Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary: Obesity: The "Achilles heel" for COVID-19?

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Coronavirus disease-2019 (COVID-19) is the infectious disease caused by the recently discovered coronavirus SARS-CoV-2. The first case of COVID-19 was reported to the World Health Organization (WHO) by Chinese authorities on December 31st 2019 as a result of a patient suffering pneumonia in Wuhan City, Hubei Province, China. Following a rapid spread in China, new outbreaks occurred in northern Italy and in several European countries. On March 12th 2020 WHO announced COVID-19 outbreak a pandemic.

COVID-19 results in a respiratory infection characterized by mild to severe symptoms such as dry cough, fever and difficulty breathing which can appear up to about 14 days after exposure to the virus. According to National Center for Immunization and Respiratory Diseases (NCIRD) high-risk categories for severe illness from COVID-19 are people aged 65 years and older, who live in a nursing home or long-term care facility, immunocompromised, or people with underlying medical conditions, particularly if not well controlled, including chronic lung diseases, serious heart conditions, type 1 or type 2 diabetes, liver diseases, chronic kidney disease undergoing dialysis and severe obesity (body mass index [BMI] of 40 or higher).

Until now, there are no data in the literature reporting that subjects with obesity have a higher risk of getting COVID-19; however, since obesity is known to increase the risk of developing severe forms of respiratory failure, it could be hypothesized that subjects with obesity could be at risk of serious illness if infected.

In particular, according to the Intensive Care National Audit & Research Centre (ICNARC) report on COVID-19 in critical care of United Kingdom (March 27th 2020), it was observed that 72.1% of 775 patients with confirmed COVID-19 were overweight or obese and that among patients with BMI > 30 who had undergone intensive care, 60.9% of them died [1].

In addition, according to Italian data published on April 6th 2020 by the Istituto Superiore di Sanità (ISS), an overall prevalence of obesity of 10.0% was found among 1290 patients died for whom there was the availability of medical records [2].

In this retrospective cohort study in a single French center evaluating 124 consecutive patients admitted in intensive care for SARS-CoV-2, it has been observed that obesity (BMI >30 kg/m^2) and severe obesity (BMI >35 kg/m^2) were present in 47.6% and 28.2% of cases, respectively, that patients who required invasive mechanical ventilation (IMV) increased with BMI categories ($p < 0.01$) and it was greatest in patients with BMI >35 kg/m (85.7%) [3].

As well known, obesity represents a state of low grade chronic inflammation that can contribute to the onset of metabolic diseases (dyslipidemia, insulin resistance and type 2 diabetes mellitus [T2DM]) and can modify innate and adaptive immune responses, making the immune system more vulnerable to infections and less responsive to vaccinations, antivirals and antimicrobial drugs [4].

Recent findings have highlighted the substantial impact that obesity have on immunity and pathogen defense, including the disruption of lymphoid tissue integrity; alterations in leukocyte development, phenotypes and activity; and the coordination of innate and adaptive immune responses. In particular, obesity has been shown to impair memory CD8+ T cell responses to influenza virus infection, resulting in increased mortality, viral titers in lung, and worsened lung pathology. These adverse effects were associated with an obesity-induced failure to maintain influenza-specific CD8+ memory T cells, which are essential in ensuring vaccine efficacy [5].

Abbreviations: COVID-19, coronavirus disease-2019; WHO, World Health Organization; NCIRD, National Center for Immunization and Respiratory Diseases; BMI, body mass index; ICNARC, Intensive Care National Audit & Research Centre; ISS, Istituto Superiore di Sanità; IMV, invasive mechanical ventilation; T2DM, type 2 diabetes mellitus; TNF-α, tumor necrosis factor α; IL, Interleukin; IFN, Interferon; CRS, cytokine-release syndrome; ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme; AHA, American Heart Association; HFSA, Heart Failure Society of America; ACC, American College of Cardiology; MAFLD, metabolic associated fatty liver disease.

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Low-grade inflammation is determined by a condition of adipocyte hypoxia and dysfunction, that results in an exuberant secretion of pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin (IL) 1β and IL-6 and the recruitment of immune cells macrophage, T-cell and B-cell, creating an auto-regenerating inflammation loop [6]. Indeed increased circulating levels of pro-inflammatory cytokines, such as TNF-α, IL-6, or C-reactive protein, have been reported in overweight and obese adults [7].

