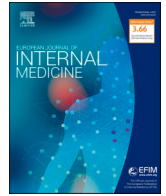


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Review article

Obesity as an adipose tissue dysfunction disease and a risk factor for infections – Covid-19 as a case study

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV2) disease (COVID-19) is a novel threat that hampers life expectancy especially in obese individuals. Though this association is clinically relevant, the underlying mechanisms are not fully elucidated. SARS CoV2 enters host cells via the Angiotensin Converting Enzyme 2 receptor, that is also expressed in adipose tissue. Moreover, adipose tissue is also a source of many proinflammatory mediators and adipokines that might enhance the characteristic COVID-19 cytokine storm due to a chronic low-grade inflammatory preconditioning. Further obesity-dependent thoracic mechanical constraints may also incise negatively into the prognosis of obese subjects with COVID-19. This review summarizes the current body of knowledge on the obesity-dependent circumstances triggering an increased risk for COVID-19 severity, and their clinical relevance.

1. Introduction

Obesity is a chronic disease with complex pathophysiology characterized by excessive hypertrophy and hyperplasia of adipose tissue that presents a risk to health, caused by a chronic imbalanced energy state [1]. Obesity is a fast growing, non-communicable disease (NCD) of pandemic proportions for already several decades with a current global prevalence of 39% according to the World Health Organisation (WHO). Besides being a storage site, adipose tissue is also responsible for secretion of various adipokines that, in the context of obesity, are misregulated [2]. Adipocyte dysfunction along with altered adipokines release results in various metabolic disturbances, mainly insulin resistance/type 2 diabetes mellitus, hypertension, cardiovascular diseases and cancer [3,4].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for Coronavirus Disease 2019 (COVID-19) has so far infected over 85 millions and killed over 1.8 million people worldwide. The

increased hospitalization and mortality linked to COVID-19 are associated with older age and a number of underlying conditions such as obesity [5–8] and related comorbidities along with secondary medical complications [hypertension [5,6,9], diabetes [6,9–11], and history of cardiovascular diseases [6,9,11] among others]. Moreover, a strong correlation of obesity with influenza and other respiratory viral infections had already been established [12,13]. Severe cases of COVID-19 are associated with high circulating levels of inflammatory cytokines akin to a cytokine release syndrome that frequently results in respiratory failure, multiorgan failure and death [14]. Histologically, pneumonitis and morphological features of acute respiratory distress syndrome (ARDS) have been described as the pathological substrate of the most severe cases [15]. It is noteworthy that obesity is associated with increased risk of severity especially in younger patients [16,17].

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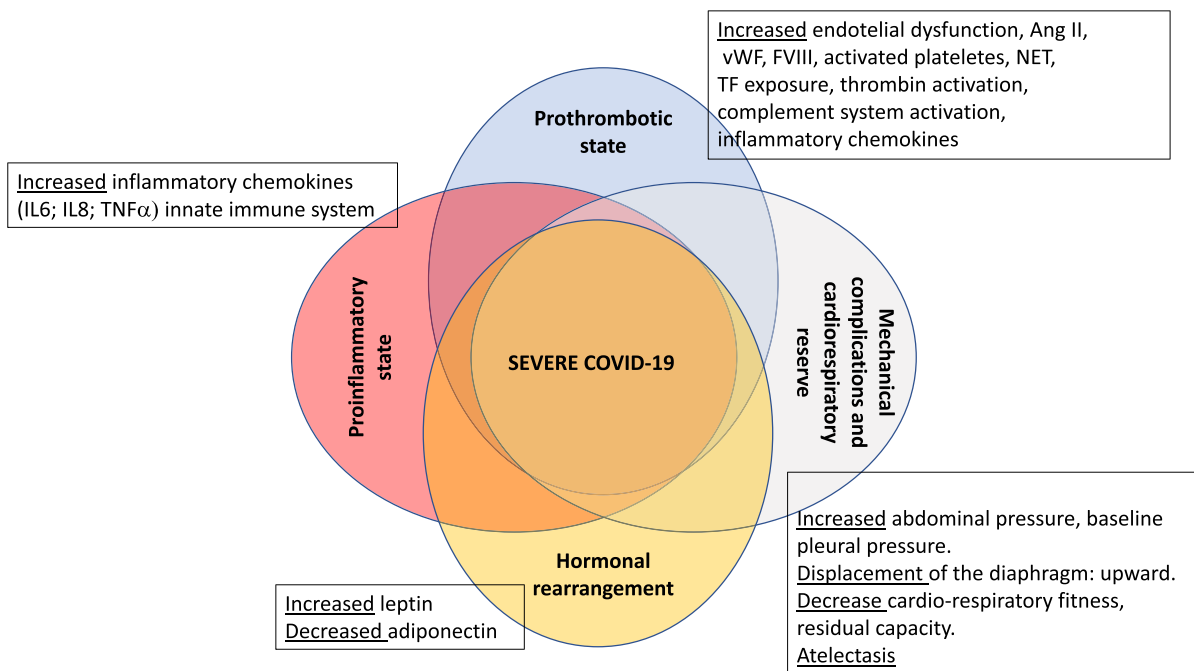


