



Obesity and COVID-19: What are the Consequences?



Authors

Charlotte Steenblock¹ , Mohamed Hassanein², Emran G. Khan³, Mohamad Yaman⁴, Margrit Kamel⁵, Mahmoud Barbir⁶, Dietrich E. Lorke⁷, Dean Everett⁸, Saqipi Bejtullah⁹, Tobias Lohmann¹⁰, Uwe Lindner¹¹, Ermal Tahirukaj¹, Feras Jassim Jirjees¹², Sameh S.M. Soliman¹², Friederike Quitter¹³ , Stefan R. Bornstein^{1,14}

Affiliations

- 1 Department of Medicine III, Universitätsklinikum Carl Gustav Carus, Dresden, Germany
- 2 Department of Diabetes and Endocrinology, Dubai Hospital, Dubai, United Arab Emirates
- 3 Endocrinology and Diabetology, King's College Hospital London, Dubai, United Arab Emirates
- 4 Building 6, Nesmah Technology, Dubai, United Arab Emirates
- 5 Center for Regenerative Therapies Dresden, Technische Universität Dresden, Dresden, Germany
- 6 Department of Cardiology, Harefield Hospital, Harefield, United Kingdom of Great Britain and Northern Ireland
- 7 Department of Anatomy and Cellular Biology, Khalifa University, Abu Dhabi, United Arab Emirates
- 8 Department of Pathology and Infectious Diseases, Khalifa University, Abu Dhabi, United Arab Emirates
- 9 Research Unit, College Heimerer, Prishtina, Republic of Kosovo
- 10 MK5, Städtisches Klinikum Dresden, Dresden, Germany
- 11 Internal Medicine II, Klinikum Chemnitz, Chemnitz, Germany
- 12 College of Pharmacy, University of Sharjah, Sharjah, United Arab Emirates
- 13 Klinik für Kinder- und Jugendmedizin, Universitätsklinikum Carl Gustav Carus, Dresden, Germany
- 14 School of Cardiovascular and Metabolic Medicine and Sciences, Faculty of Life Sciences & Medicine, King's College London, London, UK

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Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence

Dr. Charlotte Steenblock
University Hospital Carl Gustav Carus, Technische Universität Dresden, Department of Medicine III
Fetscherstraße 74
01307 Dresden
Germany
Tel.: +493514586130, Fax: +493514586398
Charlotte.Steenblock@uniklinikum-dresden.de

ABSTRACT

Obesity is an increasing health problem all over the world. In combination with the current COVID-19 pandemic, this has turned into a massive challenge as individuals with overweight and obesity at all ages show a significant increase in their risk of getting severe COVID-19. Around 20% of all patients that were hospitalized for COVID-19 suffered from obesity alone, whereas obesity in combination with other metabolic comorbidities, such as type 2 diabetes and hypertension, account for up to 60% of all hospitalizations in relation to COVID-19. Therefore, it is of immense importance to put the spotlight on the high incidence of obesity present already in childhood both by changing the individual minds and by encouraging politicians and the whole society to commence preventive interventions for achieving a better nutrition for all social classes all over the world. In the current review, we aim to explain the different pathways and mechanisms that are responsible for the increased risk of severe COVID-19 in people with overweight and obesity. Furthermore, we discuss how the pandemic has led to weight gains in many people during lockdown. At the end, we discuss the importance of preventing such an interface between a non-communicable disease like obesity and a communicable disease like COVID-19 in the future.

