Obesity & COVID-19: mechanistic insights from adipose tissue

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Abstract

Obesity is associated with an increase in morbidity and mortality from COVID-19. The risk is related to the cytokine storm, a major contributor to multiorgan failure and a pathological character of COVID-19 patients with obesity. While the exact cause of the cytokine storm remains elusive, disorders in energy metabolism has provided insights into the mechanism. Emerging data suggest that adipose tissue in obesity contributes to the disorders in several ways. First, adipose tissue restricts the pulmonary function by generation of mechanical pressures to promote systemic hypoxia. Second, adipose tissue supplies a base for SARS-CoV-2 entry by overexpression of viral receptors (ACE2 and DPP4). Third, impaired antiviral responses of adipocytes and immune cells result in dysfunction of immunologic surveillance as well as the viral clearance systems. Fourth, chronic inflammation in obesity contributes to the cytokine storm by secreting more pro-inflammatory cytokines. Fifth, abnormal levels of adipokines increase the risk of a hyper-immune response to the virus in the lungs and other organs to enhance the cytokine storm. Mitochondrial dysfunction in adipocytes, immune cells and other cell types (endothelial cells and platelets, etc.) is a common cellular mechanism for the development of cytokine storm, which leads to the progression of mild COVID-19 to severe cases with multiorgan failure and high mortality. Correction of energy surplus through various approaches is recommended in the prevention and treatment of COVID-19 in the obese patients.

Key words: Obesity, COVID-19, Chronic inflammation, Cytokine storm, Mitochondrial dysfunction
Introduction

COVID-19 (coronavirus disease 2019) is an infectious disease caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2) identified in 2019. As of Feb. 1st, 2022, the virus and its variants have infected more than 377 million people with 5.7 million deaths worldwide (https://coronavirus.jhu.edu/map.html). The COVID-19 pandemic has generated a huge challenge to the global healthcare community due to the high mortality rate. Although the infection and mortality have been effectively reduced by virus-targeting vaccinations, the threat remains serious as current vaccinations may lose efficacy to emerging mutant strains of virus, and a large portion of world’s population remains unvaccinated. It is generally accepted that multiorgan failure is a major cause of the high mortality rate in COVID-19 with cytokine storm as the primary underlying event (1,2).

Obesity is a well-established risk factor for severe COVID-19 with high mortality (3,4), which was first reported in April 2020 and currently supported by epidemiological data from the World Health Organization (WHO) (https://ourworldindata.org/). Based on WHO data in 2016, obesity has become a pandemic, with 39% of adults (age>18 years) being overweight or obese worldwide, leading to 4.7 million premature deaths each year (https://www.who.int/). The combination of the COVID-19 and obesity pandemics has resulted in a significant increase in the death rate in COVID-19 patients. The underlying mechanism linking obesity to the high death rate remains to be established, however, the chronic inflammation and tissue structure changes derived from obesity appear to be the major factors. For example, obesity may reduce the function of the respiratory system by complications, such as asthma, obstructive sleep apnea (OSA), and chronic obstructive pulmonary disease (COPD) (5-7). The same applies to the H1N1 influenza virus infection (7).

In obesity, adipose tissue expansion induces multiple structural and functional changes in the body, which contribute to the development of severe COVID-19 (8,9) (Figure 1). The cellular and molecular events of adipose tissue dysfunction leading to sever COVID-19 will be discussed in this review.

1. Obesity is a strong risk factor for severe COVID-19

Obesity, defined by a body mass index (BMI) over 30 kg/m$^2$, increases morbidity and mortality of COVID-19. The relationship was first reported by a French group in a study with a small sample size, in which obese patients (BMI greater than 35 kg/m$^2$) had a 7.36-fold increase in need for invasive mechanical ventilation over the lean patients (BMI below 25 kg/m$^2$). The first large-scale clinical study of 5,700 hospitalized COVID-19 patients in New York, USA, provided subsequent support that the most common comorbidities were obesity (41.7%), hypertension (56.6%) and
diabetes (33.8) (10). This relationship is consistently supported by later studies. A retrospective study containing 150 patients in China showed that a larger proportion of obese patients (33.3%) progressed to severe COVID-19 relative to the non-obese patients (11). Another retrospective study of 1,158 patients in Kuwait also found obesity as an independent risk factor for severe COVID-19 (12). A cohort study in the United Kingdom reported a linear increase in hospitalization for COVID-19 patients with high BMI (13). A study of 1,795 patients in Boston, USA, found a relationship between high BMI, longer hospital stays, and ICU admission rates in patients with acute respiratory distress syndrome (ARDS) syndrome (14). The relationship is also supported by a recent systematic review and meta-analysis that covered a total of 45,650 patients from 30 studies with obesity and 3 controlled studies with visceral obesity. Obesity not only aggravates COVID-19, but also promotes the occurrence of the entire course of COVID-19 (15). The impact of obesity is particularly pronounced in patients over the age of 60 (16). The relationship between COVID-19 and obesity is considered as “a Pandemic Within a Pandemic” (17). These reports consistently support that obesity increases the risk of severe COVID-19.