Fig. 1. Severe COVID-19 obesity tetrad. Obesity entails an increased proinflammatory, prothrombotic state associated with a hormonal rearrangement in a context of decreased cardio-respiratory fitness and limited respiratory capacity. IL6: interleukin 6; IL8: interleukin 8; TNF α : tumor necrosis factor α ; Ang II: angiotensin II; vWF: von Willebrand Factor; FVIII: coagulation-cascade factor VIII; NET: Neutrophil extracellular trap; TF: tissue factor.

1.1. Obesity as a risk factor for infections

Despite being a NCD, obesity has gained a preponderant impact on communicable diseases since it increases the risk for incident and severe infections [18–20]. As a consequence of the 2009 H1N1 influenza A virus pandemic, obesity was identified as a risk factor for increased disease severity and mortality in infected individuals [19]. A multi-centre study evaluated 4778 participants with influenza and influenza-like infections. Moser et al. [13] found that adults with excessive adiposity and influenza had an increased Odds Ratio (OR) for hospital admission compared to normal-weight adults, that was OR: 3.2 for obesity and OR: 18.4 for severe obesity. In the same report, an increased risk for hospital admission (OR: 2.8) in adults living with severe obesity and with influenza-like infections (including coronavirus) was also reported [13]. Systemic alterations to antiviral immunity, including both the innate and adaptive responses, baseline alterations in the obese lung environment and limitations for the spontaneous and mechanical ventilation explain, at least in part, the poorer outcomes. In addition to excess adiposity itself, most people with obesity are also sedentary. Clinical and translational studies on humans have demonstrated that regular bouts of short-lasting (i.e., 45–60 min), moderate-intensity exercise (50–70% VO₂max), performed at least 3 times a week is beneficial for the host immune defense, particularly in older adults and people with chronic diseases [21].

1.2. Obesity and SARS-CoV-2

SARS-CoV-2 is a betacoronavirus that uses the angiotensin-converting enzyme-related carboxypeptidase (ACE2) receptor to gain entry into cells mediated by the transmembrane spike glycoprotein. Following receptor binding, the virus must gain access to the host cytosol, which is accomplished by acid-dependent proteolytic cleavage of the spike protein by cellular transmembrane protease serine 2 (TMPRSS2) [22]. The infection by SARS-CoV-2 likely eliminates the ACE2/ANG(1–7)/MASR regulatory axis leading to sudden exaggeration of the ACE/ANGII/AT1R activity that directly facilitates ARDS, and that

is further enhanced by MHC-dependent antigen presentation and an aggressive inflammatory infiltrate [22]. SARS-CoV2 also infects and activates monocytes, macrophages, and dendritic cells. Cytokine release then instigates an amplification cascade that results in *cis* signalling with TH17 differentiation, among other lymphocytic changes, and *trans* signalling in many cell types, such as endothelial cells. The resulting increased systemic cytokine production contributes to the pathophysiology of severe COVID-19, including hypotension and ARDS [23].