Introduction

Obesity increases the risk of severe COVID-19 by giving rise to a worse clinical outcome and increased mortality, when compared to the general population [1]. Obesity alone is responsible for 20% of COVID-19 hospitalizations, whereas obesity in combination with type 2 diabetes and hypertension accounts for up to 60% of all COVID-19 hospitalizations [2]. In addition, infected people with obesity (particularly those under 60 years of age) are more likely to require acute care, admission to the intensive care unit, intubation, and mechanical ventilation [3]. Even young patients are at higher risk for a nonfavorable COVID-19 prognosis if they suffer from metabolic dysfunctions [4, 5]. Children usually develop an asymptomatic to moderate infection causing few hospitalizations; but a recent meta-analysis indicates that even childhood obesity is likely to increase the risk of severe COVID-19 [6]. Albeit severe courses of COVID-19 in children are rare, a novel pediatric hyper-inflammatory condition termed pediatric inflammatory multisystem syndrome, temporally associated with SARS-CoV-2 (PIMS-TS) or multisystem inflammatory syndrome (in children) (MIS(-C)), causes a severe to fatal disease. Even though underlying factors are unclear, it turns out that childhood obesity is a significant comorbidity [7]. This is a worldwide problem since, according to WHO reports, around 40% of the world population was estimated to be overweight or obese in 2016, and the numbers are still increasing, thus obesity has reached pandemic levels [8] (► **Table 1**).

Emerging data suggest that several mechanisms are responsible for this increased susceptibility of people with obesity for severe COVID-19 including, amongst others, an impaired immune system and changes in SARS-CoV-2 entry receptors in obese individuals [9–12]. In the current review, we discuss these mechanisms in order to understand why patients with obesity have a higher risk of developing severe COVID-19 symptoms not only in the acute phase of the disease but also in relation to long-COVID, vaccine breakthrough infections and re-infections. Furthermore, we discuss the effects of lockdown on obesity, and we comment on possibilities for avoiding this interface between metabolic and infectious diseases in potential future pandemics.

Adipose tissue

The adipose tissue is the largest endocrine organ in humans and, in addition to adipocytes, it consists of pre-adipocytes, endothelial cells, fibroblasts, leukocytes, and bone-marrow-derived macrophages [13]. Adipose tissue is classified into two main types, white adipose tissue and brown adipose tissue. White adipose tissue is the more predominant form in the human body, where it plays a major role in energy storage. The main function of brown adipose tissue is thermogenesis [14–16]. It is becoming increasingly clear that adipose depots serve distinct functions in males and females and have specific physiological roles. However, the mechanisms that regulate the size and function of specific adipose tissues in men and women remain poorly understood [17].

In addition to energy storage via triacylglycerols stored in adipocytes, adipose tissue secretes “adipocytokines” or “adipokines”, including, for example, adiponectin, leptin, resistin, and visfatin [13]. Other important factors produced include the cytokines tumor necrosis factor (TNF), interleukin-6 (IL-6), interleukin-1 (IL-1),

CC-chemokine ligand 2 (CCL2), plasminogen activator inhibitor type I (PAI-I), and a number of complement factors [18, 19]. Most of these factors are known as pro-inflammatory mediators that induce immune cell infiltration (e. g., macrophages) and play a major role in infectious diseases.

The major adipokines in adipose tissue are leptin and adiponectin, where leptin is pro-inflammatory, and adiponectin is anti-inflammatory. In obesity, leptin is increased and adiponectin is decreased compared to normal weight individuals [20]. Oppositely, circulating adiponectin concentrations increase during caloric restriction [21].

Leptin is almost exclusively expressed in differentiated adipocytes of the white adipose tissue with subcutaneous fat showing a higher expression than visceral adipose tissue [22, 23]. Leptin released from adipocytes acts on neurons to reduce appetite and to increase energy expenditure [20]. Leptin is closely linked to the immune system where it stimulates the proliferation and activation of immune cells and cytokine production [20].

Disease-specific subpopulations of adipose-resident immune cells can be found in adipose tissue. These immune cells can be further separated into populations specific for either visceral or subcutaneous adipose tissue [24]. An example of these immune cells are the macrophages, which are heterogenous and can generally be defined in two separate polarization states, M1 and M2 [25, 26]. M1 macrophages are induced by pro-inflammatory mediators, such as lipopolysaccharide (LPS) and interferon- γ (IFN- γ), produce pro-inflammatory cytokines (TNF- α , IL-6, IL-12) and generate reactive oxygen species, such as nitric oxide (NO) via activation of iNOS (*Nos2*) [27]. M2 macrophages are induced, by among others, IL-4 and IL-13, and they produce high levels of the anti-inflammatory cytokines IL-10 and IL-1 α . Additionally, iNOS activity is blocked [27]. Overall, M2 macrophages are believed to participate in the inhibition of inflammatory responses and in the promotion of tissue repair and angiogenesis [25]. Both in mice and humans, it has been shown that distinct macrophage populations with unique characteristics direct inflammatory versus physiological changes in adipose tissue [28].

