



# Evaluating Possible Mechanisms Linking Obesity to COVID-19: a Narrative Review

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## Abstract

Currently, pneumonia caused by the coronavirus disease 2019 (COVID-19) is a pandemic. To date, there is no specific antiviral treatment for the disease, and universal access to the vaccine is a serious challenge. Some observational studies have shown that COVID-19 is more common in countries with a high prevalence of obesity and that people with COVID-19 have a higher body mass index. In these studies, obesity increased the risk of disease, as well as its severity and mortality. This study aimed to review the mechanisms that link obesity to COVID-19.

**Keywords** COVID-19 · SARS-CoV-2 · Obesity · Adipokines · Inflammation · Cardiovascular system · Insulin resistance · Thromboembolism · Respiratory

## Introduction

According to the World Health Organization (WHO) report, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known as COVID-19, is currently a pandemic.

### Key Points

- Obesity can damage the vascular endothelium and activate the RAAS by hyperinflammation and insulin resistance.
- Obesity may change pharmacokinetics of the antiviral drugs and the effectiveness of the COVID-19 vaccine.
- Obesity is associated with worse clinical course and outcome of COVID-19.
- COVID-19 may increase the prevalence of obesity and its treatment failure.

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Although most patients have flu-like symptoms, severe disease or death may occur in these patients. [1–4] Risk factors and underlying health issues may affect the progression of COVID-19 as well as its prognosis. The mortality was higher in elderly (age over 65 years) and patients with comorbidities. [5]

According to the WHO reports, 50% of the world population is currently overweight or obese. The risk of infectious diseases and related complications is increased due to obesity. Also, obesity has been suggested as a risk factor for COVID-19 [6–8] (Table 1).

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The researchers have compared the prevalence of obesity in 20 countries with the highest COVID-19 deaths according to the WHO reports. Mortality is directly related to the prevalence of obesity in these countries. [9] Body mass index (BMI) above 40 was the second leading risk factor for hospitalization in elderly people with COVID-19 [10]. In many studies with different methods, the relationship between obesity and COVID-19 has been evaluated. According to their results, COVID-19 prevalence and severity were significantly higher in obese patients compared to general population. [11–13].

Obesity is more common in people with COVID-19 than in the general population. Obesity is associated with a higher rate of positive polymerase chain reaction (PCR) tests for COVID-19, severe illness, hospitalization rate, admission to intensive care unit (ICU), and sometimes higher mortality. [14–25].

In this study, we briefly reviewed the published articles on the relationship between obesity and COVID-19 up to July 5, 2021. Table 1 summarizes the findings of several systematic review and meta-analysis studies.

## Methodology

In this mini review, we searched these words “obesity & covid,” “obese & covid,” “BMI & covid,” “body mass index & covid,” “obesity & covid-19,” “obesity & covid19,” “obese & covid19,” “BMI & covid19,” “body mass index & covid19,” “risk & covid,” “severity & covid,” “mortality& covid,” “risk & covid19,” “severity & covid19,” and “mortality& covid19” in the title and abstract of “pubmed/medline,” “Scopus,” and “web of science.” Totally, 1310 articles were found. The English free full-text article from January 1, 2020, to December 30, 2020, was selected. Finally, 82 articles were included in this study.

## Results

All 82 articles were studied. Full-text articles on risk factors, disease severity, and mortality from COVID-19 disease were included. Studies that had more participants and were newer are listed in Table 1. In addition, all articles were studied for epidemiological, pathophysiological, and etiological explanations, and each that explained the relationship between COVID-19 and obesity was used in the “Discussion” section of the article.

## Discussion

Obesity increased the risk of COVID-19 disease, as well as its severity and mortality. This study aimed to review the mechanisms that link obesity to COVID-19.

The major pathophysiology complications related to obesity in COVID-19 disease are not fully understood. The relationship between obesity and COVID-19 can be explained in different pathways. First, obesity may cause these effects alone or in combination with comorbidities. Second, obesity changes immune system balance. Third, obesity changes respiratory physiology and aggravates hypoxia and hypercapnia due to COVID-19 pneumonia. Fourth, deep vein thrombosis (DVT) and pulmonary-thromboembolism (PTE) complicate the course of COVID-19. Obesity may play a role in these complications by hypercoagulopathy. Finally, COVID-19 can also increase the prevalence of obesity and failure of obesity treatment protocols. These pathways are summarized in Fig. 1.