The level of ACE2 expression in adipose tissue is higher than that in lung tissue, a major target tissue affected by COVID-19. This is an important finding because adipose tissue might also be vulnerable to COVID-19, and weight loss is among the most prevalent symptoms of the disease. It should be noted, however, that there was no difference in the expression of ACE2 protein by adipocytes between lean and obese individuals [24]. However, individuals with obesity have more adipose tissue, which ultimately translates into an increased number of ACE2-expressing cells and, consequently, a larger amount of ACE2. Adipose tissue constitutes a reservoir for SARS-CoV-2 increasing the integral viral load.

1.3. Obesity and COVID-19

1.3.1. Proinflammatory state

Obesity promotes a chronic low-grade inflammatory state that develops following activation of resident macrophages in adipose tissue, promoting the recruitment of M1-polarized macrophages, which display a proinflammatory phenotype [3,20], increasing the local and systemic production of proinflammatory cytokines (TNF α , IL-6, and others). A type 1 immune response (Th1), which is usually activated acutely in response to infection, characterizes this adipose pro-inflammatory state. In the case of obesity, this immune response in adipose tissue is chronic and involves effector T cells, B cells, and natural killer (NK) cells that produce cytokines orchestrating the accumulation and activation of proinflammatory M1 macrophages. A chronic proinflammatory state via IL-6 and other factors [25] may skew the immune system to enable SARS-CoV-2 to unleash the cytokine storm and the deadly inflammatory

complications of COVID-19 [20,26]. Critically ill COVID-19 patients experiencing a cytokine storm have a worse prognosis and an increased fatality rate. In COVID-19 patients, the cytokine storm is reportedly important to the pathogenesis of several severe manifestations: ARDS, thromboembolic diseases (acute ischemic strokes caused by large vessel occlusion, myocardial infarction) encephalitis, acute kidney injury, and vasculitis (Kawasaki-like syndrome in children and renal vasculitis in adults) [27].

Many of the aforementioned complications are associated to vascular disease. In this context, the potential role of specific dysfunctional deposits merits consideration. Perivascular adipose tissue (PVAT) surrounds most blood vessels except the cerebral vasculature, and is elevated in obesity. Noteworthy, PVAT is capable of interacting with inflammatory cells, the nervous system, and vascular cells to promote or modulate vascular disease [28]. In physiological conditions, PVAT plays a fundamental role in vasodilation via production of adipokines, including adiponectin. Under inflammatory states, such as obesity, vasodilatory adipokine release is diminished from inflamed, dysfunctional PVAT, thus promoting vasoconstriction [2,28] (Fig. 1).

1.3.2. Hormonal rearrangement

Leptin released from adipocytes can stimulate macrophages to produce proinflammatory cytokines [28]. Immune cells infiltrating PVAT in obesity can also promote vasoconstriction and endothelial dysfunction via cross talk with vascular cells, suggesting that the crosstalk between immune cells and adipocytes may be an important feature driving a proinflammatory environment. It may be worthwhile to establish the potential relevance of PVAT in the COVID-19 vascular complications.

Leptin is an essential hormone secreted in a pulsatile fashion to the bloodstream involved in maintaining energy homeostasis besides its role in regulation of neuroendocrine functions. The typical modern-diet induced obesity is characterized by hyperleptinemia and resistance to the weight control effects of leptin, but not to its proinflammatory effects. Leptin has structural similarities with IL-6, and the leptin receptor, as the receptor for IL-6, is a class I cytokine receptor family member [29]. Leptin acts as a potent inflammatory cytokine and stimulates innate immune responses by promoting the activation of monocytes/macrophages, which are a mainstay of COVID-19. Leptin also stimulates the production of a myriad of proinflammatory chemokines (IL-6, CCL11/eotaxin, CCL2/MCP-1, CXCL8/IL-8, and CXCL10/IP-10) [30] that may promote the cytokine storm associated to COVID-19. Notably, in patients with pneumonia unrelated to COVID-19, plasma leptin levels were found to correlate positively with subsequent mortality due to ARDS, suggesting that the association between obesity and elevated risk of pulmonary infection may be driven, at least in part, by hyperleptinemia [31].