Having so far limited scientific evidence regarding the pathophysiological mechanisms linking obesity and COVID-19, some interesting information can be extrapolated from studies conducted on subjects with H1N1 infection: it has been shown that subjects with obesity compared with normal-weight individuals evince in H1N1 infection more intense IL-8 release, which is a chemokine of innate immunity involved in chemotaxis, being a major chemokine for neutrophil activation and migration into tissue, a mechanism involved in response to infection [8].

In parallel, one of the most important mechanisms underlying the severity of lung disease in COVID-19 is represented by the "*cytokine storm*" which can lead to acute respiratory distress syndrome or even multiple organ failure. It represents a phenomenon of immune hyper activation very similar to Cytokine-release syndrome (CRS) typically described in the setting of T cell-engaging immunotherapy and characterized by increased levels of IL-6, interferon (IFN) γ and other cytokines, causing consequences and symptoms related to immune activation, ranging from general malaise, myalgia and fever to severe organ toxicity, respiratory failure and death [9]. In support of the importance of counteracting the inflammatory response to avoid the progression of COVID-19, the use of tocilizumab in subjects with severe respiratory impairment is being tested with encouraging results. Tocilizumab is a recombinant humanized monoclonal antibody, which binds the human IL-6 receptor, inhibiting its signal transduction, currently used for rheumatoid arthritis, but its efficacy has also been demonstrated against other forms of lung immune-related pneumopathy [10]. Whereas, considering that subjects with obesity have a proinflammatory milieu, it is expected that COVID-19 could further exacerbate inflammation exposing them to higher levels of circulating inflammatory molecules compared to lean human subjects. This could explain the increased risk of severe complications of COVID-19 for subjects with obesity.

Obesity-related comorbidities could also represent an additional risk factor for complications of COVID-19 in obesity. In fact T2DM, hypertension and cardiovascular diseases were frequently detected in subjects died from COVID-19 in Italy, suggesting that they could increase the risk of mortality for COVID-19. Regarding T2DM, four risk factors for diabetic patients with COVID-19, compared to COVID patients without diabetes were proposed, which can increase the risk of poor outcomes: susceptibility to hyperglycemia from corticosteroid therapy, inadequate glycemic control, lack of contact with healthcare professionals and inappropriate discontinuation of an angiotensin receptor blocker (ARB) or an angiotensin converting enzyme (ACE) inhibitor, which individually or synergistically could justify the worst prognosis in the patients with T2DM and COVID-19 [11].

In fact, it has also been questioned that ACE inhibitors or ARBs, usually used as treatment for hypertension, could increase the risk of SARS-CoV-2 infection and COVID-19 severity, since they increase the expression of ACE 2 whose receptor is used by the virus SARS-CoV-2 to enter into the host cell [12]. However, currently there are no sufficient data to support this hypothesis and therefore The American Heart Association (AHA), the Heart Failure Society of America (HFSA), and the American College of Cardiology (ACC) released a statement recommending continuation of these drugs for patients already receiving them for heart failure, hypertension, or ischemic heart disease. In addition, subjects with obesity often suffer from chronic obstructive bronchopathy, asthma, hypoventilation syndrome, obstructive sleep apnea and other mechanical anomalies due to excess of thoracic and abdominal fat mass that could be a "*breeding ground*" for respiratory complications [13].

Another clinical condition frequently encountered in subjects with obesity is metabolic associated fatty liver disease (MAFLD) defined by the evidence of hepatic steatosis, in addition to one of the following three criteria: overweight/obesity, presence of T2DM or evidence of metabolic dysregulation [14]. In MAFLD patients, especially those with obesity, IL-6 levels independently predicted increasing liver inflammation, which might play an additive/synergistic role in promoting greater severity of COVID-19 [15]. In this regard, in a study conducted in three Chinese hospitals, 66 patients with MAFLD evaluated by computed tomography and laboratory-confirmed COVID-19 were analyzed [16].It has been observed that: MALFD patients with obesity had more severe COVID-19 disease than non-obese ones (37.5% vs.9.5%, $p = 0.021$), subjects with severe COVID-19 were more obese compared to those with non-severe disease (89.5% vs.59.6%, $p = 0.021$), while, the presence of obesity in MAFLD patients was associated with a ~6-fold increased risk of severe COVID-19 illness, and this association remained significant even after adjusting for age, sex, smoking, diabetes, hypertension and dyslipidemia, suggesting that, in the context of MAFLD, obesity represents an important risk factor for COVID-19 severity.