Several factors have been proposed in the mechanism of severe COVID-19 in obese patients, which include anatomical changes and functional alterations derived from obesity (Figure 1). Hyperlipidemia in obesity increases blood viscosity, which creates a prothrombotic environment to impair blood circulation. Thrombotic microangiopathy, arterial thrombosis and venous thrombosis are major pathological changes seen in blood vessels of severe COVID-19 patients (18). OSA, a common complication in obesity with difficulties in breathing, causes systemic hypoxia leading to severe hypoxemia following lung injury in COVID-19 patients. The hypoxemia may contribute to severe COVID-19 through cytokine storm (19). Other complications of obesity that may contribute to severe COVID-19 include hyperglycemia (20), type 2 diabetes mellitus (21), dyslipidemia (22), hypertension (23), atherosclerosis (24) and vitamin D deficiency (25). Obesity may dampen the innate and adaptive immune responses to virus, which contributes to viral spread across organs and failure of vaccinations (26). Obesity contributes to vaccination failure through induction of senescence in immune cells, such as natural killer (NK) cells (27), cytotoxic T cells (28) and B cells (29). These factors will not be extensively discussed here as they have been well documented in other reviews (30-32).

2. Mechanical effects of fat depots in severe COVID-19

White adipose tissues include subcutaneous and visceral fat depots. Excessive subcutaneous adipose tissue around the chest and abdomen restricts lung expansion during respiration. Lung activity is dependent on expansion of the chest cavity and intra-abdominal cavity. The subcutaneous
fat depots physically limit chest cavity expansion, which decreases respiratory vital capacity to limit pulmonary function (7).

The visceral depots are mainly located in the abdominal cavity, which include omental, mesenteric, and retroperitoneal spaces. In obesity, there is huge expansion in visceral adipose tissue in addition to the subcutaneous fat. These fat depots increase peritoneal cavity pressure thereby restricting diaphragm movement and limiting lung activity. Both subcutaneous and visceral fat depots have been assessed in COVID-19 patients, and visceral fat depots were proven to increase the risk for severe COVID-19 (33). Therefore, visceral fat accumulation may serve as a predictive factor for intensive care admission in COVID-19 since fat depots contribute to pulmonary dysfunction and lung failure through the mechanical effects(34). In addition, visceral fat depots may contribute to severe COVID-19 through biological activities such as production of pro-inflammatory cytokines, which may be exacerbated by the virus infection contributing to the progression to cytokine storm.

Epicardial fat is ectopic fat deposition surrounding the myocardium and may fuel COVID-19-induced cardiac injury and myocarditis (35). Epicardial fat is a unique fat depot with multifaceted features and induces local and systemic physiological effects (36). Epicardial fat quantified from chest CT are independently associated with the extent of pneumonia and adverse outcomes in patients with COVID-19, supporting their application to clinical risk stratification (37). The fat volume of epicardial fat is a perfect indicator for severe COVID-19 in some obese patients (38).

3. Reservoir effect of adipose tissue in COVID-19

The SARS-CoV-2 virus has a non-segmented, positive single-stranded RNA genome with approximately 30,000 bases. The genome encodes four structural proteins, including the surface-located trimetric spike (S) protein, membrane (M) proteins, the nucleocapsid (N) combined with the RNA genome and the envelope (E) proteins (39). SARS-CoV-2 is an obligate intracellular microorganism that uses the RNA genome as a template to encode the replicase and structural proteins for self-replication. The virus typically infects host cells by interacting with cell surface proteins, such as angiotensin-converting enzyme (ACE) and dipeptidyl peptidase 4 (DPP4), to enter the host cell and nucleus (Figure 2). This propagation can interfere with normal cellular activities such as protein synthesis and energy metabolism, causing subcellular organ damage and ultimately cell death. Adipose tissue is a reservoir for other virus including influenza A virus, human adenovirus AD-36 and cytomegalovirus (40). Adipose tissue expresses ACE and DPP4 for SARS-CoV-2 virus infection, and the increased volume of adipose tissue in obesity may serve as a larger reservoir for SARS-CoV-2.
The first virus receptor found in adipose tissue is ACE2. SARS-CoV-2 uses the viral spike (S) protein for host cell entry. The protein consists of two subunits with distinct functions. The surface subunit (S1) binds to ACE2 on the host cell membrane, whereas the transmembrane subunit (S2) facilitates fusion of the viral membrane with the host cell membrane (41). The spike protein binds to ACE2 through the receptor-binding domain (RBD) region (42). Transmembrane protease serine 2 (TMPRSS2) cleaves the spike protein to facilitate the fusion of SARS-CoV-2 and host cell membranes. Because of this, the spike protein is a major target in exploration of anti-virus vaccines worldwide. Interestingly, ACE2 is expressed by adipocytes in the adipose tissue (43,44). ACE2 gene expression is higher in the visceral and subcutaneous adipose tissues than lung tissue in the human body according to gene expression profile (44). Moreover, an increase in transcription, expression, and enzymatic activity of ACE2 was observed in adipose tissue in obese mice (45). A study of a large cohort of obese patients with COVID-19 revealed serum ACE2 elevation (46). The high adipose ACE2 expression was reported with more mortality in obese COVID-19 patients (44). These studies suggest that adipose tissue may contribute to the severity of COVID-19 through expression of high expression of ACE2 (47). However, mechanism of the ACE2 action remains unknown.