Adiponectin is also secreted almost exclusively by adipocytes, and decreases in most persons living with obesity [2]. Both leptin and adiponectin have been related to cardiometabolic risk factors. The adiponectin/leptin ratio has been proposed as a marker of adipose tissue dysfunction. Moreover, the adiponectin/leptin ratio is negatively correlated with markers of low-grade chronic inflammation, such as C-reactive protein [2,32] (Fig. 1).

1.3.3. Prothrombotic state

COVID-19 has also a direct effect on endothelial cells that ease the thrombus formation with a bidirectional enhancement of the proinflammatory state and hormonal rearrangement [22,23]. Direct infection of the endothelial cells through the ACE2 receptor also leads to endothelial activation and dysfunction, expression of tissue factor, and platelet activation and increased levels of von Willebrand Factor and Factor VIII, all of which contribute to thrombin generation and fibrin clot formation [33]. This effect may be potentiated by the local effect of PVAT, especially under inflammatory states (i.e. excessive dysfunctional adiposity). Thrombin, in turn, causes inflammation through its effect on platelets, which promote neutrophil extracellular trap formation. It also

activates endothelium through the PAR receptor, which leads to release of C5A that further activates monocytes [33,34]. Venous thromboembolism is the most common thrombotic manifestation of COVID-19, about 25% [35], and thus thromboprophylaxis should always be considered. In comparison to venous thrombosis, the incidence of arterial thrombosis in COVID-19 appears to be less in prevalence [36], but due to their risk of major long-term sequels, myocardial infarction, ischemic stroke and microvascular thrombosis [15,36] prevention requires further studies (Fig. 1).

1.3.4. Mechanical complications due to obesity

The respiratory physiology of people living with obesity might also contribute to the increased incidence of ARDS criteria in these patients. Anatomic and physiological alterations are observed in patients with obesity, affecting the face, neck, pharynx, chest wall and lungs. Excess abdominal fat may increase abdominal pressure. The displacement of the diaphragm upwards, added to the increased chest wall weight, may raise baseline pleural pressure. While total lung capacity and spirometric values usually remain normal, there is a decrease in functional residual capacity. Reduced functional residual capacity can trigger the closure of peripheral dependent airways during tidal ventilation, and decreased lung compliance due to tidal ventilation below the lower inflection point of the inspiratory pressure–volume curve. These changes result in atelectasis and ventilation–perfusion mismatch together with hypoxemia, which are increased in the supine position (Fig. 1).

1.3.5. Non-intubated obese patient with acute lung injury

Our and other COVID-19 protocols [37] encourage patients to prone themselves for variable periods, 2 to 3 times per day. In our experience, persons living with obesity tolerate proning worse than lean ones do, albeit tolerance-dependent repeated periods being better than nothing. Prone positioning of a subject with obesity, even without mechanical ventilator support, might have ergonomic challenges for the patient if unable to prone himself/herself and/or keep the prone position. Anyway, obesity alone should not discourage prone positioning, as long as the patient is able to tolerate the position and is monitored at appropriate intervals.

Prone positioning in patients with ARDS helps improve pulmonary physiology and oxygenation through different mechanisms, regardless of being intubated or not [38]. Prone helps alveolar recruitment in the dorsal lung by increasing the transpulmonary pressure (TPP) gradient, due to the local drop in pleural pressure. Once recruited, alveolar patency can be maintained even with minimal positive end expiratory pressure (PEEP), hence, the benefits may persist even after the patient returns to the supine position. Prone also reduces over distension of the ventral lung due to the drop in the trans pulmonary pressure. These physiological changes make ventilation more homogeneous throughout the lung. On the other hand, the blood flow pattern is relatively unaffected with change from supine to prone position [38]. In the setting of acute hypoxemic injury, in persons living with obesity, ventral to dorsal lung TPP gradients are exaggerated, leading to easier decruitment of alveoli, as compared to nonobese individuals. Thus, homogenization of ventilation and caudal movement of abdominal contents might have even more benefits in patients with obesity. However, for a patient in obvious ARDS, a prone position assay should never delay intubation.