Infection with SARS-CoV-2

Entry of SARS-CoV-2 into cells depends on binding of the viral spike glycoproteins to extracellular domains of cellular angiotensin-converting enzyme 2 (ACE2). ACE2 exists in two forms, a membrane-spanning cellular and an unbound soluble form [29]. Membrane-bound ACE2 (mACE2) constitutes the majority of ACE2; it contains a transmembrane domain anchoring the cleavable N-terminal domain. A membrane-bound protease (secretase) generates soluble ACE2 (sACE2) by enzymatic cleavage of mACE2. sACE2 appears in the circulation in very low concentrations. Both mACE2 and sACE2 are capable of binding the spike protein on the surface of SARS-CoV-2. After binding to mACE2, the spike proteins are proteolytically activated by host cell proteases [29–31], resulting in fusion of the viral envelope with the plasma membrane or the endosome membrane of the host and viral entry into the cell.

ACE2 is part of the renin-angiotensin-aldosterone system (RAAS), where it mainly controls the generation of the vasodilating angiotensin 1–7 from angiotensin II. ACE2 also cleaves angiotensin I to angiotensin 1–9, which can be further converted to

► **Table 1** Key facts about obesity [7].

- Worldwide obesity has nearly tripled from 1975–2016.
- In 2016, 39% of adults aged 18 years and over (39% of men and 40% of women) were overweight.
- Overall, about 13% of the world's adult population (11% of men and 15% of women) were obese in 2016.
- Over 340 million children and adolescents aged 5–19 were overweight or obese in 2016.
- The prevalence of overweight and obesity among children and adolescents aged 5–19 has risen dramatically from just 4% in 1975 to just over 18% in 2016.
- 39 million children under the age of 5 were overweight or obese in 2020.
- Overweight and obesity are linked to more deaths worldwide than underweight.

angiotensin 1–7 by ACE [29]. ACE2, Ang-(1–7), and its mitochondrial assembly (Mas) receptor constitute the vasoprotective arm of the RAAS leading to anti-inflammatory and anti-fibrotic responses [29, 32–34].

Diet and obesity have been shown to affect the expression of ACE2 in adipose tissue [35]. Recently, it was demonstrated that a decrease in sACE2 during weight loss was associated with improvements in metabolic health [36]. Another factor, neuropilin 1 (NRP-1), known to facilitate SARS-CoV-2 cell entry is highly abundant in subcutaneous adipose tissue, and both NRP-1 and ACE2 levels are decreased after weight loss [37]. However, it is still not clear whether a high or a low expression is beneficial in relation to health (reviewed in [32]). Similarly, it is debated whether high levels of ACE2 in adipose tissue in relation to SARS-CoV-2 is an advantage or not. Thus, it seems that not only the abundance but also the functionality of the enzyme may be of importance.

Viruses including coronaviruses are primarily dependent on the host metabolism in several stages of their life cycle. For example, an association of dyslipidemia with the pathological development of COVID-19 was reported [38]. This raises the possibility that exploitation of the host lipid metabolism, by using potential inhibitors, can exhibit therapeutic benefits against COVID-19 [39]. Additionally, specific lipid supplementation can represent another strategy to error-prone the formation of viral particles. Furthermore, switching the lipid metabolism through the implementation of ketogenic diet might be an approach to limit the effects of viral infection [40]. An experimental study associated with computational analysis identified the potential inhibitory effect of flavonoids against SARS-CoV-2 as they bind to essential viral targets required in virus entry and/or replication [41]. Flavonoids also showed excellent immunomodulatory and anti-inflammatory activities including the inhibition of various inflammatory cytokines. Further, flavonoids showed a significant ability to reduce the exacerbation of COVID-19 in the case of obesity via promoting lipid metabolism [41].