Glucose may increase the binding activity of ACE2 to SARS-CoV-2 in obesity (48). Glycosylation of ACE2 and the viral spike protein under hyperglycemic conditions was found to increase the affinity and interaction of the two proteins promoting virus entry into host cells (49-51). Glycosylation of the human ACE2 receptor contributes substantially to virus binding. The glycan at the N322 site in ACE2 interacts tightly with the receptor-binding domain of the spike protein to strengthen the complex (50). Cryo-electron microscopy indicates that the viral spike protein is extensively glycosylated to facilitate binding to the ACE2 receptor (49). Uncontrolled hyperglycemia might induce glycosylation of ACE2 and the spike protein of SARS-CoV-2, however, the stable glucose adducts require long-term exposure to hyperglycemia. The glycosylation effect remains to be verified as the exposure time to hyperglycemia is only few weeks in COVID-19. However, clinical studies have demonstrated that hyperglycemia independently increased the risk of progression of mild and moderate COVID-19 to severe cases (52,53).

Cholesterol is essential for viral entry into host cells. Obesity may increase the cholesterol load by 40% in COVID-19 (54). Cholesterol facilitates SARS-CoV-2 infection of cells by augmenting lipid raft formation which increases the number of viral entry sites on the cell surface promoting subsequent binding of ACE2 and the virus (55). Therefore, cholesterol may also facilitate virus infection in COVID-19.
DPP4 may be a potential receptor in the facilitation of SARS-CoV-2 infection. DPP4 is an enzyme expressed in on the surface of a wide variety of cells, and its expression is elevated in obesity (56). Based on bioinformatic and protein docking models, the spike protein of SARS-CoV-2 binds to DPP4 with a high affinity (57). High expression of DPP4 in obese patients may facilitate SARS-CoV-2 viral entry into adipocytes resulting in a strong inflammatory immune response. Adipose tissue is also a significant source of circulating soluble DPP4 (58). A high level DPP4 secretion was demonstrated in adipose tissues of obese patients.Interestingly, soluble DPP4 may serve as a receptor to block SARS-CoV-2 infection activity, however, it may also protect the virus(59,60). DPP4 is a well-established enzyme in the degradation of glucagon-like peptide-1 (GLP-1), a gut hormone used for treatment of type 2 diabetes (61). Up-regulation of DPP4 in obesity may reduce the anti-inflammatory activity of GLP-1 contributing to adipose tissue inflammation and the pathogenesis of cytokines storm (62). It has been suggested that the use of DPP4 inhibitors, such as gliptins, in patients with COVID-19 even without type 2 diabetes, may be protective against virus entry and the development of cytokine storm (59). In summary, the interaction between DPP4 and SARS-CoV-2 may promote COVID-19 disease severity, but infection and disease progression may be blocked by a DPP4 inhibitor.

However, the use of DPP4 inhibitors in COVID-19 remains to be investigated among diabetes patients with COVID-19 (63). Eleftheriou, et al. reported that better glucose control with DPP4 inhibitors in diabetic COVID-19 patient might be beneficial in the control of COVID-19 infection (64). This point was supported by a systematic review and meta-analysis of 4,477 patients from 9 studies, in which DPP4 inhibitors were found to significantly reduce the mortality rate of COVID-19 patients(65). In contrast, an epidemiological study showed that DPP4 inhibitor did not affect hospitalization of COVID-19 patients in Italy (66). In addition, a meta-analysis including six observational studies with 1,581 COVID-19 patients concluded that use of DPP4 inhibitors provided neither benefit or side effect in the patients (67). While, a multinational retrospective cohort study suggests that use of DPP-4 inhibitors may improve COVID-19 outcomes for patients with T2DM (68). The effect of DPP4 inhibitors needs more investigation in COVID-19 patients.

The benefits of GLP-1 receptor agonists (GLP-1RAs) in the control of COVID-19 are more consistent. As another type of glucose-lowering agents, GLP1RAs exhibit benefits in the treatment of COVID-19 patients with and without diabetes mellitus type 2 (T2DM) (69). One meta-analysis reported that GLP-1RAs did not increase the risk for respiratory tract infection, pneumonia, or acute respiratory distress syndrome in patients with T2DM and cardiovascular comorbidities (70). In addition, another meta-analysis spanning 9 studies with a total of 19,660 diabetic patients with COVID-19 found that pre-admission use of GLP-1RAs reduced mortality (69). These results suggest a
benefit of GLP-1RAs in the treatment of COVID-19. However, more randomized clinical trials are required to confirm this conclusion.

