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Review

# Mechanisms and pathophysiology of SARS-CoV-2 infection of the adipose tissue

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**Obesity is an independent risk factor for severe COVID-19, yet there remains a lack of consensus on the mechanisms underlying this relationship. A hypothesis that has garnered considerable attention suggests that SARS-CoV-2 disrupts adipose tissue function, either through direct infection or by indirect mechanisms. Indeed, recent reports have begun to shed some light on the important role that the adipose tissue plays during the acute phase of infection, as well as mediating long-term sequelae. In this review, we examine the evidence of extrapulmonary dissemination of SARS-CoV-2 to the adipose tissue. We discuss the mechanisms, acute and long-term implications, and possible management strategies to limit or ameliorate severe disease and long-term metabolic disturbances.**

## The potential role of adipose tissue in coronavirus disease 2019 (COVID-19)

Since the start of the pandemic, several large epidemiological studies have explored the relationship between risk factors, comorbidities, and development of severe COVID-19. Initial studies have found obesity, characterized by a high body mass index (BMI), to be an independent risk factor for hospitalization, requirement of mechanical ventilation in the intensive care unit, and fatal outcomes in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected individuals [1–5]. Since then, several published meta-analyses have verified these initial findings [6–9]. The use of BMI as a sole indicator of obesity can be misleading, as it does not consider the distribution of adipose tissue and muscle-to-fat ratio. However, adiposity measurements, such as waist circumference, waist-to-hip ratio, and waist-to-height ratio, were also associated with a greater risk of COVID-19 mortality [3]. Indeed, adiposity, measured by BMI and the proportion of body fat, is strongly and likely causally associated with severe COVID-19 [10–13]. The underlying mechanisms linking obesity with severe COVID-19 are not yet fully understood, likely because of their multifactorial nature.

Cypess recently wrote 'The riskiest approach to human adipose tissue is to dismiss its importance' [14]. The adipose tissue is one of the largest organs in the human body, yet is largely overlooked as an active player in many chronic and acute conditions. The adipose tissue can generally be divided into two distinct types: white and brown. The white adipose tissue (WAT) regulates the storage and release of triglycerides, whereas the brown adipose tissue consumes glucose and triglycerides to produce heat [14]. The primary function of the adipose tissue is to store energy; however, it also plays an important role as an endocrine organ and in energy metabolism [15,16]. Dysfunction in these processes is closely related to metabolic disorders, including obesity and metabolic syndrome. WAT is composed of adipocytes and a stromal vascular fraction (SVF), comprising immune, endothelial, and stromal cells [17]. However, not all WAT subpopulations or depots within the human body are the same. Over the past decade, several differences have been observed in the cellular composition and physiological activity of different WAT compartments, including the subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) and how they may play a role in disease [17,18]. Genetic background, age, and sex also affect the characteristics of adipose tissue depots, including location, size, and metabolic behavior [19].

## Highlights

Recent studies have identified adipose tissue as a target for extrapulmonary SARS-CoV-2 infection in COVID-19 patients, as well as *in vivo* experimental studies.

SARS-CoV-2 RNA has been identified in 44% of subcutaneous and 39% of visceral adipose tissue biopsies from patients with severe COVID-19. This might indicate that, in certain patients, adipose tissue serves as an additional reservoir for SARS-CoV-2 replication. Based on the limited data available, adipose tissue viral load was not associated with sex, total body fat content, body weight, BMI, or age, suggesting that the potential of SARS-CoV-2 to infect adipose tissues is independent of these known COVID-19 risk factors.

Adipocytes and macrophages appear to be the main SARS-CoV-2 target cells within the adipose tissue of patients with severe COVID-19.

SARS-CoV-2 infection in adipose tissue induces a robust antiviral inflammatory response. Importantly, SARS-CoV-2 infection also leads to changes in the metabolic function of adipose tissue, similar to those commonly observed in patients with obesity and/or type 2 diabetes.

Several studies have reported new-onset cardiometabolic diseases such as hypertension, hyperlipidemia, and diabetes after COVID-19; however, the precise underlying mechanisms remain unknown. We propose that SARS-CoV-2 replication in adipose tissue and/or metabolic and inflammatory alterations resulting from adipose tissue infection contributes to insulin resistance and the onset or worsening of cardiometabolic diseases.

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There are several hypotheses on the mechanisms linking obesity and COVID-19 severity [20,21], including the possibility that SARS-CoV-2 affects adipose tissue function either directly by infecting adipocytes or SVF cells situated within WAT and/or indirectly through antiviral immune mechanisms that influence adipose tissue function. The concept of SARS-CoV-2 directly infecting WAT stems from the fact that adipocytes and SVF cells express *ACE2* [22], the canonical receptor for SARS-CoV-2 entry. WAT has also been reported to express similar *ACE2* levels to the lungs of the same individual [23]. Moreover, adipocyte *ACE2* expression was increased in obese mice [24] and ACE2 expression in adipose tissue from obese individuals was higher than that in lean individuals [25]. As such, the adipose tissue has been investigated as a site of active SARS-CoV-2 infection and is potentially a site of virus persistence that could contribute to the acute and long-term sequelae associated with COVID-19.

In this review, we provide an overview of the evidence of extrapulmonary dissemination of SARS-CoV-2 to the adipose tissue in COVID-19 patients. We discuss the mechanisms, acute and long-term implications, and possible management strategies to limit or ameliorate severe disease and long-term metabolic disturbances.