Mechanisms responsible for an increased risk of severe COVID-19 in obesity

Obesity, in particular visceral obesity, is a risk factor for the development of metabolic syndrome, cardiovascular disease [42, 43],

blood hypercoagulability [44], and vitamin D deficiency [45], which are furthermore all risk factors for COVID-19 severity [46].

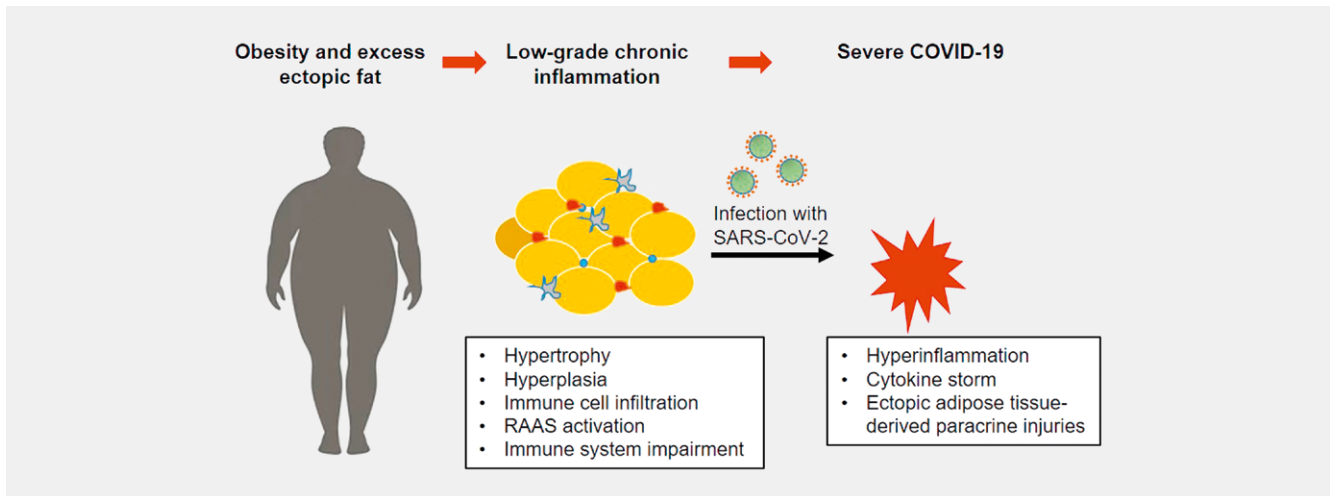
A number of mechanisms are responsible for the increased risk of severe COVID-19 and mortality in people with adiposity [47–49]. One explanation may be the physical stress on ventilation by obstructing diaphragm excursion. Furthermore, obesity is associated with an increased risk of pulmonary fibrosis, chronic obstructive pulmonary disorder, and reduced respiratory function [50].

Another reason is an impairment of the immune system in people with adiposity. Obesity is characterized by hyperplasia and hypertrophy of adipocytes and accumulation of macrophages in the adipose tissue, resulting in the development of crown-like structures of necrotic adipocytes encircled by macrophages [42] (► **Fig. 1**). In obesity, a switch from an anti-inflammatory M2 type to the pro-inflammatory M1 form of macrophages is observed [14]. Adiponectin can also affect macrophages by stimulating the production of anti-inflammatory cytokines [51]. Similarly, adiponectin-deficient mice display an increased expression of pro-inflammatory M1 type markers and decreased anti-inflammatory M2 type markers [52]. Thereby, obesity may lead to a baseline state of chronic inflammation. In adipose tissue of people with obesity the expression of pro-inflammatory cytokines, such as TNF- α , IL-6 and IL-1 β , is upregulated.