4. Obesity impairs local and systemic immunity

The antiviral immune response requires the innate immune system (including natural killer cells (NK), dendritic cells (DC), monocytes, macrophages, NKT cells) and the adaptive immune system (T and B cells) (71,72). Coordination between the two systems is essential in the control of viral dissemination (73,74). The innate immune system responds first with recognition of the virus by tissue-resident dendritic cells and subsequent recruitment of NK cells, monocytes, macrophages, and NKT cells to clear the virus. In adipose tissue, this antiviral response is regulated by adipocytes (75).

There is immune dysfunction in severe COVID-19, which is characterized by reduced interferon production from innate immune cells in the early stage, delayed adaptive immune responses, and over production of cytokines in the late stage (76). This dysfunction is enhanced in obese COVID-19 patients, in which the immune system is unable to generate an effective anti-viral response due to obesity (77). Immune dysregulation in obesity is multifactorial and metabolism disorder in the immune cells is an important factor. Immune cells use their reserve capacities to gain extra energy from glucose, fatty acids, and ketones in the response to viral and bacterial pathogens (78,79). The extra energy is required for the production of signal mediators and effector molecules to control the infection. However, this metabolic reserve is impaired in obesity due to energy surplus, which leads to mitochondrial dysfunction in immune cells (discussed below). The cytokines produced by immune cells serve as signals in the coordination of immune responses and in the maintenance of body energy homeostasis (80). However, this activity is reduced by the chronic inflammation and energy surplus in obesity, which make the immune cells (Macrophages, NK cells, iNKT cell, T cells and B cells) fail to operate properly as reflected in failure of the antiviral immune response and tissue damage from the cytokine storm in severe COVID-19.

Adipocytes

Adipocytes secrete type I interferon (IFN) in response to viral infection, but they may also serve as host cells for SARS-CoV-2 (81-84). IFNs are the major cytokines in antiviral immunity (85). Adipocytes sense viruses through multiple pattern recognition receptors (PRRs) including toll-like receptor (TLR) 7/8, melanoma differentiation-associated antigen 5 (MDA5), and retinoic acid-inducible gene I (RIG-I) (82,86). The TLR7/8 receptor activates transcription factor IRF7 for IFN-α/β expression in the Myd88-dependent pathway. The double stranded RNA that is formed during viral replication is recognized by the cytosolic PRRs (RIG-I and MDA5), which interact with mitochondrial
antiviral signaling protein (MAVS) leading to expression of IFN-α/β. The cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway detects mtDNA, but not viral RNA. However, the cGAS/STING pathway limits RNA virus infection through the non-canonical STING pathway, which involves formation of a complex with MAVS at mitochondrial-associated endoplasmic reticulum membranes to activate IRF3/IRF7 (87) (Figure 3). This complex represents a crosstalk between the RNA and DNA sensing pathways. Adipocytes may use several pathways, such as TLR7/8, MDA5, RIG-I, and the non-canonical STING pathway to sense SARS-CoV-2 and initiate production of IFNs.

SARS-CoV-2 uses multiple strategies to antagonize the IFN system (75,85), which include the viral non-structural proteins (Nsp)16, Nsp3, and Nsp1. NSP16 suppresses global mRNA splicing to diminish viral RNA recognition by intracellular helicase receptors. Nsp16 encodes 2’-O-methyltransferase for posttranscriptional modification of the 5’-terminal RNA cap to a methylated 5’-cap-1 allowing viral RNA to mimic the host cell’s mRNA (88). Therefore, the viral RNA is capable of escaping detection by TLR-7/8 and MDA5. Nsp3 inhibits the innate immune response by inhibiting phosphorylation, dimerization, and nuclear translocation of the transcription factor IRF7 or IRF3 (89). Nsp1 is found in the closest portion of the 5’ end encoded by ORF1a/b. Nsp1 inhibits IFN-β production by accelerating degradation of IFN-β mRNA (Figure 3). Expression of IFN-stimulated genes (ISGs) is significantly decreased in obesity contributing to impaired immune responses. These studies suggest that adipocytes have an innate immune activity against SARS-CoV-2 and a defect in this activity occurs in obesity increasing the risk of severe COVID-19.

**NK cells and lymphocytes**

Immune cells are subject to metabolic reprogramming in the circulation, lymph nodes, and adipose tissue in obesity. The metabolic changes decrease the activities of NK, INKT, T and B cells, which compromise the antiviral immune response in COVID-19.

NK cells are effector lymphocytes of the innate immune system, which recognize and destroy infected cells through production of cytotoxic molecules, such as granzymes and perforins, fragment receptor ligand (FasL), and TNF-related apoptosis-inducing ligand (TRAIL). NK cells recognize infected cells marked with antibodies through Fc receptors and destroy them through antibody-dependent cellular cytotoxicity (ADCC) (Figure 4). In obesity, the number of NK cells is increased in visceral adipose tissue due to local cell proliferation (90) however, NK cells activity is reduced (91). There is reduced expression of activating receptors KIR2DS4 and Nkp46, increased expression of inhibitory receptor NKG2A, and decreased TRAIL expression on NK cells (92). This suppression is related to the
energy metabolism disorder in NK cells in obesity (27,93). NK cell activity is highly dependent on
glycolysis, which is inhibited in obesity by the increased activity of peroxisome proliferator-activated
receptors (PPARs) (27). Glycolysis inhibition together with other changes, such as excessive exposure
to FFA and IL-6, may inhibit NK cell production of granzyme B and perforin in obesity(94). In
summary, NK cell function is reduced in obesity through metabolic reprogramming and glycolysis
inhibition.