## Comorbidities

Obesity, especially visceral obesity, is one of the most important risk factors for metabolic syndrome, cardiovascular disease [26, 27], and vitamin D deficiency [28]. Obesity, along with the abovementioned diseases, can increase the severity and mortality of COVID-19 (Table 1).

Insulin resistance, abnormal lipid metabolism, and diabetes along with obesity can change pulmonary vascular endothelium and pulmonary artery pressure and increase airway smooth muscle (ASM) proliferation and airway hyperresponsiveness (AHR). [29, 30].

Diseases such as type 2 diabetes, which are often associated with obesity, increase the risk of pneumonia by impairment of immune system. [31].

Lipotoxicity increases free fatty acids (FFAs). High levels of FFAs increase adipokines, myokines, and/or cytokines. These mediators promote inflammatory processes and amyloid deposition. These cytokines damage vascular endothelium and activate the renin–angiotensin–aldosterone (RAAS) system. Activation of this pathway by angiotensin-converting enzyme (ACE) receptors and insulin resistance increases blood pressure, atherosclerosis, and thrombosis. [32].

ACE2 is a homolog of ACE that converts angiotensin I to angiotensin II, which alleviates RAAS-related vasoconstriction. There are two forms of ACE2: soluble and membrane-bound. SARS-CoV-2 binds to ACE2 receptor on the cell membrane of host cell. Cell entry of corona virus depends on binding of viral spikes (S) protein to cellular receptors and on S protein priming by host cell proteases. So, the ACE2 receptor has a key role in the respiratory system involvement by SARS-CoV-2 and occurrence of acute respiratory complications of COVID-19. Obesity can propose patients to acute respiratory complications due to RAAS dysfunction. [33–35].

**Table 1** Literature review for the relationship between obesity and COVID-19

Author	Date of publication	Method of study	Number of studies, population	Aim	Key findings
Yang et al. [14]	2021 May	Systematic review, meta-analysis	41 studies with 219,543 cases (115,635 COVID-19 patients)	Positive SARS-CoV-2 test result, hospitalization, ICU admission, invasive mechanical ventilation and in-hospital mortality according to obesity and degree of obesity	<p>Subjects with obesity were more likely to have:</p> <ul style="list-style-type: none"> <li>• Positive SARS-CoV-2 test results (OR = 1.50; 95% CI = 1.37–1.63, <math>I^2 = 69.2\%</math>)</li> <li>• A higher incidence of:                             <ul style="list-style-type: none"> <li>- Hospitalization (OR = 1.54, 95% CI = 1.33–1.78, <math>I^2 = 60.9\%</math>)</li> <li>- Intensive care unit admission (OR = 1.48, 95% CI = 1.24–1.77, <math>I^2 = 67.5\%</math>)</li> <li>- Need to invasive mechanical ventilation (OR = 1.47, 95% CI = 1.31–1.65, <math>I^2 = 18.8\%</math>)</li> <li>- In-hospital mortality (OR = 1.14, 95% CI = 1.04–1.26, <math>I^2 = 74.4\%</math>)</li> </ul> </li> </ul>
Thakur et al. [15]	2021 Apr	Systematic review and meta-analysis	120 studies with 125,446 patients	To determine the differences in the prevalence of major comorbidities associated with COVID-19 and the severity and mortality of COVID-19	<p>The overall prevalence of comorbidities in patients with COVID-19:</p> <ul style="list-style-type: none"> <li>• HTN (32%, 95% CI = 28–36%)</li> <li>• Obesity (25%, 95% CI = 17–34%)</li> <li>• DM (18%, 95% CI = 15–20%)</li> <li>• CVD (16%, 95% CI = 13–19%)</li> <li>• Lung disease (9%, 95% CI = 7–11%)</li> <li>• CKD (6%, 95% CI = 5–8%)</li> </ul> <p>There was no association between the prevalence of obesity and the severity, and mortality of COVID-19</p>
Du et al. [16]	2021 Apr	Systematic review, meta-analysis	16 observational studies with 109,881 cases	Random-effects models and dose-response meta-analysis	<p>Patients with obesity (BMI <math>\geq 30</math> vs. BMI <math>&lt; 30</math> kg/m<sup>2</sup>) had a more:</p> <ul style="list-style-type: none"> <li>• Critical COVID-19, OR = 2.35, 95% CI = 1.64–3.38, <math>P &lt; 0.001</math></li> <li>• Mortality, OR = 2.68, 95% CI = 1.65–4.37, <math>P &lt; 0.001</math></li> </ul> <p>The risk of critical COVID-19 and mortality increased by 9% (OR = 1.09, 95% CI = 1.04–1.14, <math>P &lt; 0.001</math>) and 6% (OR = 1.06, 95% CI = 1.02–1.10, <math>P = 0.002</math>) for each 1 kg/m<sup>2</sup> increase in BMI, respectively</p>

