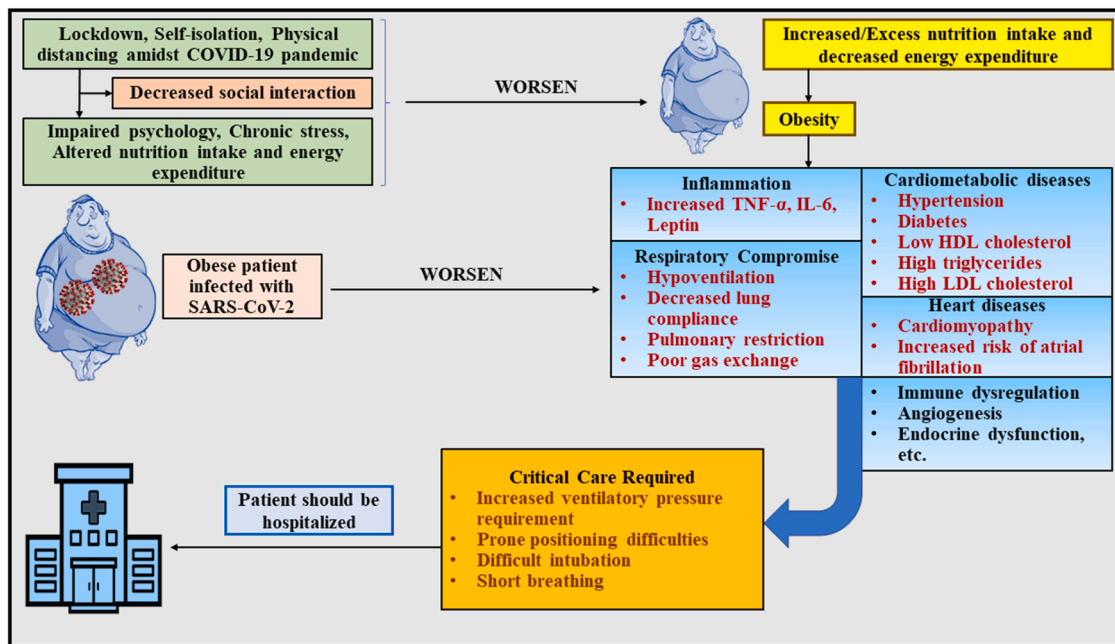
Fig. 2. Impact of SARS-CoV-2 infection on obese patients [33–38]. [SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TNF-α: tumour necrosis factor-alpha; IL-6: interleukin-6; HDL: high-density lipoprotein; LDL: low-density lipoprotein].

Thrombosis, vasoconstriction, peroxidation, atherosclerosis, impaired hemostasis, vascular inflammation, mitogenesis, increased leukocyte adhesiveness, and platelet hyperactivation are all signs that the vascular endothelium is headed for a proatherogenic and prothrombotic state, with increased CVD as a result [46,47]. These factors contribute to the onset and progression of vascular endothelial dysfunction, which can lead to damage to a key organ.

1.4. Link between covid-19 and obesity

According to the Centers for Disease Control and Prevention, obesity is associated to a majority of the high-risk factors for infection of SARS-CoV-2, either directly or indirectly [9]. According to an observational study, extremely unwell subjects had a greater BMI (mean: 24.78) than non-severely ill subjects (mean: 23.20) [48]. This meant that a greater BMI meant a higher risk of COVID-19 severity. Obesity is prevalent in 21.9% of developing South-East Asian countries, according to WHO data [49]. Being overweight has been acknowledged as a self-governing risk reason for the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), with MERS-CoV (50%) and SARS-CoV & SARS-CoV-2 (80% genetic similarity) [50]. A Brazilian study looked at the risk variables related with the infection of SARS-CoV-2 in the general adult population. In a survey of 51,770 people based on the domestic population, it was discovered that 22% of people, regardless of age, were fatty and at risk of infection [51]. A prospective report in New York found that among patients with COVID-19, a rise in BMI (greater than 40 with 2.6 odds) was highly related with hospital admission [48]. The investigator looked at biobank data of the UK and discovered that patients who were obese or overweight had a greater risk of contracting COVID-19 in a dose-response fashion [52]. Extremely obese (BMI⩾35), obese, and overweight participants showed a 1.57, 1.55, or 1.31 times greater risk of COVID-19 positive than healthy weight subjects [52]. According to a Chinese study, no patients who were underweight had severe COVID-19, but obese individuals advanced to critical cases (19.2% within the healthy weight group, 29.3% within the overweight group and 39% within the obese group) [53]. A meta-analysis involving 18,506 participants looked into the link between COVID-19 and diabetes, and discovered that