iNKT cells are a subset of T lymphocytes that co-expresses NK-lineage receptor and an invariant
T-cell receptor. iNKT cells are in high abundance in adipose tissue and sense lipid-related antigens
presented by adipocyte. iNKT cells produce perforin and Fas ligand to generate cytotoxic effects on
virus-infected cells (95) (Figure 4). iNKT cells may secret cytokine IL-4 to regulate other immune cells.
In obesity, the number of iNKT cells is decreased in adipose tissue (96) contributing to impaired virus
immunity in obesity.

Cytotoxic CD8⁺ T lymphocytes play an important role in the adaptive immune response by
eliminating virus-infected cells through perforin and granzyme released in an antigen-specific
manner (Figure 4). However, the numbers of CD8⁺ T and CD4⁺ T lymphocytes are decreased in the
circulation of patient with severe COVID-19. CD8⁺ T cells require INF-γ and IL-2 secreted from CD4⁺ T
lymphocytes to activate and proliferate. Decreased numbers of CD4⁺ T lymphocytes in obese
patients with COVID-19 leads to lower levels of circulating INF-γ and IL-2 cytokines and decreased
activation of CD8⁺ T cells(97) (98). CD4⁺ T cell alterations from metabolic disorders in obesity along
with increased T cell exhaustion and reduced T cell proliferation lead to reduced levels of circulating
T cells(99). Therefore, obesity impairs the adaptive immune responses in COVID-19 by causing
metabolic disorders in CD4⁺ and CD8⁺ T cells.

B lymphocytes produce antibodies in the humoral immune response to virus infection. The
antibodies mark virus antigens for neutralization and elimination and involves complement-
dependent cytotoxicity (CDC) and ADCC in the clearance of infected cells (Figure 4). In obesity there
is inhibition of deaminase activation, leading to B cell inability to produce antibodies, compromising
humoral immunity(100). In addition, B cells produce more pro-inflammatory cytokines in obese
subjects further contributing to immune disorder in COVID-19 (101,102). B cells suffer functional
deficiency in obesity, increasing the risk for severe COVID-19 infection and cytokine storm.

5. **Macrophages contribute to the cytokines storm**

Chronic low-grade inflammation is a well-established characteristic of obesity, in which white adipose
tissues, especially visceral fat deposits, are the major players (103). The inflammation is featured by an
increased number of macrophages, regulatory T (Treg) cells, and eosinophils in the adipose tissue.
Subpopulations of macrophages are altered with a decrease in M2-like macrophages (alternatively activated macrophages) and an increase in M1 macrophages. This alteration leads to a reduction in anti-inflammatory cytokines, such as IL-10, IL-4 and IL-13 (Figure 5) and an elevation in pro-inflammatory cytokines contributing to sustained low-grade inflammation. The response induces neutrophil infiltration followed by accumulation of pro-inflammatory CD8^+ T cells and CD4^+ Th1 cells. These cells further increase the levels of TNF-α, IL-1, IFN-γ, and IL-6 to exacerbate the existing inflammatory state to culminating into cytokine storm (Figure 5).

A cytokine storm is a quick and robust release of pro-inflammatory mediators following an inappropriate immune response to antigens. Severe COVID-19 cases are associated with an uncontrolled immune response leading to an immense elevation of pro-inflammatory (INF-γ, TNF-α, IL-6, and IL-8, etc.) and anti-inflammatory cytokines (IL-10, IL-4, etc.) (104). The cytokine storm is closely associated with severe COVID-19 and responsible for multiorgan failure (105,106). Infection further adds to the already elevated levels of cytokines in obesity and increases the risk of cytokine storm in severe COVID-19.

6. Adipokines in severe COVID-19

Several studies suggest significant roles of adipokines/hormones in severe COVID-19 (107). Adipokines, such as leptin and adiponectin, are produced by adipocytes to maintain the energy homeostasis in physiological conditions.

Leptin levels are elevated in the circulation of obese subjects resulting in hyperleptinemia and leptin resistance (108). Leptin is a pro-inflammatory adipokine that activates macrophages and T cells resulting in expression of TNF-α, IL-1β, and IL-6 (109). The protein structure of leptin is similar to that of other proinflammatory cytokines including IL-6, IL-11, IL-12, G-CSF, etc., which may permit cross-talk of these cytokines with the leptin receptor (109,110). Increased leptin contributes to chronic low-grade inflammation in obesity (Figure 5) and obesity-related complications. A study found that COVID-19 patients with higher levels of serum leptin were more likely to require mechanical ventilation over the control group (111). The hyperleptinemia may increase the risk of cytokine storm by induction of super-activation of immune cells. However, this role of leptin remains to be tested in experiments. If proven, pharmacological interference of leptin may be considered in the treatment of obese COVID-19 patients.