In patients who died from COVID-19, a higher prevalence of CD68-positive macrophages in visceral adipose tissue was observed compared to control patients without COVID-19. As expected, these were accompanied by crown-like structures, signs of adipocyte stress and death [46].

Previously, obesity was shown to increase the duration of type A influenza virus shedding in adults, whereas this was not the case for type B influenza [53]. Adipocytes and other adipose tissue-resident cells, such as adipo-stromal cells, and macrophages have also been shown to be targets for adenovirus subtype 36, but not subtype 2 [54]. Therefore, it has been suggested that adipose tissue may act as a reservoir for the SARS-CoV-2 virus, whereby it would facilitate the spread of the virus and stimulate the immune response [54]. Indeed, a recent study showed that SARS-CoV-2 RNA could be found in adipose tissue of both men and women that had died due to COVID-19. In male individuals who were obese with a body mass index (BMI) > 30, SARS-CoV-2 could also be detected in the liver. In women, there was no correlation between BMI and viral load in the adipose tissue [55]. In another study, the presence of SARS-CoV-2 in adipose tissue was confirmed in more than 60% of COVID-19 autopsy cases. In 25 out of the 29 COVID-19 cases in this study, comorbidities were present with 34% patients being overweight or with obesity [56].

It was demonstrated that SARS-CoV-2 is able to infect mature differentiated and lipid-laden adipocytes but not preadipocytes or immature precursors [55]. Whether this is due to different ACE2 concentrations, or another mechanism is not known yet. An alteration in carbon metabolism with increased circulating levels of glucose and free fatty acids were observed in COVID-19 patients [57]. High levels of such free fatty acids may increase the levels of adipokines, myokines and cytokines, which further promote inflammatory processes. Furthermore, cytokines are able to damage the vascular endothelium and activate the RAAS, which may lead to increased blood pressure, atherosclerosis, and thrombosis [58].



► **Fig. 1** Chronic inflammation in adipose tissue of obese individuals: There are several reasons why obesity can lead to a severe course of COVID-19. One possible cause is the chronic inflammatory reaction in the adipose tissue. In adipose tissue with hypertrophic adipocytes, there is a mass production of pro-inflammatory cytokines, such as IL-6, IL-1 β , and TNF- α . In addition, more and more immune cells invade the adipose tissue. These cells produce inflammatory substances themselves. Being overweight thereby leads to a low-grade chronic inflammation. If an infection with SARS-CoV-2 then occurs, there is a high risk of an overreaction of the immune system leading to hyperinflammation and cytokine storm. This represents a potentially life-threatening derailment of the immune system, which can further lead to paracrine injuries.

This chronic inflammation and imbalance between pro-inflammatory and anti-inflammatory factors in obesity is a risk factor for additional pathogenic infections, such as SARS-CoV-2, which may lead to an abnormal immune response reaching pathogenic levels [1].

The upregulation of TNF- α , IL-6 and IL-1 β in people with obesity inhibits insulin signaling [59], and consecutively this cytokine upregulation leads to an increase in leptin and plasminogen activator inhibitor-1 and a reduced release of adiponectin [60]. An inverse correlation to glucose intolerance and type 2 diabetes has been observed [61]. Adiponectin modulates a number of metabolic processes, including glucose regulation and fatty acid oxidation [62]. Low adiponectin blood levels thereby cause an inappropriate increase in the immune response in COVID-19.

Overall, these impairments of the immune system may contribute to a chronic state of low-grade inflammation in the ectopic visceral adipose tissue in people with obesity (► **Fig. 1**). In combination with an infection like SARS-CoV-2, this may lead to an overreaction of the immune system, a so-called hyperinflammation resulting in a cytokine storm that can lead to paracrine injuries in other organs with progression to acute respiratory syndrome [63].