1.3.6. Intubated obese patient with acute lung injury

There are some specific issues regarding ARDS in people living with obesity. Despite a similar pulmonary injury, persons with obesity might be more prone to hypoxemia because of a greater incidence of atelectasis. Alveolar recruitment might be more frequently needed, when compared with a lean patient. In addition, the increased prevalence of gastroesophageal reflux disease and difficult intubation can also increase aspiration incidence during intubation, and the underlying insult of ARDS. On the other hand, transthoracic pressure is higher in patients with obesity than in non-obese patients. Finally, to counteract the onset

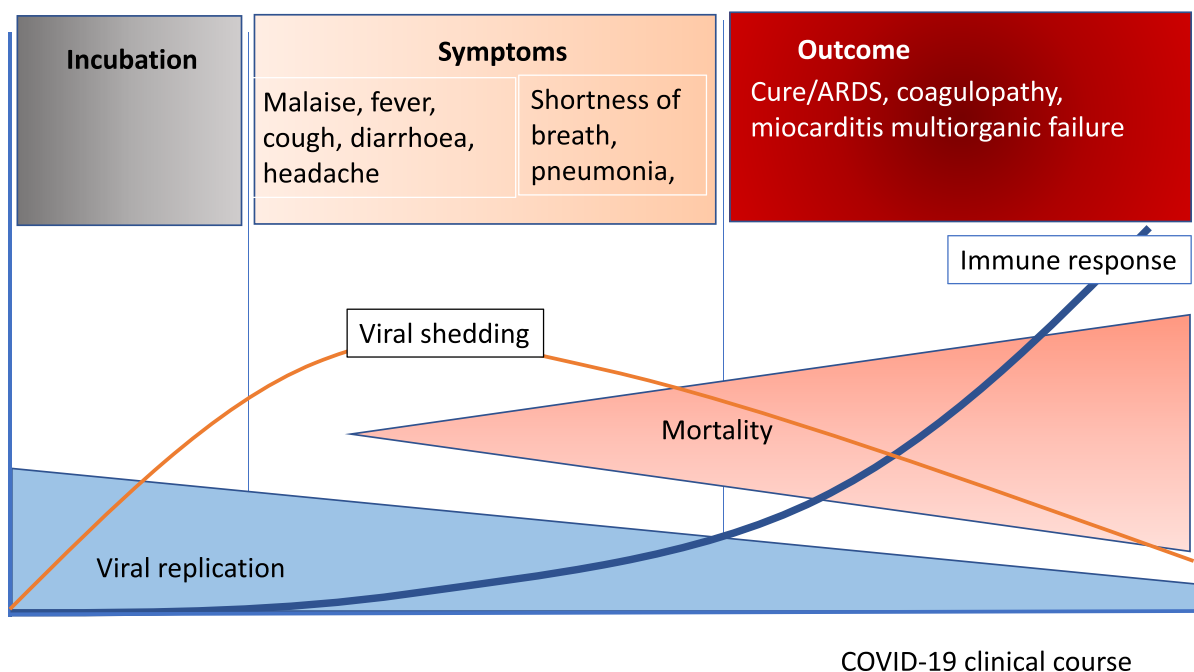


Fig. 2. COVID-19 clinical course. ARDS: acute respiratory distress syndrome.

of atelectasis in the dependent region of the lungs, prone positioning may be advised in patients living with obesity and ARDS by a trained team [39]. A study by Pelosi et al [38] supported that the prone position in persons with obesity improves pulmonary function and increases functional residual capacity, lung compliance, and oxygenation [38]. However, in people with obesity and ARDS, the prone position may worsen visceral hypertension in the abdomen, and lead to subsequent renal and hepatic dysfunction. Thus, it is reasonable to monitor intra-abdominal pressure while the patient is in a prone position and consider using an air mattress or a suspended abdomen if abdominal pressures become excessive [40]. It is also relevant that, as in non-intubated ones, prone positioning of an intubated patient with obesity has ergonomic challenges for the patient and requires numerous staff to perform it safely. Studies have reported increased vomiting and decreased tolerance of high-volume enteral feeding while in a prone position, that worsens the high prevalence of gastroesophageal reflux in these patients.