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## Evidence of SARS-CoV-2 dissemination to adipose tissue in COVID-19 patients

The idea that the adipose tissue may serve as a viral reservoir is not new. Several human studies have reported the presence of human immunodeficiency virus (HIV), simian immunodeficiency virus (SIV), and adenovirus-36 within this tissue [26,27]. Moreover, evidence of viral replication within the adipose tissue of *in vivo* experimental animals has also been reported for viruses such as HIV, SIV, and H1N1 influenza A [26,28–31]. Numerous autopsy studies have investigated SARS-CoV-2 infection in the lungs and extrapulmonary organs [32–35]. Despite the clear relationship between obesity and COVID-19 severity, not all studies have investigated the presence of SARS-CoV-2 in adipose tissue biopsies collected from patients who died of severe COVID-19. This is likely because the pathological examination of adipose tissue is generally not a standard practice; as such, the role of adipose tissues as active mediators of severe COVID-19 is underestimated.

Numerous postmortem biopsy studies have been published and made publicly available since the beginning of the COVID-19 pandemic. Here, we selected studies in which the adipose tissue was a significant component of the reported data. We identified seven studies that investigated possible SARS-CoV-2 infection of adipose tissues in COVID-19 patients (Table 1). The rapid communication by Poma *et al*. found SARS-CoV-2 RNA and nucleocapsid protein in ten out of 16 patient samples. Later, the same authors published comparable results for 23 patients [36]. Since we could not determine whether patients overlapped, we included only the latter as it examined the most adipose tissue samples. Safari *et al*. investigated SARS-CoV-2 infection in SAT and VAT samples collected during emergency surgery from four patients testing positive for SARS-CoV-2 with mild COVID-19 symptoms [37]. All of the SAT and VAT samples tested negative for SARS-CoV-2 RNA. The authors commented that the presence of viremia and extent of viral load were unknown at the time of sampling and that they were concerned about the accuracy of the methods used to determine viral RNA in the tissues. Colleluori *et al*. used various techniques to identify infection of VAT in 19 patients with severe COVID-19. PCR for SARS-CoV-2 and immunohistochemical staining for both the nucleocapsid and spike proteins were negative. Electron microscopy of four adipose tissue biopsies from COVID-19 patients identified 'virus-like' structures within the adipose tissue [38]. However, whether the structures were specifically related to SARS-CoV-2 replication, a cellular response secondary to infection within the adipose tissue or elsewhere remained unclear [38]. Owing to the technical uncertainties highlighted by the authors, we excluded the studies by Safari *et al*. and Colleluori *et al*. from subsequent discussions.

Table 1. Summary of studies examining SARS-CoV-2 infection in adipose tissue biopsies from COVID-19 patients

| Number of patients | Sex (m/f) (% m) | Age (y) (mean) (median) (range) | BMI (kg/m$^2$) (mean) (median) (range) | Adipose tissue depot analyzed[a] | Methods to detect SARS-CoV-2 *in situ* | SARS-CoV-2 present in adipose tissue, *n* (%) | Refs |
|---|---|---|---|---|---|---|---|
| 16[b] | N/A | N/A | N/A | SAT | qPCR<br>IHC NC (*n* = 16) | SAT- 10/16 (62)<br>SAT- 10/16 (62) | [119] |
| 4[b] | 3/4<br>75 | 44<br>35.5<br>30–75 | N/A | SAT<br>VAT | qPCR | SAT- neg, 0/4<br>VAT- neg, 0/4 | [37] |
| 19[b] | 11/19<br>58 | 69<br>70<br>51–92 | 30<br>29.4<br>22.8–46.7 | VAT | qPCR<br>IHC NC, spike<br>TEM (*n* = 4) | qPCR- neg<br>IHC- neg<br>virus-like structures | [38] |
| 30 | 18/12<br>60 | 71.9<br>75.5<br>26–100 | 28.7<br>27.2<br>14.1–51.2 | SAT<br>VAT | qPCR | SAT- 10/30 (33)<br>VAT- 10/30 (33)<br>SAT & VAT- 6/30 (20) | [39] |
| 23 | 16/7<br>69 | Mean<br>65.4-SC2-<br>74-SC+ | Mean<br><BMI<br>25–8<br>>BMI<br>25–15 | SAT | qPCR<br><br>IHC NC (*n* = 22) | SAT 13/23 (56) | [36] |
| 47 | 23/24<br>49 | 65<br>65<br>38–88 | 31.5<br>28.7<br>21.3–55.4 | SAT | qPCR<br><br>IHC spike (*n* = N/A) | SAT- 23/47 (49) | [40] |
| 10 | 6/4<br>60 | 78.3<br>82.5<br>58–85 | 29.7[c]<br>26<br>24–47 | EAT (*n* = 5)<br>SAT (*n* = 2)<br>VAT (*n* = 3) | qPCR<br>ISH-EAT-spike mRNA<br>(*n* = 2) | EAT- 4/5 (80)<br>SAT- 2/2 (100)<br>VAT- 3/3 (100) | [68] |

[a]Abbreviations: BMI, body mass index; EAT, epicardial adipose tissue; f, female; IHC, immunohistochemistry; ISH, *in situ* hybridization; m, male; N/A, data not available; neg, negative; SAT, subcutaneous adipose tissue; SC2, SARS-CoV-2; TEM, transmission electron microscopy; VAT, visceral adipose tissue.
[b]Excluded from our analysis.
[c]Missing data *n* = 2.

In total, the current literature reports 110 SAT samples obtained postmortem from four distinct cohorts of patients with severe COVID-19 (Table 1). SARS-CoV-2 RNA was identified in 48 of 110 SAT samples examined (44%). SARS-CoV-2 RNA was also found in VAT from COVID-19 patients, according to two studies. In total, 13 of the 33 examined biopsies (39%) contained SARS-CoV-2 RNA. The adipose tissue viral load was not associated with sex [39,40], total body fat content [39], body weight, BMI, or age [40], suggesting that the potential of SARS-CoV-2 to infect adipose tissues is independent of these known COVID-19 risk factors. Individual patient data were available for only two of the four studies. The limitations of the aforementioned studies include the limited sample size, postmortem interval, and autolysis of biopsies, which might have influenced the adipose tissue SARS-CoV-2 viral content. Saccon *et al.* performed minimally modified invasive autopsy within 1 h after death, which preserves RNA integrity and pathology due to limiting the effects of postmortem tissue autolysis [40]. However, even under these optimal conditions, SARS-CoV-2 was still present in only half of all SAT biopsies. This might mean that the adipose tissue in a subpopulation of patients is susceptible to SARS-CoV-2. Not all studies mentioned in Table 1 validated PCR findings by either SARS-CoV-2 spike/nucleocapsid immunohistochemical staining or *in situ* hybridization; it was also unclear whether there was an overlap between the different methods used to detect SARS-CoV-2. The duration of severe disease was not noted and may have influenced the viral load in the adipose tissue. Stein *et al*. recently performed a comprehensive autopsy study investigating SARS-CoV-2 infection and persistence in respiratory and extrapulmonary organs [32]. They found that SARS-CoV-2 could disseminate early during infection and there was evidence of virus persistence and replication