Table 1 (continued)

Author	Date of publication	Method of study	Number of studies, population	Aim	Key findings
Pranata et al. <sup>17</sup>	2021 Mar	Systematic review, meta-analysis	12 studies with a total of 34,390 patients	Evaluation of the dose-response relationship between body mass index (BMI) and poor outcome in patients with COVID-19. The primary outcome was a poor outcome consisting of mortality and disease severity. Secondary outcomes were mortality and severity	Obesity in patients with COVID-19 was associated with: <ul style="list-style-type: none"> <li>• Composite poor outcome, OR = 1.73, 95%CI = 1.40–2.14, <math>P &lt; 0.001</math>, <math>I^2 = 55.6\%</math></li> <li>• Severity, OR = 1.90, 95%CI = 1.45–2.48, <math>P &lt; 0.001</math>, <math>I^2 = 5.2\%</math></li> <li>• Mortality, OR = 1.55, 95%CI = 1.16–2.06, <math>P = 0.003</math>, <math>I^2 = 74.4</math></li> </ul> <p>The dose-response meta-analysis showed an increased risk of composite poor outcome by aOR = 1.052, 95%CI = 1.028–1.077, <math>P &lt; 0.001</math> for every 5 kg/m<sup>2</sup> increase in BMI (<math>P</math> non-linearity &lt; 0.001)</p>
Yang et al. [18]	2020 Dec	Systematic review, meta-analysis	A total of 50 studies, including data on 18,260,378 patients, were available	Risk of COVID-19 and severity of COVID-19 (severe case, ICU admission, and intensive mechanical ventilation) studied based on BMI	Obesity was associated with a higher risk of SARS-CoV-2 infection as compared to those without obesity (OR: 1.39; 95% CI 1.25–1.54; $P < 0.00001$ ) <p>Obesity was associated with a more severity of COVID-19 disease:</p> <ul style="list-style-type: none"> <li>• Hospital admission rate, OR = 2.45, 95% CI = 1.78–3.39; <math>P &lt; 0.00001</math></li> <li>• Severe cases, OR = 3.74, 95% CI = 1.18–11.87; <math>P: 0.02</math></li> <li>• Need for ICU admission, OR = 1.30, 95% CI = 1.21–1.40; <math>P &lt; 0.00001</math></li> <li>• Need for invasive mechanical ventilation, OR = 1.59, 95% CI = 1.35–1.88; <math>P &lt; 0.00001</math></li> <li>• Obesity was associated with higher mortality, OR = 1.65, 95% CI = 1.21–2.25, <math>P: 0.001</math></li> </ul>