Adiponectin is one of the most abundant proteins in the serum. Its level is reduced in obesity. In contrast to leptin, adiponectin has an anti-inflammatory activity, which induces expression of anti-inflammatory cytokine IL-10 and inhibits expression of pro-inflammatory cytokines like TNF-α and IL-6. Adiponectin deficiency in obesity is associated with an exaggeration of inflammation. A study for
screening glucoregulatory hormones revealed that adiponectin level is also reduced in the circulation of COVID-19 patients (81). Hamsters infected with SARS-CoV-2 exhibited a strong antiviral response in adipose tissue with a reduced expression of adiponectin (81). The exact role of adiponectin remains to be investigated in COVID-19 although it is considered beneficial in the control of severe COVID-19 (112).

7. **Dysfunctional mitochondria in cytokine storm**

Mitochondria produce 90% of the ATP and ROS in cells for execution of various cellular activities (113). According to classical biochemical principles, ATP is produced on demand and intracellular ATP levels are maintained at a set point between 1.5-2.5 mM in a cell type-dependent manner. However, over supply of energy materials including glucose, fatty acids, and amino acids in obesity leads to “mitochondrial overheating” and ATP overproduction in cells (114). The extra ATP causes mitochondrial dysfunction by inhibiting mitochondrial biogenesis and mitophagy, which are essential in the maintenance of the quality and quantity of mitochondria. Dysfunctional mitochondria predispose to more mtROS production, oxidative stress, and exposure of mitochondrial DNA (mtDNA) in the cytoplasm. mtROS and mtDNA both promote inflammatory responses and immune dysregulation (Figure 6).

In the course of SARS-CoV-2 infection, oxygen supply is reduced in the peripheral tissues due to structural damage in the lungs by the viral infection. Hypoxia causes energy metabolism reprogramming in mitochondria with shift from oxidative phosphorylation towards glycolysis (113). The mechanism is related to activation of the hypoxia signaling pathway including the hypoxia inducible factor 1 (HIF-1). The metabolic reprogramming may lead to an increased production of mtROS and mtDNA through HIF-1 activation, which in turn promotes the inflammasomal activation for IL-1β and IL-18 release, all contributing to the pathogenesis of cytokine storm. The NLRP3 inflammasome, containing the pyrin domain-containing protein 3 (NLRP3), is activated by several mitochondrial ligands, such as mtDNA, ATP, and mtROS (115). After NLRP3 activation, an adaptor protein of apoptosis-associated speck-like protein (ASC) recruits pro-caspase-1 to the inflammasome. Caspase-1 cleaves pro-IL-1β and pro-IL-18 to generate the mature cytokines for secretion (Figure 6).

Mitochondrial DAMPs (mtROS and mtDNA) are important factors in the cell detection of infection. However, the pathway may cause an undesirable immune response resulting in unwanted inflammation in certain conditions, such as obesity. In obesity, mitophagy is defective leading to accumulation of damaged mitochondria and release of mitochondrial DAMPs into the cytosol. Accumulation of DAMPs triggers an uncontrolled pro-inflammatory response in obesity, which is
further enhanced in COVID-19. This may contribute to progression to severe cases with cytokine storm in obese COVID-19 patients.

The mitochondrial dysfunction may also contribute to cytokine storm through production of intermediate metabolites of the TCA cycle. One example is α-ketoglutarate (α-KG), which plays an important role in the pro-inflammatory response. α-KG is found to be elevated in macrophages after lipopolysaccharide (LPS) stimulation and plays a role in the production of cytokines. Elevation of α-KG levels have been reported in T cells in rheumatoid arthritis (116). LPS levels in the circulation and α-KG levels in the liver of obese mice are elevated (117), which supports a role of α-KG in the pro-inflammatory response in obesity. Succinate is another example of a proinflammatory metabolite of the TCA cycle. Succinate elevation promotes macrophage activation and production of pro-inflammatory cytokines (118). Succinate is elevated in the circulation of obese mice and patients with T2DM and promotes inflammation through succinate receptor (SUCNR1) (119). In addition, protein modification by succinylation is another mechanism in the regulation of the inflammatory response. Therefore, the increased levels of mitochondrial metabolites (α-KG and succinate) may contribute to cytokine storm in the pathogenesis of severe COVID-19 in obese patients.

8. Impact of obesity in the treatment and prevention of COVID-19

Given the strong impact of obesity in the immune system, obesity may negatively affect the treatment and prevention of COVID-19. To control the negative effects, weight loss is the first choice, which may be achieved through behavioral modifications including calorie restriction, physical activity, or exercise training.