in non-respiratory tissues up to several months after infection. Unfortunately, the adipose tissue was not investigated in this study; therefore, no conclusions could be drawn regarding viral persistence in adipose tissues.

Viral RNA persistence in tissues has been associated with the severity and long-term sequelae of several other RNA virus infections [41]. It is also worth investigating in the context of WAT because with the median turnover rate of adipocytes being approximately 8% per year [42], the replacement of all adipocytes in the human body would take approximately 15 years. It is important to note that the persistence of virus RNA does not directly translate to efficient virus replication and infectivity. The efficiency of SARS-CoV-2 replication and infectivity of newly produced virus particles, such as for all viruses, can vary in different tissues and organs. In addition to the differences in the permissiveness of the cells to infection, the autocrine and paracrine effects of the antiviral immune response influence the infectivity of the virus. The selective pressure and relatively high mutation rate of RNA viruses can give rise to virus quasi-species. These 'mutant clouds' can differ in their cell and tissue tropism and capacity to evade the immune system. It would be interesting to determine the infectivity of adipose tissue-associated virus, as this would have implications for the pathophysiology of COVID-19. *In vitro* studies have found that susceptibility to infection and cellular response depends on the viral lineage [40]. Therefore, future studies should determine whether SARS-CoV-2 dissemination to the adipose tissue differs among different SARS-CoV-2 variants.

## Animal models of COVID-19 and adipose tissue tropism of SARS-CoV-2

Experimental animal models of SARS-CoV-2 infection have helped us understand host–virus interactions and advance our knowledge of COVID-19 pathophysiology. Since the beginning of the pandemic, various animal models have been developed, each with unique benefits and drawbacks [43]. Mice are often used for preclinical studies. However, SARS-CoV-2 does not infect wild-type mice because it cannot bind to the murine ACE2 entry receptor. To overcome this issue, transgenic mice expressing the human ACE2 receptor controlled by human keratin 18 (K18 promoter), including respiratory epithelial cells (K18-hACE2 mice), have been used in various studies because these mice become highly susceptible following intranasal inoculation with SARS-CoV-2 [44,45]. A limitation of this model is the abnormal expression of hACE2 compared with the human situation, which might artificially lead to increased extrapulmonary tropism and viral replication in organs expressing epithelial cells. Moreover, comorbid conditions that might alter ACE2 expression, as reported in adipose tissues and other organs in obesity [25,46], will not be apparent in this model. In addition to mice, numerous studies have been performed on hamsters because they are susceptible to SARS-CoV-2 infection and can transmit the virus [47]. Non-human primates, such as macaques, are the closest related species to humans studied in the context of infection, prevention, and therapeutic interventions and have provided additional insights into the pathophysiology of COVID-19 [48].

Of all published studies addressing the effect of SARS-CoV-2 infection on adipose tissues *in vivo*, we identified five that investigated whether SARS-CoV-2 disseminates to different adipose tissue depots (Table 2). All relevant studies used Syrian hamsters, macaques, or genetically modified mice expressing the human ACE2 receptor intranasally inoculated with SARS-CoV-2. Studies in hamsters found evidence of SARS-CoV-2 presence in over 80% of SAT samples investigated at 1, 2, and 3 days post-infection (dpi), but not at 6 dpi [39,49]. SARS-CoV-2 was also detected 2 dpi [49]. The viral load in the adipose tissue and lungs differed between male and female K18-hACE2 mice at 10 dpi, with female mice having a higher viral load in the adipose tissue [50]. In female macaques, SARS-CoV-2 was found only at 7 dpi and not in the VAT or epicardial adipose tissue [51]. Although all tested models identified the ability of SARS-CoV-2 to reach and/or

Table 2. *In vivo* experimental studies examining the extrapulmonary dissemination and adipose tissue tropism of SARS-CoV-2

| Animal model | Sex m/f | Age (weeks) | SARS-CoV-2 dose and delivery[a] | Adipose tissue analyzed | DPI | Detection methods | Number of animals with SARS-CoV-2 in adipose tissue, *n* (%) | Refs |
|---|---|---|---|---|---|---|---|---|
| Golden Syrian hamster | N/A | 3–5 | 100 PFU In[b] | SAT<br>VAT | 2 | qPCR | 2 dpi SAT 5/6 (83)<br>2 dpi VAT 5/6 (83) | [49] |
| Golden Syrian hamster | m | 8–12 | $10^5$ PFU In[c] | Inguinal SAT | 1<br>3<br>6 | Plaque assay | 1 dpi 5/5, (100)<br>3 dpi 5/5 (100)<br>6 dpi 0/5 (0) | [39] |
| Macaque | f | 7 years | $10^6$ PFU In & It[d] | SAT<br>VAT<br>EAT | 7 | qPCR | SAT 4/5 (80)<br>VAT 0/5 (0)<br>EAT 0/5 (0) | [51] |
| K18-hACE2 C57BL/6J mice | m/f | N/A | $10^4$ PFU In[b] | Mesenteric VAT | 10 | qPCR<br>IHC NC (*n* = 4/sex) | Significantly more viral load female WAT versus male (very low levels) | [50] |
| Golden Syrian hamster | f | ~8<br>~88 | $1.4 \times 10^4$ PFU In[e] | Inguinal SAT<br>Epididymal VAT | 7<br>22 | IHC spike (SAT) *n* = N/A | AT viral load N/A<br><br>IHC- SAT 2 and 22 dpi | [52] |