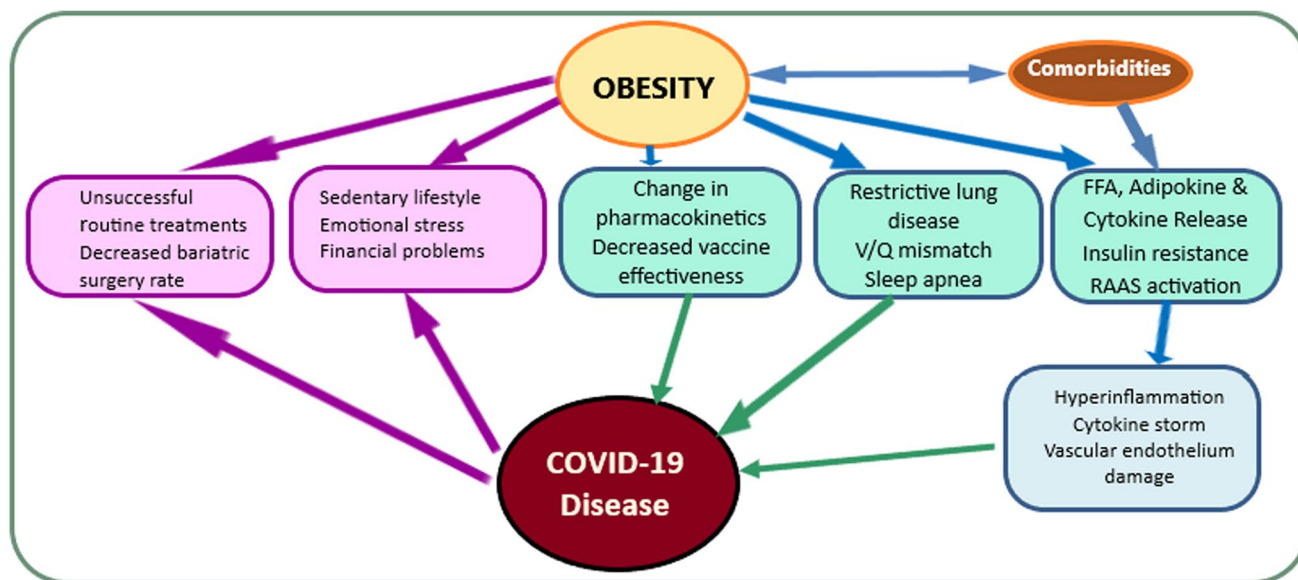
**Table 1** (continued)

Author	Date of publication	Method of study	Number of studies, population	Aim	Key findings
Ho et al. [19]	2020 Dec	Systematic review, meta-analysis	61 studies on 270,241 patients	Prevalence of obesity in hospitalized patients, ICU admission or critical illness, and severity of disease Obesity is define as BMI $\geq 27.5$ for Asia-Pacific area and BMI $\geq 27.5$ for others	<ul style="list-style-type: none"> <li>• Pooled prevalence of obesity was 27.6% (95% CI = 22.0–33.2)</li> <li>• A positive COVID-19 test (OR = 1.50, 95% CI = 1.25–1.81, <math>P &lt; 0.001</math>)</li> <li>• ICU admission or critical illness (OR = 1.25, 95% CI = 0.99–1.58, <math>P = 0.062</math>, <math>I^2 = 31.0</math>)</li> <li>• Severe disease (OR = 3.13, 95% CI = 1.41–6.92, <math>P = 0.005</math>, <math>I^2 = 82.6</math>)</li> <li>• Mortality (OR = 1.36, 95% CI = 1.09–1.69, <math>P = 0.006</math>, <math>I^2 = 88.5</math>)</li> </ul>
Moazzami et al. [20]	2020 Dec	Systematic review, meta-analysis	13 studies on 2,602, 7,632, and 15,268 patients with COVID-19 were included in the analysis of obesity, diabetes, and hypertension, respectively	To assess the association of metabolic risk factors and risk of COVID-19	<p>The pooled prevalence of obesity in COVID-19 patients was 29% (95% CI = 14–7%, <math>I^2 = 98%</math>, <math>P &lt; 0.001</math>)</p> <p>For diabetes was 22% (95% CI = 12–33%, <math>I^2 = 99%</math>, <math>P &lt; 0.001</math>)</p> <p>For hypertension was 32% (95% CI = 12–56%, <math>I^2 = 99.7%</math>, <math>P &lt; 0.001</math>)</p> <p>Obesity was associated with more risk for:</p> <ul style="list-style-type: none"> <li>• Positive COVID-19 test, OR = 1.46, 95% CI = 1.30–1.65, <math>P &lt; 0.0001</math></li> <li>• Hospitalization, OR = 2.13, 95% CI = 1.74–2.60, <math>P &lt; 0.0001</math></li> <li>• ICU admission, OR = 1.74, 95% CI = 1.46–2.08</li> <li>• Mortality, OR = 1.48, 95% CI = 1.22–1.80, <math>P &lt; 0.001</math></li> </ul>
Popkin et al. [21]	2020 Nov	Systematic review, meta-analysis	75 studies with 399,461 cases	To provide insight into the relationship between being an individual with overweight/obesity and COVID-19	<p>The prevalence of obesity was (42%, 95% CI = 34–49%)</p> <p>The pooled ORs of the obesity in patients with severe or fatal vs. non-severe/fatal COVID-19 were:</p> <ul style="list-style-type: none"> <li>• Obesity, overall OR = 1.72 (95% CI = 1.04–2.85, <math>I^2 = 69.8</math>)</li> <li>• Obesity, OR for clinical symptom or disease severity = 2.29 (95% CI = 1.22–4.29, <math>P = 0.01</math>, <math>I^2 = 38.5</math>)</li> <li>• Obesity, OR for death = 1.15 (95% CI = 0.98–1.34, <math>P = 0.08</math>, <math>I^2 = -</math>)</li> </ul>
Zhou et al. [22]	2020 Oct	Systematic review, meta-analysis	34 studies with 16,110 cases	To evaluate the association between different comorbidities and the severity of COVID-19	<p>The prevalence of obesity was (42%, 95% CI = 34–49%)</p> <p>The pooled ORs of the obesity in patients with severe or fatal vs. non-severe/fatal COVID-19 were:</p> <ul style="list-style-type: none"> <li>• Obesity, overall OR = 1.72 (95% CI = 1.04–2.85, <math>I^2 = 69.8</math>)</li> <li>• Obesity, OR for clinical symptom or disease severity = 2.29 (95% CI = 1.22–4.29, <math>P = 0.01</math>, <math>I^2 = 38.5</math>)</li> <li>• Obesity, OR for death = 1.15 (95% CI = 0.98–1.34, <math>P = 0.08</math>, <math>I^2 = -</math>)</li> </ul>