Obesity-driven chronic inflammation and impaired fibrinolysis contribute to increase the risk of developing thrombosis, which currently seems to be one of the mechanisms potentially involved in worsening lung damage and in death, this justifies the use of heparin for both prophylactic and therapeutic purposes in different protocols used in patients with COVID-19 [17].

In fact, using pulmonary and cutaneous biopsy and autopsy samples from individuals with severe COVID-19 it has been documented that some SARS-CoV-2-infected patients who became critically ill suffered a generalized thrombotic microvascular injury [18].

Another common finding in obesity is vitamin D deficiency that has been reported to increase the risk of systemic infections and to impair immune response [19]. Conversely vitamin D supplementation can prevent respiratory infections through several immunoregulatory functions including the decreased production of pro-inflammatory cytokines by the innate immune system, therefore reducing the risk of a cytokine storm leading to pneumonia [20]. Interestingly, epidemiological data report that Italy is one of the Countries with the highest prevalence of hypovitaminosis D in Europe, with a very high prevalence in subjects with obesity and elderly women with diabetes [21,22]. Therefore, based on the previous considerations it could be hypothesized that vitamin D deficiency could potentially take part to the link between obesity and increased susceptibility to complications and mortality due to COVID-19 [23].

Gut dysbiosis is another important factor potentially involved in the increased risk of developing severe forms of COVID-19 in obesity. As well-known obesity per se is associated to a blunted composition of gut microbiome that in turn is paramount for the regulation of the host's immune system and for the protection from infection. Moreover, gut microbiome also has a role in attenuating the damage consequent to infection. In fact some protocols for the treatment of COVID-19 include the use of probiotics to maintain the balance of intestinal microecology and therefore indirectly strengthen immune system [24,25].

Finally, subjects with obesity have also mechanical issues related to excessive weight that make difficult an early diagnosis with pulmonary ultrasound and thus leading to a diagnosis of COVID-19 in the advanced stage which is most associated to highest mortality. The lack of medical or intensive care units not designed to accommodate patients with severe obesity, the difficulties of intubation and insertion of catheters related to excess of weight may lead to a slowdown in therapeutic steps, worsening prognosis in patients with obesity and COVID-19.

Furthermore, in no infected subjects with obesity currently subjected to strict measures to contain the pandemic, close monitoring including the use of telemedicine is required, because of less physical activities, unhealthy food consumption (processed and long-life foods, caloric foods), reduction in healthier fresh options (fruits and

vegetables), stress anxiety and sleep deprivation under the pressure of social distancing [26,27].

Taken all together, subjects with obesity are high-risk and complicated group of patients to treat for COVID19, with an increased requirement of hospitalization. Subjects with obesity need intensive attention to reduce the risk of fatalities. Thus, it is paramount that these subjects avoid infections following the general prevention advices given by the authorities in order to reduce the spread of the virus.

This manuscript has some limitations related to the lack of scientific evidence produced so far due to the recent onset and rapid spread of the pandemic, however it represents an accessible summary of the epidemiological evidence and possible pathophysiological mechanisms regarding obesity and COVID-19. Retrospective studies on a larger sample of the population will be needed, as well as autopsy studies and especially randomized clinical trials with the aim of understanding which individuals are most at risk of becoming infected or developing complications, what are the causal mechanisms on which it is possible to intervene with prophylactic and therapeutic measures and what the long-term consequences will be on the health of patients with obesity.

Contributions of authors

Giovanna Muscogiuri: Conceptualization, data curation, writing - review & editing. **Gabriella Pugliese**: Conceptualization, data curation. **Luigi Barrea**: Conceptualization. **Silvia Savastano**: Writing - review & editing. **Annamaria Colao**: Writing - review & editing.

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Declaration of competing interest

All authors declare no conflict of interests.

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