diabetic condition was linked to 65% more chance of death [54]. Obesity appears to be a risk reason for the severity of COVID-19, as per the findings. Furthermore, Yang et al. in their review, found a linear link among BMI and the requirement for IMV, with the risks being 3.06 times greater in individuals with a BMI of less than 40 [48]. A retrospective review of 112 SARS-CoV-2 subjects found that 88.2% of causalities had a BMI of 25 or less, in comparison to 18.8% survivors [55].

The moniker "MicroCLOTS" (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) has also gained traction to characterise microvascular thrombosis with an enlightened pulmonary endothelial syndrome, explaining the coagulation factors activation (D-Dimer increment) [56,57]. The machinery after the observation that being obese or overweight can make SARS-CoV-2 worse has yet to be discovered. Previous studies have suggested possible mechanisms. ACE2 enhances SARS-CoV-2 cellular entrance; according to Ziegler et al., obesity and SARS-CoV-2 illness appear to share some metabolic and inflammatory response mechanisms [58].

1.5. COVID-19 associated with pulmonary dysfunction and obesity

The majority of COVID-19 patients have respiratory illness symptoms. Obese people had greater hospitalisation rates and a larger frequency of respiratory infections than normal-weight patients [59]. Obesity is linked to a number of respiratory dysfunctions and poor respiratory processes; all of them can worsen the progression of COVID-19 [59,60]. To begin with, obese people have poor gas exchange and amplified airway exchange [59]. Hindrance of ventilation of the base of the lung and restriction of diaphragmatic excursion can be due to the larger quantity of adipose tissue in the abdomen area, resulting in lower blood oxygen saturation [61]. In addition, persons with obesity have lesser lung volume and muscle strength. Jones and colleagues found that when BMI grew, ERV and FRC in obese subjects dropped exponentially, reaching 75% and 47% of the standards for lean persons, correspondingly [62]. Patients with excessive obesity may have lower total lung capacity and vital capacity [62]. Second, obesity has been associated to asthma, OSA (obstructive sleep apnea), pulmonary hypertension, OHS (obesity hypoventilation syndrome), and COPD [63]. Furthermore, being overweight affects the progression of COPD & ARDS and

pulmonary functioning in the course of acute episodes [63]. When ARDS is present, obesity raises the likelihood of hypoventilation conditions in ICU patients, which can progress to the failure of respiration [63,64]. The mechanisms underlying these consequences are unknown; however, it is thought that adipokine disproportions induced by obesity can compromise the functioning of pulmonary vascular endothelial and lead to lung injury [65]. Additionally, leptin has been linked to both physiological and pathological diseases of the lungs, including asthma, OSA, and COPD [66]. In fact, overexpression of SOCS-3, which also depressingly controls antiviral INFs (interferons) signalling, might cause leptin resistance in people with obesity due to elevated leptin levels [67]. Furthermore, IFN deficiency may be a relationship between risk factors for pulmonary illnesses, such as the severity of disorders and obesity [65,67].