Table 1 (continued)

Author	Date of publication	Method of study	Number of studies, population	Aim	Key findings
Földi et al. [23]	2020 Jul	Systematic review, meta-analysis	24 retrospective cohort studies with 3279 cases	To examine whether obesity is a risk factor for the critical condition in COVID-19 patients	Obesity (BMI $\geq 25$ vs. BMI $< 25$ ) is a significant risk factor for: <ul style="list-style-type: none"> <li>• ICU admission (OR = 1.21, CI = 1.002–1.46, <math>I^2 = 0.0\%</math>)</li> <li>• IMV requirement (OR = 2.63, CI = 1.64–4.22, <math>I^2 = 0.0\%</math>) in COVID-19</li> </ul>
Caussy et al. [24]	2020 Jul	Case control observational study	1674 cases Three groups: A, 464 severe COVID-19 cases (240 cases non-critical and 224 critical cases); B, 1210 cases admitted to ICU due to non COVID-19 disease; C, general population	To assess the prevalence of obesity (BMI $\geq 30$ kg/m <sup>2</sup> ) among patients requiring hospitalization for severe COVID-19	25% of group A, 26% of group B, and 15.3% of group C had obesity The risk of obesity in group A is more than group C (OR = 1.35, 95% CI = 1.08–1.66, $P = 0.003$ ). The prevalence of obesity was higher in patients with critical COVID-19 than in ICU patients without COVID-19 (OR = 1.69, 95% CI = 1.10–2.56, $P = 0.017$ ) after adjustment for age and sex The risk of obesity in critical severe COVID-19 is more than general population (OR = 1.96, 95% CI = 1.13–3.42, $P = 0.018$ )
Petrilli et al. [25]	2020 May	Prospective cohort study	5279 cases	To describe outcomes in patients with COVID-19 (admission to hospital, critical illness, intensive care, mechanical ventilation) and discharge or death	BMI $\geq 40$ was a risk factor for hospitalization (OR = 2.45, 95% CI = 1.78–3.36, $P < 0.001$ ); critical illness (OR = 1.71, 95% CI = 1.10–2.7, $P = 0.02$ ), and maybe mortality (OR = 1.45, 95% CI = 0.99–2.13, $P = 0.05$ )

\* Articles are sorted by date and number of participants



**Fig. 1** Possible pathways linking obesity to COVID-19

Vitamin D deficiency (VITDD) is more prevalent in obesity, and it can promote obesity by increasing lipogenesis. [36, 37] A variety of factors can lead to VITDD in obese people, including decreased synthesis through sunlight, vitamin D entrapment in fat cells, fatty liver complications, and lifestyle factors. Vitamin D can potentially control COVID-19 because it strengthens the body's physical barrier against pathogens, modulating the immune system to prevent the proliferation of SARS-CoV-2 and the cytokine storm. Adequate vitamin D can reduce pulmonary injury, acute respiratory distress syndrome, as well as cardiovascular and thrombotic complications by increasing ACE2, nitric oxide, and NF- $\kappa$ B1 and decreasing inflammatory cytokines. [38–40].