[a]Abbreviations: DPI, days post-infection; EAT, epicardial adipose tissue; f, female; IHC, immunohistochemistry; In, intranasal; It, intratracheal; m, male; N/A, data not available; NC, nucleocapsid protein; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.
[b]SARS-CoV-2 variant: NR-52281, USA-WA1/2020 CoV-2.
[c]SARS-CoV-2 variant: SARS-CoV2/Germany/Hamburg/01/2020.
[d]SARS-CoV-2 variant: BetaCoV/France/IDF/0372/2020.
[e]hCoV-19_IPL_France SARS-CoV-2.

replicate in the WAT, there were differences between virus tropism to the different WAT depots in hamsters and macaques. Moreover, while age and obesity are known to affect the cellular composition and function of adipose tissue, very young, lean hamsters were adopted for the initial experimental studies, which does not reflect the most vulnerable group of patients developing severe COVID-19.

The impact of age and obesity on adipose tissue function in healthy and SARS-CoV-2-infected animals has been addressed by Bogard *et al*. The authors found that the cellular and molecular characteristics of SAT, but not VAT, of aged hamsters were altered compared with young animals [52]. Interestingly, SARS-CoV-2 infection induced structural differences in the adipose tissue and affected adipocyte size independent of age but had longer-lasting effects in aged mice. Although the adipose tissue viral load was not assessed, SARS-CoV-2 S protein staining was observed in SAT-residing macrophages, particularly within crown-like structures (CLS), representing dead adipocytes encircled by macrophages. Furthermore, adipocyte death is more frequent in aged hamsters than in young animals. However, no CLS were found in the VAT and the presence and/or persistence of SARS-CoV-2 within the VAT was not reported. CLS persisted for at least 22 dpi in the SAT of aged animals, which might reflect impaired removal of dead adipocytes by macrophages. These results further substantiate the possibility that SARS-CoV-2 viral particles may persist for longer periods, which might facilitate chronic inflammation and mediate long-term metabolic dysfunction.

Studies focusing on obesity have adopted a high-fat, high-sugar diet (Western diet), obese hamsters with dyslipidemia and non-alcoholic steatohepatitis (obese-NASH hamsters), or diet-induced obese (DIO) K18-hACE2 mice in an attempt to replicate the human situation more closely [53–55]. Hamsters fed a high-fat and high-sugar diet, mimicking a Western diet, developed worse pulmonary injury and exacerbated disease severity than hamsters fed a regular diet following SARS-CoV-2 infection [54]. Only male mice and one age group were evaluated; therefore, further studies are required to determine whether there is a sex- or age-bias with the Western diet and

disease severity. Moreover, the dissemination of SARS-CoV-2 to adipose tissues and its functional consequences have not been investigated. Similarly, compared with control animals, obese NASH hamsters infected with SARS-CoV-2 had more lung and liver inflammation, despite a similar lung viral load. Additionally, higher levels of lung fibrosis, sustained dyslipidemia, inflammatory profiles, and liver damage are indicative of poor recovery [53]. Again, the viral load was not determined in the adipose tissue depots of these hamsters in either the acute or recovery phases. Furthermore, the lung viral load was shown to be greater (100-fold) in DIO female K18-hACE2 mice than in mice receiving a normal diet and was accompanied by increased morbidity and mortality compared with male DIO mice [55]. This suggests that DIO impairs the ability of female mice to clear the virus, resulting in increased inflammation and morbidity, or that excess inflammation due to DIO impairs viral clearance. Unfortunately, SARS-CoV-2 tropism in the adipose tissue, viral burden, and associated adipose tissue responses were not investigated in this study.

Together, these studies highlight the role of age and obesity in mediating a severe disease phenotype, corroborating epidemiological studies in COVID-19 patients. However, contrasting results have been reported regarding SARS-CoV-2 localization in the adipose tissue in experimental animals, which might be a result of the non-standardized protocol and analyses performed. Additional studies are also necessary to identify differences in the adipose tissue viral load during the acute phase, how this might influence recovery, and whether residual virus lingers behind in the adipose tissue, which might mediate persistent inflammation and long-term sequelae.

## How does SARS-CoV-2 disseminate to adipose tissue depots?

Substantial evidence indicates that while most SARS-CoV-2 is present in respiratory tissues, it can also reach other tissues and organs [32]. However, the exact mechanism by which the virus disseminates throughout the body remains unclear. Four most likely routes have been considered thus far: via the bloodstream, cell trafficking, and/or the nervous and/or lymphatic system. The ability of the virus to reach the blood was noted early on [56,57]. However, the low levels and incidence of viremia would render this route of dissemination relatively inefficient. In addition, most studies have shown that neither immune nor vascular endothelial cells are likely to participate in replicating the virus [58–60]. Yet, SARS-CoV-2 was found to be localized in the vascular endothelium [61], raising the possibility that the virus might infiltrate these barriers for dissemination. Several studies have shown that direct SARS-CoV-2 infection of endothelial cells is unlikely [59,60]. However, even if pulmonary endothelial cells are not directly infected with SARS-CoV-2, they may become permeable because of the secondary responses to infection in other respiratory and immune cells. This may allow SARS-CoV-2 virions, infected cell fragments, or SARS-CoV-2-hijacked monocytes and macrophages to transmigrate and enter the blood. In line with this hypothesis, SARS-CoV-2 viremia has been shown to predict severe COVID-19 outcomes [62] and systemic dissemination mediates many of the pathophysiological features of COVID-19 [35,62]. Alternatively, the adipose tissue is known to be innervated by sympathetic nerves that regulate the adipose tissue function; therefore, dissemination through the central nervous system (CNS) might be possible [63]. Despite early speculation that SARS-CoV-2 may enter the CNS via migration through the nasal cavity and olfactory pathway or trafficking across the blood–brain barrier, studies have failed to provide substantial evidence of viral infection in the CNS [64]. Moreover, recent studies have found that human sensory nerves are susceptible to SARS-CoV-2 *in vitro* but are unable to replicate and produce new virus [65]. As such, it is unlikely that the dissemination of SARS-CoV-2 to the adipose tissue is regulated by infection of the CNS and migration of SARS-CoV-2 from sensory nerves localized in the adipose tissue. An additional route of dissemination may be through the lymphatic system. The lymphatic system maintains fluid homeostasis by removing protein-rich lymph from the extracellular space of tissues into the bloodstream [66]. Additionally, lymphatic vessels transport pathogens such as viruses and