1.6. Inflammatory mediators in obesity

Cytokine, such as IL-6, has several natural functions. It's a liver severe stage reactant which aids in the control of effector and regulatory T cells and the control of B cell activation [69]. It is involved in the control of metabolic, regenerative, and numerous brain functions, in addition to inflammatory and infectious responses. It works through dual signalling mechanisms: the classic signalling mechanism, which is accountable for IL-6's anti-inflammatory effects, and the trans-signalling mechanism, which is responsible for pro-inflammatory activity [69]. The complex of a type I signal transducer protein (gp130) and an IL-6 binding type I glycosylated transmembrane protein (IL-6 receptor) is responsible for IL-6's biological function [70]. Contrasting IL-6R that is only articulated on a small number of cells, while the gp130 is found on every cell surface [70]. Cells which are shown to have both complex constituents are directly receptive to IL-6, which is known as the traditional signalling mechanism, while the cells lacking IL-6R react to IL-6 coupled to sIL-6R (solvable form of IL-6R), which is known as the trans signalling mechanism [69,70]. By the assistance of metalloproteinase and disintegrin enzyme, sIL-6R is produced by proteolytic breakdown of IL-6R bounded to the membrane [71]. An underlying mechanism of the clinical pathophysiology of obesity is low-grade systemic inflammation [33]. Adipocytes are only one type of cell found in adipose tissue, which also contains pre-adipocytes, fibroblasts, macrophages, and vascular components [28]. As a result, macrophages are essential contributors to inflammation, and adipocytes have also been shown to have strong inherent inflammatory capabilities. Adipocytes, like macrophages, have several receptors which are stimulated by infective illness mediators [68]. When these receptors are stimulated, transduction cascades of inflammatory signals are activated and mediated by cytokines, resulting in the secretion of various powerful, provocative cytokines and severe stage reactants [33]. The JAK/STAT (Janus Kinase) signal transduction mechanism is further activated when cells are activated by IL-6 through either of the complexes [72]. Based on their molecular weight, a unique adipokine (adiponectin) produced by fat tissues appears in plasma in three primary oligomeric states (low, medium, high) [73]. Adiponectin levels are known to be adversely correlated with the quantity of adipose tissue. COVID-19 pneumonia patients showed increased IL-6 expression, a lower adiponectin/leptin ratio, and higher leptin levels. With a threshold of 7852 pg/mL, leptin had acceptable discriminatory accuracy for COVID-19 pneumonia in individuals with a BMI > 30 and was linked with maximum respiratory support. In individuals with a BMI of 25 or below, adiponectin/leptin demonstrated high discriminatory accuracy for COVID-19 pneumonia with a threshold of 2.23 [74]. It's an anti-inflammatory hormone that has a negative relationship with the levels of IL-6 and CRP in overweight people (lesser adiponectin with raised inflammatory intermediaries) [70]. The results were supplementarily supported by the fact that obese people who lost weight saw their IL-6, CRP, and adiponectin levels reverse [75]. Obesity-related metabolic and cardiovascular problems are exacerbated by the reciprocal and inequality connection of pro- and anti-inflammatory adipokines [76].

Adipose tissue serves as an active endocrine tissue or cells as well as an energy storage site [77]. Adipose tissue can produce a variety of chemicals that impact the immune response, including adipokines and leptin [77]. Insulin and leptin play important roles in the relationship between nutrition and immunity. These two hormones are crucial in the development of severe COVID-19 in people with inflammation because they are disrupted in obesity and metabolic syndrome. Leptin and insulin resistance affect T-cell function by modifying the metabolic set-point, resulting in a reduced T-cell response to infection [78]. As a result, a lower adiponectin/leptin ratio indicates adipose tissue malfunction [112]. Age, obesity, type 2 diabetes, and impaired renal function are all major risk factors for COVID-19 mortality, but leptin and insulin resistance are common denominators. In individuals with type 2 diabetes and severe COVID-19, the major role of leptin on the immune system is cytokine storm, lymphopenia, and the particular loss of cytotoxic CD^{8+} cells and classical monocytes. Immunity alterations and the changes in the respiratory tract can be mediated by obesity, particularly essential at this time when there is a pressing need to figure out which problems or illness and circumstances can impact and promote COVID-19 infection. While BMI data from individuals hospitalised with SARS-CoV-2 were not initially used to characterise risk sets, few recent studies have shown the link between COVID-19 pandemic and obesity [79]. One hundred and twenty-four BMI reports of hospitalised individuals were studied in a recent study in France; all of them were in ICU with COVID-19 and found a link between the need for aggressive mechanical ventilation, demonstrating the great prevalence of hospitalised obese and severely obese individuals, as well as the worst condition of the diseased patients [80]. In another study, Obesity was found to be an extrapolative aspect for the requirement for hospitalisation of SARS-CoV-2 infected individuals in New York City, and obese COVID-19 patients in Shenzhen, China, had a significantly higher risk of severe pneumonia, especially in men [81,82]. Overweight ARDS individuals have a lesser or same death risk than non-obese ARDS individuals; on the other hand, there was no variance in the necessity for an ICU stay or hospitalisation among the two groups [83]. The discharge of free radicals of oxygen like hydrogen peroxide and superoxide anion by polymorphonuclear cells and neutrophils is influenced by an increase in leptin. Leptin can also influence neutrophil migration by activating p38 MAPK and Src kinases and increasing TNF-a production by monocytes while decreasing the chemotaxis process by blocking IL-8 [84]. This is critical for SARS-CoV-2 mediated lung damage because an increased amount of leptin causes an increase in neutrophilic lung inflammation, which increases the severity of lung injury [84]. SARS-CoV-2 can cause critical ARDS type pulmonary inflammation [83].