Post-COVID and long-term consequences in relation to obesity

During the COVID-19 pandemic, social isolation and (semi)-lockdown were imposed upon populations in the interest of infection control. All over the world, obesity increased during the pandemic due to dramatic changes in the daily routines, such as a reduction in physical activity and negative changes in the eating habits [64]. In the US, the COVID-19 pandemic promoted weight gains in adults with those already being obese being more susceptible [65]. However, in particular children with obesity have been shown to be at a higher risk of negative lifestyle changes and weight gain during lock-

down [66]. As such, several studies have shown that not just adults gain weight, but that also obesity in adolescents and children has increased due to COVID-19 lockdowns [67]. For example, in China, a study performed on 12 889 Chinese college students aged 17–27 years showed that their weight significantly increased during a 4-month lockdown in early 2020. This weight gain was associated with increased sedentary time and an increase in COVID-19-related stress and depression [68]. Another study from South Korea showed that in 226 children between 4 and 14 years old, school closure was significantly associated with an increased BMI [69].

Different studies have shown that an unhealthy, high-fat diet might increase the susceptibility to various infectious diseases [70]. For example, experimental animals on a high-fat diet had exhibited a two-fold increase in mortality, an enhancement in respiratory lesions and an increased production of cytokines when infected with H1N1 influenza [71]. The individual nutrition pattern is also known to be able to change the gut microbiota, which might cause metabolic changes that might affect the susceptibility for getting infected with SARS-CoV-2 in a positive or negative direction [70].

Numerous factors contribute to childhood and adolescent obesity, including amongst others gender, biology, geographical and socio-economical aspects [72–74]. Non-communicable diseases, such as overweight and obesity are largely preventable. At the individual level, people can choose to limit energy intake by eating healthier food consisting of, for example, fruit, vegetables and whole grains. Furthermore, regular physical activity spread throughout the week is important. However, for individuals to follow these recommendations, supportive environments and communities are fundamental in shaping people’s mind, by making the choice of healthier foods and regular physical activity the easiest choice. This means that the healthiest alternative should be accessible, available and affordable [8].

Evidence from the SARS-CoV-1 outbreak in 2002–2003 suggests that there is a likelihood of long-term metabolic sequelae from COVID-19. In survivors of SARS-CoV-1, long-term metabolic abnormalities including dyslipidemia and cardiovascular disease as well as signs of abnormal glucose metabolism with insulin resistance and hyperglycemia, and diabetes have been observed for up to 12 years [75, 76]. More and more studies are emerging showing similar tendencies after infections with SARS-CoV-2, where up to 40% of people that were infected with SARS-CoV-2 suffer from symptoms of long-COVID [77–79], such as difficulties in concentration, cognitive dysfunction, amnesia, depression, fatigue, and anxiety [80–82]. Therefore, people post discharge following COVID-19 will need close monitoring for risk factor control [83].

To avoid severe COVID-19, vaccination was proven to be highly effective [84]. However, currently a high number of SARS-CoV-2 vaccine breakthrough infections and reinfections occur when people are exposed to the Omicron SARS-CoV-2 variants. The relationship between obesity and vaccine efficacy remains unclear, but as T-cell responses in obese individuals are impaired, it might imply that COVID-19 vaccines are less effective in obese individuals [85]. This was supported in latest findings indicating that obesity and other metabolic dysfunctions might promote vaccine breakthrough SARS-CoV-2 infections [84, 86, 87]. Furthermore, for reinfections, it was recently shown that at least one of the comorbidities obesity, diabetes, asthma, heart disease, lung disease, and high blood pressure was present in 50% of all cases [88].

Conclusion

The number of people with overweight and obesity is increasing all over the world making these people more susceptible to infectious diseases, such as COVID-19, which in the current corona pandemic turned out to be devastating. Therefore, the importance of preventing obesity already from childhood on has been further put into the spotlight [89]. The COVID-19 pandemic has taught us that nutrition education interventions, access to healthy food, as well as family nutrition counselling should be covered by pediatric services to prevent obesity, which worsens disease outcomes related to SARS-CoV-2 infection and to potential other new epidemics in the future [66]. Individually-targeted evidence-based health promotion, weight management, behavioral change and psycho-social support services need vigorous support from physicians and other health personnel [90].

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Conflict of Interest

The authors declare that they have no conflict of interest.

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