Adequate nutritional status is an essential element for antiviral defense. In a systematic review, vitamins (A, C, D and E), omega 3 fatty acids, and minerals (zinc and iron) were found to be fundamental for an adequate antiviral immune response to SARS-CoV-2 (120). Obesity is recognized as a vitamin deficient state despite energy surplus. In particular, the prevalence of vitamin D deficiency is 35% greater in obese individuals (121). Vitamin D deficiency also increases the risk of severe COVID-19, especially in the obese population (122). However, vitamin D supplementation as prevention and adjuvant therapy for COVID-19 is controversial. Studies have concluded that there is no evidence to support taking vitamin D supplements in COVID-19 (123), and at present, there is no consensus for vitamin D supplementation in the prevention or treatment of COVID-19. Adherence to existing public health advice on vitamin D supplementation is recommended to prevent vitamin D deficiency and maintain bone and muscle health during the COVID-19 pandemic.

Vaccination is the best choice for the prevention and control of COVID-19. In fact, obesity may reduce the efficacy of vaccination against SARS-CoV-2 because of immune cell dysfunction. Reduced
efficacy of the influenza vaccine has been observed in obese individuals. One study including 21 patients suggests that obesity is associated with a reduced adaptive immune response to a COVID-19 mRNA vaccine, which can be reversed with weight loss (124). Current evidence shows that three major brands of SARS-CoV-2 vaccines, such as Pfizer-BioNTech BNT162b2, Moderna mRNA-1273, or Janssen/Johnson & Johnson Ad26.Cov2.s, have similar efficacy between obese and non-obese individuals (COVID-19 vaccines are effective in people with obesity: A position statement from The Obesity Society. Obesity, 29(10):1575-1579, 2021). However, analysis of the efficacy of SARS-CoV-2 vaccines in obesity and selection of adequate vaccines should continue to be considered in the future.

For COVID-19 patients with obesity, guidelines for supportive treatment and intensive care have been well established (125). Efficacy of antiviral medication may be reduced in obese patients. Hydroxychloroquine was reported to interfere with the replication cycle of SARS-CoV2 and reduce viral entry. However, recent studies did not show that hydroxychloroquine administration was associated with a significant reduction in the end point of incubation or death rate during COVID-19 treatment (126). Lopinavir/ritonavir, inhibitors of 3-chymotrypsin-like protease that involves in viral ribonucleic acid processing, was previously used as the first line antiviral agent in the treatment of COVID-19. The medicines have side effects including lipodystrophy and hyperlipidemia. However, the efficacy of lopinavir/ritonavir has come into question as multiple studies did not find it to reduce mortality significantly (127). The conclusion that lopinavir/ritonavir combination was no better than standard care in the treatment of COVID-19 patients still remains (128). However, favipiravir shows promising efficacy in COVID-19 patients with improvement in clinical parameters such as length of hospitalizations and clinical recovery, although the results were not confirmed in some studies (127). In this case, antidiabetic agents such as DDP4 inhibitors, GLP-RA, and antiviral agents (e.g. Favipiravir) are all considered for COVID-19 treatment.

**Concluding Remarks**

In this review, we discuss mechanisms by which obesity contributes to the high mortality of obese COVID-19 patients with a focus on adipose tissue. Accumulation of adipose tissue around the chest and in the peritoneal cavity generates a mechanical pressure that restricts the respiratory capacity of the lungs. The restriction promotes systemic hypoxia in the presence of parenchyma damage by viral infection. The hypoxia exuberates the metabolic and immunologic disorders that preexist in obesity, such as accumulation of intermediate metabolites, chronic inflammation and hyperleptinemia. Hypoxia inhibits mitochondrial respiration and promotes metabolite accumulation inside of cells. This induces gene transcription and enhances the inflammatory response through
adipocyte secretion of leptin. The elevated levels of the metabolites, leptin and cytokines, may amplify the hypoxia signal in macrophages and T cells leading to cytokine storm. ATP overproduction in multiple cell types in obesity leads to inhibition of autophagy by inactivation of AMP-activated kinase (AMPK). This leads to mitochondrial degeneration, more production of mtROS, and more exposure of mtDNA. The TLR and STING pathways may sense mtDNA in macrophages and T cells to favor cytokine production. Metabolic disorders in adipocytes and immune cells cause restriction of their immune responses to viruses such as SARS-CoV-2. In endothelial cells and platelets, metabolic disorders in combination with the cytokine storm may cause circulation defects for multiorgan failure. Additionally, adipose tissue may serve as a reservoir for the SARS-CoV-2 virus and promote virus spreading. ACE2 and DPP4 elevation in obesity may promote virus entry into host cells for increasing risk for severe infection. In summary, metabolic disorders from energy surplus occur in various cell types in obesity and serve as a foundation for the increased risk of cytokine storm and multiorgan failure in severe COVID-19. Correction of energy surplus by weight loss through various approaches is recommended in the prevention and treatment of COVID-19 in obese patients.

**Data availability statement:** The data used to support the findings of this study are included within the article and supplemental materials.
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**Figure legends**

**Figure 1.** The potential mechanistic links between obesity and COVID-19 severity from physiologic changes, comorbidities, immune system impairment, and adipose tissue dysfunction.