bacteria [67]. SARS-CoV-2 viral load was previously identified in the lymph nodes of COVID-19 patients [62]. Therefore, SARS-CoV-2 may also disseminate to adipose tissue through lymphatic vessels. Alternatively, local spread of the virus from infected organs to the vicinity of adipose tissues, such as the lungs (thoracic adipose tissue), heart (epicardial adipose tissue), kidney (perirenal adipose tissue), and intestines (mesenteric adipose tissue) could be considered. More research is needed to fully understand the mechanisms by which SARS-CoV-2 disseminates throughout the body, including in the adipose tissue.

## Which cells are the targets of SARS-CoV-2 replication within the adipose tissue?

The adipose tissue is composed of a complex network of different cell types, such as adipocytes, immune cells, endothelial cells, adipocyte precursors, fibroblasts, and myofibroblasts. Recent *in vitro* studies have investigated whether SARS-CoV-2 can infect mature adipocytes and macrophages within the SVF of the adipose tissue [68]. Interestingly, the degree of SARS-CoV-2 infection was dependent on the anatomical origin of the isolated adipose tissue stromal vascular cells used to differentiate into adipocytes for cell infection experiments [40]. Cells isolated from VAT were more susceptible to SARS-CoV-2 infection than cells from SAT, which might be related to the relatively higher ACE2 expression in VAT [40]. In fact, ACE2 expression was shown to be induced by adipocyte differentiation, suggesting that lipid droplet metabolism is critical for SARS-CoV-2 entry and replication [39]. It is currently unclear whether these findings translate to an *in vivo* patient setting in the context of the complex interplay between all cell types of the adipose tissue. *In vitro* infection experiments in isolated monocultures of preadipocytes, adipocytes, or SVF cells lack important aspects of the complex adipose tissue morphology and the likelihood of infection might be greater under such conditions. Indeed, these studies do not readily explain the presence of SARS-CoV-2 in adipocytes of both SAT and VAT in deceased COVID-19 patients [36,40,68]. Together, these data suggest that adipocytes and macrophages are the main SARS-CoV-2 target cells within the adipose tissue of patients with severe COVID-19.

## SARS-CoV-2 entry receptors in adipose tissues

As previously mentioned, human adipose tissues express ACE2 [25,39], the entry receptor for SARS-CoV-2 (Figure 1). ACE2 expression was reported to be higher in the adipose tissue of obese individuals than in lean individuals [69]; however, contrasting studies failed to identify an association between ACE2 expression and BMI [39]. ACE2 mRNA expression has been identified in differentiated preadipocytes [39,68] and sporadically detected in mature adipocytes, but not in preadipocytes in culture [68]. However, ACE2 protein levels were absent in freshly isolated or undifferentiated adipocytes or whole fixed adipose tissue, suggesting that mature and differentiated adipocytes can be infected with SARS-CoV-2 but that viral entry is ACE2 receptor-independent [68]. In contrast, Saccon *et al*. detected ACE2 expression in subcutaneous and VAT cells using immunofluorescence, western blotting, and RT-qPCR [40]. Moreover, they found that VAT cells expressed higher levels of ACE2, which was associated with increased susceptibility of the VAT cells to infection [31]. In addition to ACE2, several other molecules have been suggested to serve as alternative receptors for SARS-CoV-2, such as CD147 (Basigin) and neuropilin-1 (NRP1), dipeptidyl peptidase 4 (DPP4), and FURIN, of which the expression is higher in individuals with obesity [49,70,71]. However, the inability of CD147 to bind the SARS-CoV-2- S protein has contested the involvement of CD147 in SARS-CoV-2 infection [72]. Single-nucleus RNA sequencing data [73] revealed that NRP1 is abundantly expressed in adipocytes and other cells within the adipose tissue [40]. However, adopting NRP1 neutralizing antibodies or an NRP1-specific antagonist did not attenuate the viral load 24 h after infection, suggesting that NRP1 is not essential for SARS-CoV-2 infection of the adipose tissue cells [40] (Figure 1). In conclusion, given the conflicting findings to date, more research is required to fully elucidate the involvement of ACE2 and the possible role of alternative entry mechanisms in mediating SARS-CoV-2