### Immune System Impairment

Leptin and adiponectin are major adipokines of adipose tissue with pro-inflammatory and anti-inflammatory properties, respectively. In obesity, leptin levels are higher, and adiponectin levels are lower than in normal-weight individuals. [41].

Adiponectin reduces T cell response to pathogens, the capacity of phagocytosis by macrophages, and B cell production in the bone marrow. It disrupts immune cell activity by inhibiting activation of the NF- $\kappa$ B pathway and signaling of AMP-activated protein kinase (AMPK). The production of anti-inflammatory cytokines such as IL-10 and IL1R $\alpha$  with PI3K and p38 pathways is decreased by adiponectin. Low adiponectin blood levels have the opposite effect on obesity and cause an inappropriate increase in the immune response in COVID-19 disease.

Leptin is closely linked to the immune system and plays an important role in the regulation of T cells and the production of cytokines. [42–45] High leptin blood level signals via STAT3 and activates both polymorphonuclear neutrophils and lymphocytes. It also increases proliferation and activation of immune cells (T cells, monocyte, macrophage, dendritic cells, and natural killer cells) and cytokine production. This unfavorable hormone milieu also leads to a dysregulation of the immune response.

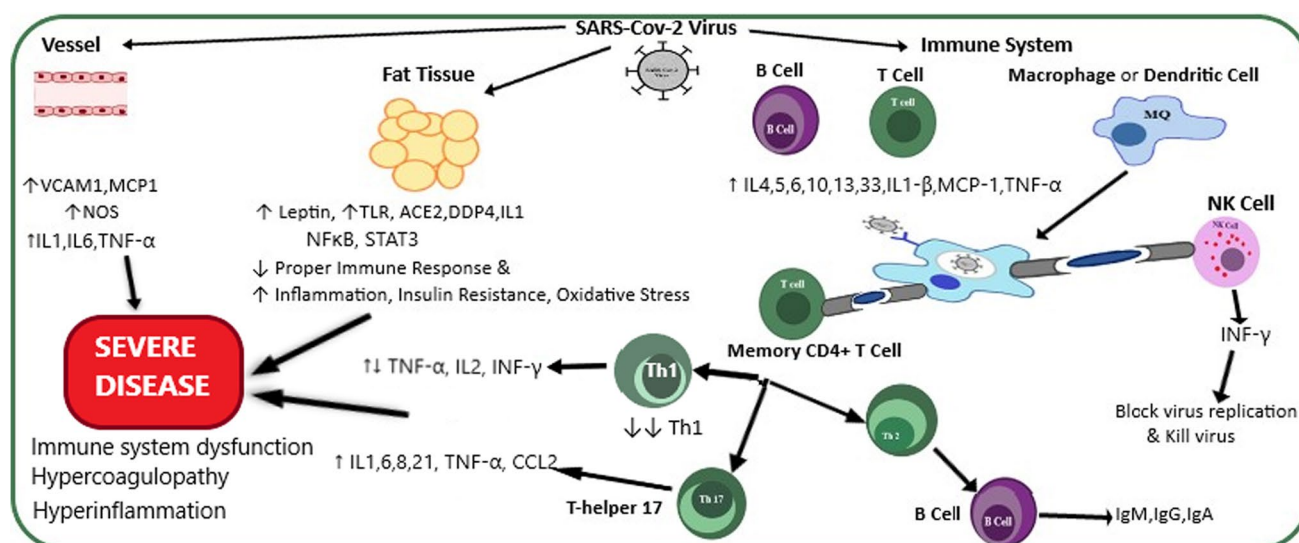
Obesity is associated with high frequency of both upper and lower respiratory tract infections due to innate immunity impairment. Long-term hyperleptinemia leads to leptin resistance and defects in host defense. Leptin resistance in T cells, natural killer (NK) cells, and peripheral blood monocytes has been demonstrated in obesity. [46–48].