1.3.7. Clinical repercussion

Clinically, most patients infected with SARS-CoV-2 have mild symptoms including sore throat, anosmia, dysgeusia, diarrhoea and others. Only a small proportion develop severe disease with progressively severe respiratory failure requiring mechanical ventilation and with a high mortality rate (Fig. 2).

The influence of obesity in fatal SARS-CoV-2 infection is clearly documented [5,16,41–43] and reinforces the hypothesis that excess adiposity, at least in part due to chronic low-grade inflammation, may be central to COVID-19 evolution facilitating the cytokine storm. In a study involving more than 3000 COVID-19 patients, with 307 obese subjects younger than 60 years, individuals with a BMI between 30 to 34 kg/m² were 2 times more likely to be admitted to acute care and 1.8 to be admitted to critical care for ARDS compared with those with a BMI below 30 kg/m². Likewise, younger patients with a BMI of 35 kg/m² or higher were 2.2 times more likely to be admitted to acute and 3.6 to be admitted to critical care than patients in the same age category who had a BMI below 30 kg/m² [16]. Consistently, a study evaluating 781,000 young adults aged 18 to 34 years hospitalized with COVID-19 found a substantial rate of adverse outcomes: 21% required intensive care, 10%

required mechanical ventilation, and 2.7% died. This in-hospital mortality rate is lower than that reported for older adults with COVID-19, but approximately doubled that of young adults with acute myocardial infarction. Severe obesity, hypertension, and diabetes were common and associated with greater risks of adverse events. Young adults with more than one of these conditions faced risks comparable with those observed in middle-aged adults without them [17]. Similar results are available in an older population with a mean age of 60 years [5], where 47% of subjects admitted to the ICU had a BMI above 30 kg/m²; whilst 28% of them were above 35 kg/m². The proportion of patients who required invasive mechanical ventilation increased with BMI categories and it was greatest in patients with a BMI above 35 kg/m² [5].

Whether the mechanical derangement due to the fat mass amount or the grade of dysfunctional adiposity is more relevant in terms of risk of death, although both factors are likely to be critical requires further investigation. Remarkably Asian-ethnic subjects with obesity also suffer a higher mortality compared with lean controls [44,45]. The Asian threshold for obesity is usually placed in 27 kg/m². This means that Asiatic ethnicity has a lesser degree of mechanical limitations with similar lipotoxicity. In a Chinese cohort of 383 COVID-19 patients, those who were overweight (BMI 24.0–27.9 kg/m²) exhibited a 1.84-fold OR, while individuals with obesity presented a 3.40-fold OR of developing respiratory failure due to COVID-19, compared with normal-weight patients (BMI 18.5–23.9 kg/m²) in the age, sex, and comorbidities adjusted model [44]. In another Chinese study involving 150 patients with COVID-19, obesity was associated with a threefold increased risk of disease severity in the logistic regression analyses and in the multivariate adjusted model. A nearly linear relationship between higher BMI and severe illness was shown with each 1-unit increase in BMI associated with a 12% increase in the risk of severe COVID-19 [45].