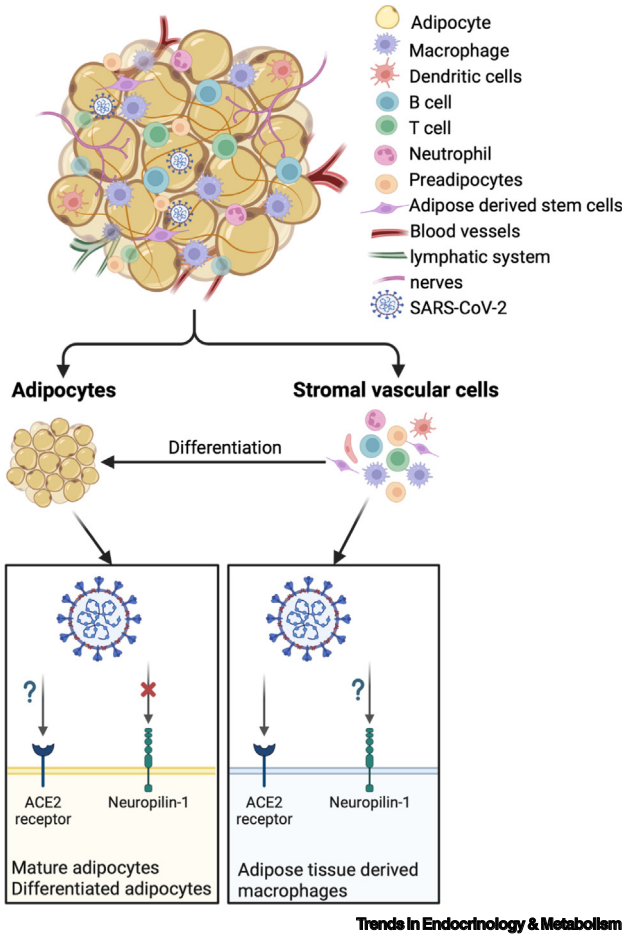


Figure 1. Possible mechanisms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into adipose tissue. White adipose tissue is comprised of multiple distinct cell types and components, the composition and function of which differ per adipose tissue depot within the body. Adipose tissue cells can be divided into adipocytes and the stromal vascular fractions (SVF). SVF comprises endothelial cells, macrophages, immune cells, and fibroblasts. Postmortem studies identified SARS-CoV-2 localized within the adipose tissue (summarized in Table 1), although in which cells was not always clear. *In vitro* cell studies have found that SARS-CoV-2 can infect mature, differentiated adipocytes and macrophages *in vitro* but not preadipocytes [40,68]. The role of ACE2 as a SARS-CoV-2 entry receptor that mediates adipose tissue cell infection is currently unclear, as contradictory studies have been published. Neuropilin-1 was shown not to mediate viral entry into adipocytes [40]. Figure created with BioRender.com.

infection of the adipose tissue. These findings may have significant implications for the development of therapeutics to prevent adipose tissue infection.

## Acute consequences of SARS-CoV-2 infection on adipose tissue function

Irrespective of the efficiency of viral replication in the adipose tissue, the presence and sensing of the virus is also likely to influence tissue function. SARS-CoV-2 was found to induce a robust antiviral response in the VAT and, to a lesser extent, in the SAT which was associated with systemic insulin resistance [49]. Proinflammatory cytokines, chemokines, and pathways associated with immune defense, such as granulocyte activation, phagocytosis, and the adaptive immune response, were increased in the adipose tissue from SARS-CoV-2-infected hamsters, which might have been induced, in part, by direct infection of the adipose tissue [39,49]. *In vivo* studies revealed that the expression of genes involved in lipolysis [52] and *de novo* lipogenesis were suppressed in the adipose tissue of SARS-CoV-2 infected hamsters [39,52]. Lipolysis was also inhibited by SARS-CoV-2 infection of human adipocytes [40]. Importantly, in line with age as a risk factor for severe COVID-19 in patients, SARS-CoV-2 infection led to altered lipid metabolism and adipose tissue remodeling that was more severe and prolonged in aged compared with adult hamsters. In addition, changes in plasma lipid profiles during SARS-CoV-2 infection were found to be associated with age [52]. Adiponectin protein levels were attenuated in the adipose tissue and the serum of SARS-CoV-2 infected hamsters [49]. Moreover, adiponectin and adipsin expression was also suppressed in

human mature adipocytes infected with SARS-CoV-2 [49]. In line with these findings, we and others have found altered circulating adipokine levels, including reduced circulating adiponectin levels and a lower adiponectin/leptin ratio, in patients with COVID-19 [49,74–77]. The latter ratio has been proposed as a marker for adipose tissue dysfunction. Collectively, empirical evidence indicates that adipose tissue dysfunction resulting from SARS-CoV-2 infection leads to metabolic disturbances and inflammatory responses similar to the mechanisms commonly found in patients with obesity and/or type 2 diabetes. Indeed, adipose tissue depots have different metabolic and endocrine functions and influence the onset of metabolic diseases [78]. Moreover, the extent and impact of SARS-CoV-2 infection on adipose tissue depots other than SAT and VAT is currently unknown. A recent study identified adipose tissue depot-specific gene expression signatures using transcriptome profiling of human adipose tissue from 15 locations dispersed throughout the human body [79]. Therefore, SARS-CoV-2 has the potential to induce differential responses, depending on the localization of adipose tissue within the body.

## What are the long-term implications of SARS-CoV-2 adipose tissue infection?

Several studies have reported a wide range of long-term consequences of SARS-CoV-2 infection, overall termed 'long COVID' or post-acute COVID syndrome. The pathophysiology behind these long-term, often debilitating, after-effects on the quality of life of COVID-19 survivors remains largely unknown. Long-term respiratory problems and persistent or chronic organ dysfunction have been reported in post-COVID-19 hospitalized patients [80] (Figure 2). Persistent inflammation is hypothesized to play a key role in the pathophysiology of long COVID [81]. Although the precise cause of prolonged inflammation is unclear, it may be linked to persistent viral infection or the presence of viral components (proteins or RNA) in different tissues, including the adipose tissue. In support of this hypothesis, several studies have identified SARS-CoV-2 proteins and nucleic acids in various tissues months after initial infection [82–85]. However, it is currently unknown whether SARS-CoV-2 viral particles persist in the adipose tissue for long periods of time. Since human adipocytes have a half-life of approximately 10 years, they could potentially serve as a reservoir for the long-term persistence of viral particles or other pathogens [86].