An imbalance between pro-inflammatory and anti-inflammatory factors is the most important key point for introducing obesity as a major risk factor for abnormal immune response and acute lung injury. [49].

Fat tissue may act as a reservoir for the SARS-CoV-2 virus and facilitate the spread of the virus, and stimulate the immune response (Fig. 2). [50].

### Coagulopathy

COVID-19 was commonly associated with increased coagulopathy, disseminated intravascular coagulation (DIC), and acute inflammation, which resulted in higher mortality. [51, 52] Recurrent venous and arterial thromboembolism have been reported as serious complications of COVID-19 in high-risk patients (ICU patients and obese individuals). Pulmonary embolism is the most common



**Fig. 2** The function of the immune system when a SARS-CoV-2 virus enters the body. Several cytokines and adipokines are released by the vascular endothelium, adipose tissue, and T cells after exposure to the virus. Inappropriate activation of the immune system results in cytokine storm and hypercoagulability state. These conditions complicated the COVID-19 disease course and its management. Abbreviations: VCAM-1, vascular cell adhesion protein 1; MCP-1, monocyte chemoattractant protein-1; NOS, nitric oxide synthase;

IL, interleukin; TNF- $\alpha$ , tumor necrosis factor alpha; TLR, toll-like receptor; ACE2, angiotensin-converting enzyme 2; DDP4, dipeptidyl peptidase-4; Nf $\kappa$ B, nuclear factor kappa-light-chain-enhancer of activated B cells; STAT3, signal transducer and activator of transcription 3; MQ, macrophage cell; NK cell, natural killer cell; IFN- $\gamma$ , interferon-gamma; Th, T helper cell; CCL-2, chemokine (C-C motif) ligand 2; IG, immunoglobulin

thrombotic event that occurs despite prophylaxis against thrombosis. Obesity increases the rate of recurrent venous thromboembolism (VTE) compared to normal-weight people. [53].

VTE results from the complex interactions of genetic and environmental factors. Increased pre-coagulation factors due to inflammation along with disorders of the anticoagulant and fibrinolytic systems lead to increased coagulation and/or decreased fibrinolysis.

Obesity can cause venous stasis and increase the rate of venous thrombosis. Serum levels of D-dimer, fibrinogen, factor VIII, and factor IX are directly related to BMI. [54] Visceral obesity is accompanied by a systemic oxidative stress process, pro-inflammatory cytokines, and insulin resistance. These changes result in the loss of the antithrombotic properties of the endothelium, platelets, and other circulating cells. The production of microprocoagulant (MP) particles, IL-1 $\beta$ , plasminogen activator inhibitor-1 (PAI-1), and tissue factor (TF), which activates the factor 7 receptor, is increased in obesity. In addition, the release of adipokines/inflammatory cytokines, such as TNF- $\alpha$ , IL-6, and IL-8, can result in Von Willebrand factor (VWF) release from the endothelium and the activation as well as aggregation of platelets. [55].

Obesity raises thrombin levels and subsequently increases blood coagulation, which decreases with weight loss after bariatric surgery. [56].

## Respiratory System Involvement

COVID-19 disease was recognized worldwide with pneumonia and involvement of the respiratory system. Obesity also causes significant changes in the respiratory system. Increased inflammation or blood coagulation due to obesity can exacerbate lung damage in COVID-19 disease.

Obesity can cause shallow breathing and a higher respiratory rate. Shallow ventilation facilitates respiratory tract infections [57]. Obesity is associated with airway hyperresponsiveness and can cause wheezing, shortness of breath, and orthopnea.

Accumulation of adipose tissue in the chest wall reduces lung compliance. Reduced lung compliance and volumes can cause focal atelectasis, which is more common in the base of the lungs. Therefore, ventilation/perfusion mismatch becomes worse at the base of the lungs and reduces blood oxygen saturation by pressing on the diaphragm.

Respiratory muscle weakness in obese patients increases the work of respiratory system. Sleep apnea and asthma are more common in obesity. Restrictive and obstructive respiratory pattern, ventilation/perfusion mismatch, muscle weakness, and atelectasis worsened hypoxia and hypercapnia in COVID-19.