In addition to obesity itself, its major complications, namely diabetes [6,9–11,46] and hypertension [5,6,9,46], are also closely associated to a worse prognosis in COVID-19. Pre-existing diabetes is associated with an approximate twofold higher risk of having severe/critical COVID-19 illness and circa threefold increased risk of in-hospital mortality [47, 48]. Furthermore, the association between obesity, diabetes and severe COVID-19 is bidirectional [49]. In a population-based cohort study of people with previously diagnosed type 1 or type 2 diabetes, deaths rose

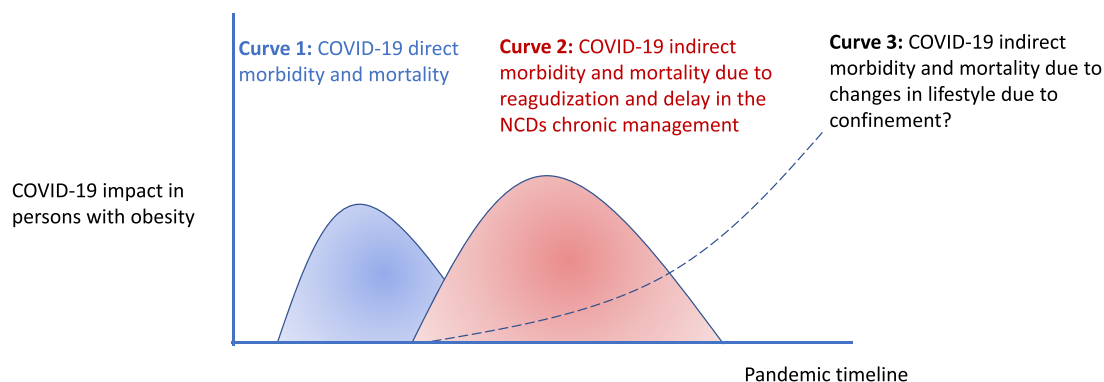


Fig. 3. Putative COVID-19 impact on health of people living with obesity.

sharply during the initial COVID-19 pandemic. Increased COVID-19-related mortality was associated not only with cardiovascular and renal complications of diabetes but, independently, also with glycaemic control and BMI [49]. Hypertension also entails a smaller but significant excess of risk for severe COVID-19 [5,6,9,46].

1.3.8. Bariatric surgery and COVID-19

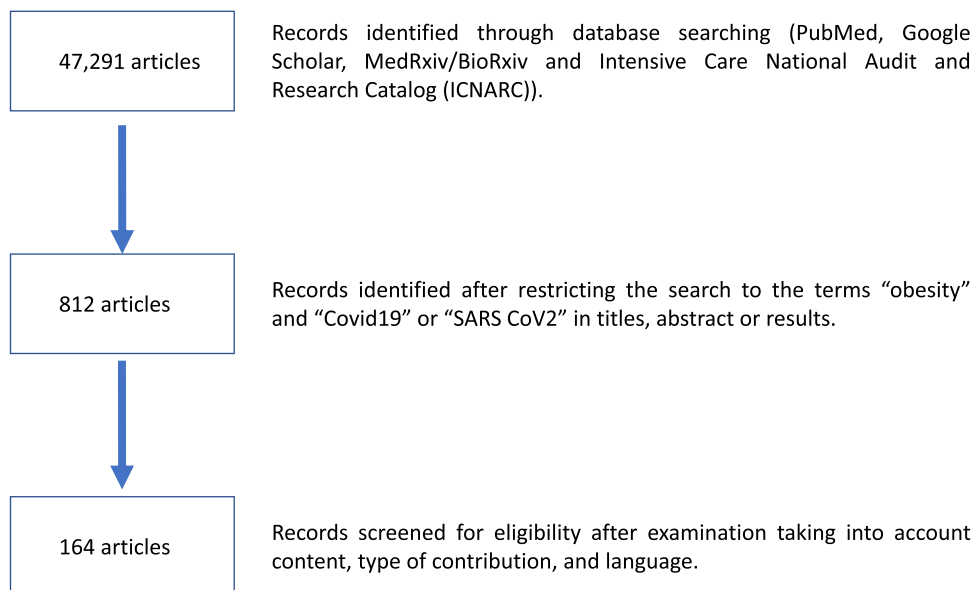
There are only a few reports on whether bariatric surgery modifies the prognosis of people living with obesity in the current COVID-19 pandemic or not [43,50–52]. In a survey-based study of 738 patients that had undergone bariatric surgery, the authors assessed the prevalence of symptom-based likelihood of COVID-19 and its risk factors, based on a retrospective comparison of characteristics at baseline, and one-year post surgery [43]. It is remarkable that pre-surgery, no differences between patients who developed COVID-19 and those who did not could be found. Symptoms suggesting COVID-19 occurred in 62 (8.4%) patients among whom 4 (6.4%) suffered a severe form requiring hospitalization and one (1.6%) died. At the time of the survey, a global estimation was performed in the greater Paris region (Ile de France), area of residence of the majority of the patients, and reported an estimated prevalence of COVID-19 cases of 9.9% [53]. The COVID-19 likely group had a higher proportion of persistent type 2 diabetes in the last follow-up and a lower BMI with higher percent weight loss [43]. Consistent data have been reported among patients operated in Italy [51]. A case-control study has also shown that post-bariatric patients