**Figure 2.** SARS-CoV-2 and surface receptors on adipocytes.

The main structural proteins of SARS-CoV-2 include the spike (S), membrane (M), nucleocapsid (N), and envelope (E) proteins. The cellular angiotensin-converting enzyme 2 (ACE2) exopeptidase acts as a receptor for SARS-CoV-2 spike protein binding. Subsequent cleavage of the spike protein by cellular transmembrane serine protease 2 (TMPRSS2) results in membrane fusion and viral entry. DPP4 acts as another receptor for SARS-CoV-2 cell entry. Obesity-induced overexpression of ACE2, TMPRSS2, and DPP4 result in more virus entry into adipocytes. Glycosylation (G) of ACE2 on adipocytes and S proteins on viruses increases the binding activity. Augmented lipid rafts supplied by cellular cholesterol also increases binding between ACE2 and the S protein further facilitating viral entry.

**Figure 3.** Suppression of antiviral responses by viral components in adipocytes.

Various pattern recognition receptors, including TLR7/8, MDA5/RIG-I, and STING, mediate innate antiviral responses. TLR7/8 senses single stranded RNA leading to activation of IRF7 and expression of IFN-α/β through the Myd88-dependent pathway; RIG-I and MDA5 detects double stranded RNA during viral replication leading to activation of IRF3 and IRF7 and expression of IFN-α/β through MAVS; STING binds with MAVS to activate IRF3/IRF7, thereby allowing crosstalk between the RNA and DNA sensing pathways. These processes can be inhibited by SARS-CoV-2-derived non-structural protein (Nsp)16, Nsp3, and Nsp1.

**Figure 4.** Obesity suppresses the crosstalk between infected adipocytes and immune cells.

Various immune cells including NK, iNKT, T and B cells, reside in the extracellular matrix of adipocytes to constitute local antiviral immunity. NK recognize virus-infected adipocytes through activating receptors and destroy the cells through cytotoxicity, FasL, TRAIL and ADCC. Cytotoxic T cells recognize antigens presented by MHC-I molecules on virus-infected cells in an antigen-specific manner. They kill the infected cells by releasing cytotoxic enzymes and induce TRAIL and FasL to bind
with targets. NKT cells sense lipid-related antigens presented by CD1 in adipocyte and produce cytotoxic effects and FasL to promote virus-infected cell death. The antiviral function of B cells is dependent on antibody secretion. Antibodies neutralize antigens and mark them for elimination, through the process of CDC and ADCC. The functions and numbers of these cells are suppressed by obesity.

**Figure 5.** Obesity-associated chronic inflammation and adipokines contribute the cytokine storm in COVID-19.

In the lean state, the adipose tissue microenvironment is a well-balanced crosstalk between the adipocyte and immune cells, including Treg cells, eosinophils, iNKT cells. M2-like resident macrophages predominate to maintain the homeostasis. These cells secrete anti-inflammatory cytokines, such as IL-10, IL-4 and IL-13. Balanced levels of leptin and adiponectin suppress pro-inflammation in an anti-inflammatory state. In obesity, hypertrophic adipocytes are characterized by a pro-inflammatory phenotype. Early transient infiltration of neutrophils is followed by infiltration and accumulation of pro-inflammatory CD8+T cells, CD4+ Th1 cells and M1 macrophages. The increased release of proinflammatory cytokines (TNF-α, IL-1, IFN-γ, IL-6) in the obese state adipose tissue microenvironment, increased leptin, and decreased adiponectin leads to a high inflammatory state and results in chronic low-grade systemic inflammation.

**Figure 6.** Dysfunctional mitochondria in obesity stimulate inflammasome activation.

Obesity induces mitochondria overheating to cause extra ATP production, which eventually results in mitochondrial dysfunction. Dysfunctional mitochondria predispose to more mtROS production and exposure to mtDNA. Mitochondrial ligands, such as mtDNA, ATP, and mtROS induces the activation of the NLRP3 inflammasome. After NLRP3 activation, an ASC adaptor protein recruits pro-caspase-1 to the inflammasome through CARD. After activation, caspase-1 cleaves pro-IL-1β and pro-IL-18 to IL-1β and IL-18 leading to their secretion.
Figure 1

SARS-CoV-2

Obesity

Basic Physical change
- hypoglycemia
- type 2 diabetes
- dyslipidemia
- vitamin D deficiency
- atherosclerosis
- hypertension

Comorbidities
- hyperglycemia
- obstructive sleep apnea

System immunity impairment
- innate immunity
- acquired immunity

Adipose tissue dysfunction
- ectopic fat deposition
- viral reservoir
- local immunity impairments
- chronic low-state inflammation
- abnormal production of adipokines
- mitochondrial and metabolic dysfunction

Clinical Manifestation
- Hospitalization
- ICU admission
- Invasive mechanical ventilation
- Mortality

adverse events
Figure 5

Lean state adipose tissue

M2 macrophage
Treg
Eosinophil
NKT
adipocyte
IL-4
IL-10
IL-13
Leptin
Adiponectin
Anti-inflammatory state

Contribution to Virus defense

Obese state adipose tissue

M1 macrophage
M2 macrophage
CD4+ T
Neutrophil
IL-6
IL-1
TNF-α
IFN-γ
Leptin
Adiponectin
Inflammatory state

Contribution to Cytokine storm