1.7. Mechanisms behind the connection between obesity and COVID-19

An immunocompromised person's 1st line of protection (nasal mucosa and skin) and 2nd line of protection (phagocytes and bactericidal compounds) are unable to stop and eliminate the virus from entering the lungs via the airway territory. Because COVID-19 is communicated through droplets or touch, obesity would certainly exacerbate the severity of COVID-19 [85]. A massive discharge of cytokines can cause cytokine storms, and an overactive immunity can cause ARDS, viremia, respiratory failure, fast deterioration of lung activity, and potentially MODS (multiple organ dysfunction syndrome) [86]. In lung cells, the ACE2 receptor is an attachment site for the viral spike protein, allowing the virus to move inside the cell, followed by the assembly, duplication, and discharge of a huge number of virus [87]. The target cells are destroyed and slaughtered by immunological T cells via the cellular immune system when the virus is phagocytised by macrophages in alveolar epithelia, and a high number of complements and cytokines are produced [88]. This autoinflammatory reaction causes lung cell death, which prevents the lung alveoli from transporting regular blood oxygen, resulting in a variety of clinical indications in subjects [87,88].

Adipocytes might have a significant function in the synthesis of circulating angiotensinogen, converting to Ang II (angiotensin II) by renin and ACE [89]. Obesity can cause changes in the RAAS, which can lead to additional COVID-19 infection abnormalities. Obesity may thus result in an overactive RAAS [90]. Ang II, elevated levels in the lungs, can cause pulmonary vasoconstriction, which can lead to a perfusion/ventilation discrepancy and hypoxemia, as well as oxidative damage and inflammation, all of which can contribute to acute lung injury [89]. Ang II levels were seen to be favourably connected to body weight in obese T2DM subjects. As a result, obese people's higher starting point of levels of Ang II might worsen SARS-CoV-2 encouraged Ang II increment, resulting in extra critical lung damage [91]. Subjects with SARS-CoV-2 were revealed to have higher Ang II intensities, which were linked to the rigorousness of lung damage as determined by the PaO$_2$ to a fraction of inhaled oxygen ratio in small study by Liu and colleagues [92]. Levels of Ang II dropped in rejoinder to nutritional weight loss, which was surprising. As a result, dietary changes and physical activity may help to reduce this putative mechanism of increased SARS-CoV-2 infection in obese people [92]. In COVID-19 subjects, cytokine storm is a leading cause of mortality. A higher amount of cytokines, interferon (IFN), and IL-6 characterise this immune hyperactivation phenomenon, which results in immunological activation-related consequences and symptoms [70]. Obesity has a negative impact on the anatomy and physiology of upper respiratory activity, respiratory drive and mechanics, all of which have a direct impact on the respiratory function of obese patients [80]. Obesity causes individuals to have a poor gas exchange, less lung volume, less respiratory muscle activity, and higher airway resistance. Though, because COVID-19 is mostly a respiratory viral infection, patients' obesity will exacerbate their respiratory function during the SARS-CoV-2 infection and might even set them to threat for pulmonary problems, resulting in a bad prognosis [93]. While few studies have shown that a greater amount of proinflammatory cytokines in critical SARS-CoV-2 reproduce an augmented viral load moderately than an unsuitable host rejoinder which necessities to be amended, inflammatory cytokines (TNF-α and IL-1/1Ra/6/8/18) connected to cytokine storm are similar to those connected with critical sepsis or ARDS [80,93]. The deleterious consequence of obesity on respiratory activities could explain why patients with concomitant obesity and COVID-19 have a higher risk of lung failure and the need for powered ventilation. On the other hand, obese individuals might be unprotected to even higher quantities of circulating inflammatory chemicals owing to their pro-inflammatory milieu. Obesity patients' unregulated inflammation and other immunological-related responses might worsen the cytokine storm, permitting for sophisticated viral dissemination and lengthier infection time, accelerating the severity of SARS-CoV-2 in these individuals [31, 34]. Obesity is strongly linked to OSA, that can give rise to recurring airway impediments in COVID-19 subjects, aggravating pro-inflammatory pulmonary processes [94].