Obesity is normally associated with multiple systemic alterations, including hormonal, metabolic, and inflammatory alterations, which may contribute to the maintenance or exacerbation of systemic inflammation post-COVID-19 (Figure 2). Moreover, given the role of obesity in the acute phase, prolonged adipose tissue dysfunction may play a role in the persistence of symptoms after acute illness. In fact, several important studies have identified obesity as a risk factor for long COVID [81,87,88]. Recently, several studies have reported new-onset cardiometabolic diseases, such as hypertension, hyperlipidemia, and diabetes after COVID-19 [89–96]. The precise mechanisms leading to new-onset cardiometabolic disease are not yet known, but are likely to be multifactorial. Plausible mechanisms might include persistently poor glycemic control due to critical COVID-19 or (in)direct effects of SARS-CoV-2 on pancreatic β-cells and other islet cell types or increased hepatic glucose production. Additionally, persistent infection(s) and/or metabolic and inflammatory alterations in the adipose tissue may also drive lipid droplet expansion and lipid signaling factors, leading to inflammation, enhanced insulin resistance, and the onset of type 2 diabetes (Figure 2). Alternatively, the adipose tissue may remain dysfunctional, albeit without persistent infection, either temporarily after acute disease or permanently. Altered adipokine secretion has been reported during the acute phase of the disease [75,97], yet whether dysregulated adipose tissues and prolonged altered adipokine secretion play a role in maintaining inflammation in the post-acute phase of COVID-19 is currently unknown.

An alternative hypothesis might be related to virus-induced senescence in the adipose tissue. Studies have identified increased expression of senescence and inflammatory markers in the

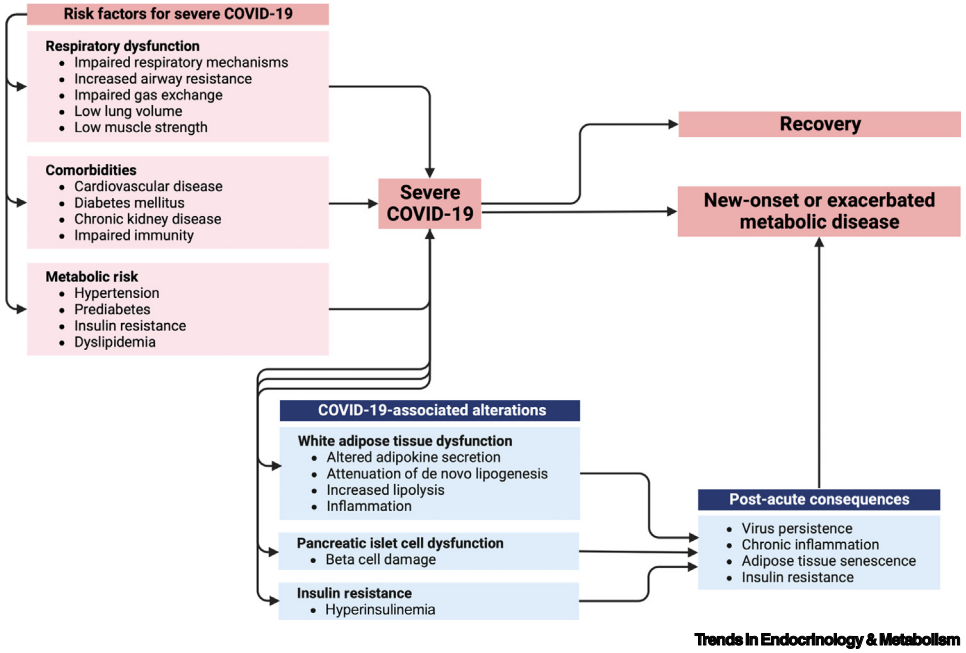


Figure 2. Obesity, severe coronavirus disease 2019 (COVID-19) susceptibility, and the mechanisms of acute and post-COVID-19 sequelae. Individuals with obesity intrinsically have impaired respiratory function, which leads to more severe COVID-19 symptoms, in which they often require mechanical ventilation support during hospitalization. Obesity is often accompanied by additional comorbidities such as hypertension, diabetes mellitus, chronic kidney disease, and impaired immunity. Moreover, even in the absence of comorbidities, prediabetes, dyslipidemia, and insulin resistance predispose individuals with obesity to severe COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of adipose tissue cells has been shown to induce a robust viral and inflammatory response and alter adipose tissue function. These dysfunctional mechanisms have also been shown to be dysfunctional in patients with diabetes mellitus, which may be accompanied by additional endocrine system alterations. Viral persistence, chronic inflammation, and insulin resistance post-acute COVID-19 might drive the onset of new-onset or exacerbated metabolic disease in some individuals. Figure adapted from Stefan *et al*. [120], with permission. Figure created with BioRender.com.

adipose tissue of mice fed an excessive calorie diet. Adipose tissue from individuals with obesity and/or diabetes have also been shown to accumulate senescent cells [98]. Moreover, senescent cells were shown to impair glucose homeostasis and promote insulin sensitivity in obese mice, which was attenuated by senolytic compounds [99]. SARS-CoV-2 infection of adipose tissue cells may also induce senescence and the corresponding senescence-associated inflammatory phenotype, which could lead to or exacerbate existing adipose tissue dysfunction. Additionally, the immune-mediated clearance of SARS-CoV-2 infected cells within the adipose tissue may be compromised because of age- and/or SARS-CoV-2-associated senescence. However, a direct causal role of SARS-CoV-2 inducing senescence of the adipose tissue remains to be identified. Many unknowns currently exist regarding long-term post-COVID-19 metabolic alterations and further studies are crucial to decipher the mechanisms leading to new-onset cardiometabolic diseases, such as diabetes, and the potential role of dysfunctional adipose tissues.