with subsequent weight loss and improvement of metabolic abnormalities developed lower rates of hospital and ICU admission, compared to patients living with severe obesity [52].

These observations add additional arguments on the benefit of bariatric surgery in the management of obesity and reinforces, as aforementioned, the relevance of diabetes itself in association with COVID-19 severity. Additionally, specifically during the COVID-19 pandemic, many candidates for bariatric or metabolic surgery are at highest risk of morbidity and mortality. For these patients, access to surgical treatment should be prioritised on the basis of the severity of the disease, rather than primarily on BMI, to mitigate harm from delaying surgery [54]. Disease-oriented, medically meaningful strategies to triage patients seeking metabolic surgery after the COVID-19 crisis should help prioritise patients in more urgent need, both now and long into the future [54].

1.3.9. Summary and perspectives

In summary, COVID-19 is causing massive health problems and suffering around the world in which obesity might take the worst part in the two sides of the coin, as the European Association for the Study of Obesity recently stated [55]. On one side, obesity is a disease that propels COVID-19 patients into a downhill course. A low grade chronic inflammatory state in obesity can enable the cytokine storm in COVID-19 patients. The globally increased amount of ACE 2 receptors in obesity, with a more aggressive distribution and changes in breathing



Records identified through database searching (PubMed, Google Scholar, MedRxiv/BioRxiv and Intensive Care National Audit and Research Catalog (ICNARC)).

Records identified after restricting the search to the terms “obesity” and “Covid19” or “SARS CoV2” in titles, abstract or results.

Records screened for eligibility after examination taking into account content, type of contribution, and language.

Fig. 4. Flow diagram of the search strategy.

physiology may be another reason why obese individuals are prone to severe COVID-19. On the other side, the health emergency caused by the COVID-19 outbreak diverts attention (and funding) from the prevention and care of NCDs to communicable diseases. Home-confinement has forced a decrease in physical activity [56] that is at high risk to entail long lasting changes in lifestyle of patients with obesity, for whom physical activity is a mainstay of their treatment but also a daily challenge (Fig. 3). Paying special attention to promote the physical reactivation and healthy nutrition of the patients, particularly for those living with obesity, is a major responsibility for attending physicians.

1.3.10. Review criteria

A search for original articles and reviews published focusing on the association between COVID-19 and obesity was performed in PubMed and MEDLINE using the following search terms (or combination of terms): “COVID-19,” “obesity,” “adiposity,” “epicardial fat,” “visceral fat,” “dysfunctional fat,” “comorbidity or comorbidities,” “outcome,” “mortality,” “adipokines,” “ARDS,” “prone ventilation,” “diabetes,” “hypertension.” Only English-language, full-text articles were included. Additional articles that were identified from the bibliographies of the retrieved articles were also used. Fig. 4 shows the Flow-diagram of the search strategy.

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CRedit authorship contribution statement

MF Landecho: Conceptualization, Writing - original draft. **M Marin-Oto:** Resources, Visualization. **B Recalde-Zamacona:** Investigation. **I Bilbao:** Writing - review & editing. **Gema Frühbeck:** Conceptualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

None.

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