Obese individuals have frequently increased leptin and decreased adiponectin levels [67]. This unbalanced hormonal stage can too result in a faulty immunological reaction. Overweight people are further vulnerable to a virus-related problems like COVID-19, increasing viral disclosure and the risk of enduring infection in obese people [61]. In a retrospective cohort study on 504 selected COVID-19 patients, there was a high risk of mortality in the overweight patients. Patients with COVID-19 who are overweight or obese have a higher risk of death and intubation than those with a normal BMI, according to the study. Obesity is a risk factor for COVID-19 problems, according to these data, and should be considered in COVID-19 care [95]. Obesity has also been linked to disruptions in phenotypes, and activity, lymphoid tissue reliability and changes in leukocyte formation, all of which have been linked to immunology and pathogen defence [96]. Obese adults and children have a reduced immune-induced response, and adults with obesity have decreased and impaired vaccine-specific T cell responses, which are required for viral infection prevention and recovery. Although

the origins of variance in the inflammatory action in COVID-19 are unidentified, adipose tissue may play a role [7]. In a clinical trial involving 248 healthcare workers, There was a considerable association between BMI classes and antibody titres: the humoral response was more efficient in the under- and normal-weight groups compared to the pre- and obese groups (p0.0001 at T1) [97]. Immunity dysfunction, inflammation related to obesity, and adipocytes may all play a role in SARS-CoV-2 infection. Because adipose tissue has the maximum ACE2 receptors' expression, which attaches to the virus and environs the heart and related veins, it's possible that adipocyte cells work as a virus pool [30,31]. ACE2 is a new coronavirus attachment site or receptor in the COVID-19 infection [58]. Yet, more studies have to be done to determine the connection among adipose tissue and SARS-CoV-2 or the occurrence of obesity and COVID-19, that necessities to be confirmed by clinical trials. Overweight individuals have a lot of "epicardial adipose tissue" (EAT) that can impact the cardiac role in SARS-CoV-2 subjects at a primary stage [28]. Furthermore, adipokines, together with different proinflammatory intermediaries that subsidise inflammatory cytokine storms, are abundant in EAT [98]. Host cells are penetrated by SARS-CoV-2 via ACE2 receptors when the host cell protease activates the spike protein; hence tissues and cells that express ACE2 could be SARS-CoV-2 targets [87]. According to tissue study, the expression of ACE2 is lesser in the lungs than in the adipose tissue, implying that obese individuals are more susceptible to the new COVID-19 strains [7,58]. Furthermore, prolonged stimulation of the RAAS in obese patients promotes high ACE-2 appearance and lesser angiotensin 1–7 availability, lowering antiviral resistance and increasing vulnerability to COVID-19 [99]. Obesity complicates the subject's diagnosis and therapy by reducing the superiority of investigative imaging, making airway supervision difficult, and making the patient resistant to prone placement.

1.8. Measures to be taken by the patients

Nutritional guidelines and tips for quarantine have been issued by organisations such as the WHO and the European Association for the Study of Obesity (EASO) [49,100]. There are no exact strategies for the nourishing management of SARS-Cov-2 subjects with obesity. Because obesity is supposed to be linked to the SARS-Cov-2 severity, it is evident that a diet with low calories should be used to lose weight. Throughout the SARS-Cov-2 epidemic, both affected people and the wider community experienced greater psychological suffering [101]. Furthermore, community separation was discovered to be a forecaster of greater mortality and a potential reason of sadness and nervousness in children and adolescents. It's worth noting that people who are obese are more likely to be distressed, and the psychological effects of the COVID-19 isolation can affect good obesity treatment [101]. Furthermore, losing weight has been made known to recover lung functioning [102]. Several behavioural and nutritional factors may be critical in obese individuals, and they should be taken into account when developing future guidelines. Obesity has been linked to psychosocial costs, such as stress or depression, and psychological care is an important part of obesity management. Psychological discomfort can too give rise to rampage and emotional eating in bariatric surgery subjects (pre- or post-surgical), which has been linked to inferior enduring outcomes [101]. Nevertheless, the link of obesity with mental factors in the recent epidemiological condition necessities to be researched further; emotional care should undoubtedly be included in the correct supervision of obesity during the COVID-19 pandemic [103].