## Management strategies for limiting the impact of acute and post-COVID-19 metabolic dysfunction

To combat the SARS-CoV-2 pandemic, multiple vaccines have been developed. However, there is mounting evidence that vaccine effectiveness for infectious diseases is lower in individuals with obesity owing to compromised immune responses to vaccinations [100–103]. To date, studies reporting the impact of obesity and vaccine effectiveness against SARS-CoV-2 have been

contradictory [104]. Moreover, it is currently unknown whether vaccination influences extrapulmonary SARS-CoV-2 infection of the adipose tissue, since all published postmortem studies so far have been carried out during the first year of the pandemic. Several studies have shown that obesity and poor metabolic health may increase the risk of breakthrough SARS-CoV-2 infections after vaccination [105–108] and a recent prospective longitudinal study found waning of the humoral response to COVID-19 vaccines in individuals with obesity [109]. An accelerated decline in antibodies was identified, which was associated with increased hospitalization and mortality from breakthrough infections. Notably, pharmacological interventions targeting metabolic abnormalities in vaccinated individuals with breakthrough infection were associated with a reduced risk of severe COVID-19 [108]. This may be due to normalizing metabolic abnormalities or combined with a direct effect on SARS-CoV-2 itself. For example, the obesity-management drug orlistat inhibits lipases to reduce the absorption of dietary fat and fatty acid synthesis. Additionally, recent studies have shown that orlistat can inhibit the replication of SARS-CoV-2 *in vitro* as well as reduce SARS-CoV-2 viral titers and the severity of COVID-19 in K18-hACE2 transgenic mice [110]. Apart from its known effect on insulin resistance, metformin is also known to have antiviral, antioxidant, antiapoptotic, and senolytic properties [111,112], which may be able to counteract adipose tissue metabolic dysfunction induced by SARS-CoV-2. Importantly, these drugs could also be implemented in individuals with long-term metabolic complications post-COVID-19. Alternative therapeutic options include SGLT2 inhibitors and GLP1RA, which improve hyperglycemia, lower blood pressure and weight, and reduce oxidative stress, insulin resistance, and low-grade chronic inflammation [113,114]. Normalizing metabolic disturbances either pharmacologically or through lifestyle modifications that promote weight loss and increased physical activity could reverse new-onset hyperglycemia, diabetes, and/or severe metabolic complications in individuals with pre-existing diabetes. This would improve the quality of life, well-being, and hopefully minimize long COVID symptoms. Alternatively, bariatric metabolic surgery can induce long-term weight reduction and improve or ameliorate type 2 diabetes [115–118]; therefore, it might also be a realistic option for individuals with obesity combined with metabolic abnormalities post-COVID-19.

It is crucial to tailor medical therapies (vaccines and/or therapeutics) for populations with a high prevalence of obesity as global obesity rates continue to rise. Moreover, the full impact of the COVID-19 pandemic on the incidence of new-onset or worsening of pre-existing metabolic diseases post-infection has only recently begun to emerge. Consequently, the number of individuals suffering from cardiometabolic disturbances is expected to increase dramatically, which will have a major impact on healthcare costs and hospitalization rates. Early identification of individuals at risk, prevention, and timely management of these conditions are imperative to reduce the burden on the healthcare system and improve patient outcomes.

## Concluding remarks and future perspectives

Our understanding of COVID-19 is evolving rapidly. Despite the clear relationship between obesity and severe COVID-19 symptoms, the amplifying role of the adipose tissue as a mediator of severe disease has largely been overlooked until recently. Studies investigating SARS-CoV-2 infection in adipose tissues have provided important insights into the role of the adipose tissue in COVID-19. Although there were differences in the efficiency of infection and the effect on different adipose tissue depot cells between *in vivo* and *in vitro* experimental models, it is evident that SARS-CoV-2 causes inflammatory and metabolic disturbances. However, several outstanding questions must be addressed to fully understand the underlying mechanisms and impact of SARS-CoV-2 infection on the adipose tissue function during the acute phase of COVID-19 and its long-term implications, including the possibility of new-onset or exacerbated metabolic disorders such as diabetes (see Outstanding questions). Given the potential health benefits and burden on the health care system,

### Outstanding questions

How does SARS-CoV-2 disseminate to adipose tissue depots?

Is SARS-CoV-2 dissemination to adipose tissue SARS-CoV-2 variant-specific? Do different variants elicit the same response in adipose tissue?

Is SARS-CoV-2 localized in the adipose tissue infectious? Either during the acute or later phases post-COVID-19?

What is the impact of age, sex, and obesity on SARS-CoV-2 infection of adipose tissue and the acute and long-term consequences? Is this associated with the distribution of adipose tissue, which is known to differ between young/aged and male/female individuals?

Does adipose tissue infection with SARS-CoV-2 and the associated cellular responses differ in metabolically healthy individuals compared with metabolically unhealthy obese individuals?

Are there racial or ethnic differences that affect the severity of inflammatory reactions and/or metabolic alterations in response to SARS-CoV-2, either acutely or over time?

From a mechanistic point of view, the role of ACE2 in SARS-CoV-2 infection of adipose tissue remains unclear. Are there other mechanisms involved? Does this differ per adipose tissue depot?

Does SARS-CoV-2 or viral remnants persist in adipose tissue long after the acute phase has resolved? Does this play a role in driving persistent or new-onset cardiometabolic diseases or metabolic disturbances that may not be immediately associated with long COVID?

Given the prevalence and variety of acute viral and bacterial infections that currently plague modern civilization, do acute infections caused by pathogens other than SARS-CoV-2 cause long-lasting metabolic disturbances, specifically through alterations in adipose tissue function?

What is the risk and burden of diabetes during the post-acute phase of COVID-19? This information is required to inform about post-acute COVID-19 care strategies.

it is essential to prioritize the identification of at-risk individuals and implement pharmacological and/or lifestyle interventions targeting metabolic dysfunction following COVID-19.

## Author contributions

J.M. wrote and edited the manuscript. M.E., P.H., and I.R.Z. provided valuable input and edited the manuscript. All authors approved the final version of the manuscript prior to submission.

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## Declarations of interests

The authors declare that there are no conflicts of interest.

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