Obesity can also damage lung by systemic inflammation. Adipokines activate macrophage infiltration and secretion of other pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6,



which damage pulmonary epithelium and parenchyma. [58–62].

Mortality rates of obese patients are higher than normal-weight patients in ICU because they have a higher risk of complications such as sepsis, ventilator-associated pneumonia, and central venous catheter infection [63]. It is also more difficult in obese people to manage anesthesia during surgery and ventilate them in the ICU. [64, 65].

## Treatment Challenges

Obesity may change the pharmacokinetics and pharmacodynamics of antiviral drugs, and thus affect the treatment of COVID-19. There are no approved guidelines for infection management and dose adjustment in COVID-19 patients with obesity. In healthy obese volunteers, clearance and distribution volumes of an antiviral drug (Oseltamivir) were higher than in normal-weight subjects. [66, 67].

The COVID-19 pandemic has also challenged obesity treatment. The most common protocol proposed by governments to control COVID-19 is home quarantine. Adherence to this protocol has reduced daily physical activity. Sedentary lifestyle increases the prevalence of obesity and other risk factors for cardiovascular disease. [68] Sedentary lifestyle, emotional stress, and financial problems increase the prevalence of obesity in the COVID-19 pandemic and reduce the success of treatments such as diet and exercise. Physical activities strengthen the immune system by increasing immune cells. [69].

Patients undergoing elective surgery during the COVID-19 pandemic are at risk of contamination by the virus [70]. In a cohort study of patients undergoing various surgeries, patients with COVID-19 had a higher risk of 30-day mortality and surgical, pulmonary, and thrombotic complications than those without COVID-19. These researchers recommend that elective surgery should be delayed for at least 9 weeks during the COVID-19 disease pandemic [71]. Hence, “the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) recommend that elective metabolic surgery for obesity should be postponed throughout the pandemic.” [72] Therefore, the number of metabolic and bariatric surgeries has greatly decreased in the COVID-19 pandemic. Patients’ access to these surgeries as an effective and long-term treatment for obesity has decreased. This has unintended consequences for obese patients and exposed them to severe forms of COVID-19 disease with complications and death. It also lengthens the waiting list for bariatric surgery and gradually reduces the skill of surgeons. [73, 74].

## Efficacy of COVID-19 Vaccine

Obesity may affect the rate of COVID-19 vaccination and its effectiveness. There is some evidence to support the role of obesity in reducing the effectiveness of influenza A virus vaccination. [75] Similar results may be obtained after the COVID-19 vaccine injection, which may raise concerns about its effectiveness. In a cohort study, the number needed to vaccinate (NNV) to prevent one COVID-19-related death over 1 year was lower for surgical patients than the general population in all age groups [76]. Limited data is available about this issue, and more data is needed to clarify the effect of obesity on vaccination.

## Conclusion

Obesity can increase the risk of COVID-19 in different ways. Obesity has paradoxical effects on immune system, and it can impair the body’s immune defense, increase inflammation, and cause cytokine storm. Negative effects of obesity on the respiratory system, comorbidities, and insulin resistance damage the vascular endothelium and activate the RAAS system. These factors result in the end organ damage, thromboembolism, and serious complication of COVID-19. Obesity may change pharmacokinetics of the antiviral drugs and the effectiveness of the COVID-19 vaccine. On the other hand, COVID-19 can increase the prevalence of obesity and its treatment failure. These issues should be investigated in future studies.

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**Author Contribution** M.V. proposed the concept of the article, searched and selected various articles, wrote the initial draft of the article, wrote and edited the final format of the article, prepared table, and draw figures and visual abstract.

Z.H. has read and summarized the selected articles related to the first and third subtitles and has written a part of the initial draft of the article in these sections.

M.R. has edited immunology issue and draw primary draft of Fig. 2.

A.A. and A.Q. have collected the materials related to the effect of obesity on the respiratory system and increased blood coagulation in COVID-19, and have written parts of the initial draft of the article in these subtitles.

## Declarations

**Ethics Approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed Consent** Informed consent does not apply.

**Conflict of Interest** The authors declare no competing interests.

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