Patients with SARS-Cov-2 who are over 60 years old and obese must be hospitalised as quickly as feasible. Further chronic or basic disorders (heart disease, hypertension, diabetes) should be treated as soon as possible [104]. They should maintain rigorous control of blood pressure, blood glucose, and blood lipids during the treatment; adequate lipid-lowering, hypotensive, and hypoglycemic regimes must be maintained throughout the treatment. Obesity raises the likelihood of severe

COVID-19 progression; hence specialist care and medical therapy in SARS-Cov-2 obese subjects should be prioritised. Obese subjects who have been unprotected to SARS-Cov-2 infected zones or SARS-Cov-2 subjects, particularly individuals who have established so-called COVID-19 indications (fever, runny nose, coughing, cold), should see a doctor as soon as possible for virus testing; those with slight indications can be checked at their residence via telemedicine and must be under 14 days of isolation prior to indications vanish [105]. To avoid "cytokine storms," immunological response pointers (CD8 +, CD4 +, immunoglobulin) and inflammatory response markers (CRP, TNF, IL-6) should be monitored throughout treatment [106]. To reduce treatment delays, the possibility of surgeries and suitable instruments must be examined in advance when treating obese people. It is unknown that vitamin D intake must be improved during the SARS-Cov-2 period, and it is currently not suggested [107]. Indeed, further randomised-controlled trials must be conducted to back up these claims. Higher intake of SFAs (saturated fatty acids) has been demonstrated to produce lipotoxicity, inflammation of adipose tissue, and enhance the innate immunity activity via TRL-4 activation (toll-like receptor-4) [66]. Increased production of TNF and interleukin-1 generated by lipopolysaccharide, and enhanced MCP-1 for macrophage permeation into lung tissue, are induced by a high-fat diet in the animal model [108]. Maintaining good immune function requires a satisfactory consumption of omega-3 fatty acids (polyunsaturated), iron, selenium, copper, zinc, folate, and vitamins (A, $B_{3/6/12}$, D, E). However, micronutrient deficiency and nutritious grade enhance the likelihood of SARS-Cov-2 infection and may impair its result; it is not yet suggested to utilise supraphysiologic levels to improve COVID-19's course [109]. Though, studies have shown that the consumption of various micronutrients (iron, calcium, magnesium, or potassium) and vitamins like vit-A/B_1/C are frequently insufficient in obese people and should be considered [109]. Greater intensities of plasma interleukin-6 and TNF may be linked to a high protein and fat intake [110]. However, because the relationship among immunology and nutrition is vast and compound, further randomised-controlled experiments in this area are needed.

2. Conclusion and future prospects

Obesity is common among SARS-CoV-2 individuals stayed in ICUs, and the rigorousness of COVID-19 pandemic upsurges with BMI. Obese individuals are more prone to further problems like renal failure and heart failure, necessitating renal support and advanced respiratory care, according to recent studies. Through downregulation of ACE2 or direct injury to pancreatic ß-cells, SARS-CoV-2 infection disrupts glucose homeostasis in diabetic and nondiabetic people. Insulin therapy has been hypothesised to lessen the severity of SARS-CoV-2 infection in these patients via modulating ACE2 receptor expression. SARS-CoV-2 and diabetes are linked through the virus's direct interaction to the ACE2 receptors on ß-cells. SARS-CoV-2 infection of pancreatic islet cells causes either direct ß-cell damage or downregulation of ACE2. Angiotensin II is produced in response to viral infection, which may limit insulin secretion. COVID-19 aggravates and starts type 2 diabetes, respectively, in pre-existing and new cases. Most of the studies to date have concentrated on finding treatments for COVID-19, but metabolic changes caused by the world's obese population (about 2 billion overweight individuals) might pose a further obstacle for the growth of effective medicines. To determine the link among COVID-19 and obesity, comprehensive, countrywide or worldwide retrospective clinical investigations and autopsy reports will be required. Autopsy findings that will indicate the link between COVID-19 and obesity have been published, despite the lack of large series of patients. Available clinical and laboratory evidence, on the other hand, unambiguously illustrate this link. It is critical to collect and measure the factors of obese people, such as hip circumference, waist circumference, weight, height, and so on, during follow-up clinical therapy. To correctly allocate medical resources, importance must be given to the management and therapy of SARS-CoV-2 infected obese individuals.

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