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Pathways to Severe COVID-19 for People with Obesity

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Study Importance Questions

- What is already known about this subject?

- Obesity is a risk factor for severe COVID-19 disease

- What does your study add?

- We provide a broad overview of the potential mechanisms by which pulmonary physiology, metabolic dysfunction, adipose tissue biology, and inflammatory pathways may modify COVID-19 outcomes in people with obesity.

How might your results change the direction of research or the focus of clinical practice?

- Our review highlight gaps in clinical and research knowledge that need to be addressed to improve prevention and treatment of COVID-19 for people with obesity

Abstract

Increased morbidity and mortality from SARS-CoV-2 coronavirus disease (COVID-19) in people with obesity has illuminated the intersection of obesity with impaired responses to infections. While data is being rapidly generated on mechanisms by which COVID-19 impacts health, there is a critical need to better understand the pulmonary, vascular, metabolic, and immunologic aspects that drive the increased risk for complications from COVID-19 in people with obesity. In this review, we provide a broad overview of the intersection between COVID-19 and physiology of obesity to highlight potential mechanisms by which COVID-19 disease severity is increased by obesity, and to identify areas for future investigation towards developing tailored therapy for people with obesity who develop COVID-19.

Introduction

SARS-CoV-2 is the third highly pathogenic coronavirus to emerge in the past two decades, preceded by MERS-CoV in 2012 and SARS-CoV-1 in 2002. Age, obesity, and type 2 diabetes (DM) are established risks factors for Coronavirus disease (COVID-19) severity (1). Obesity has been identified as an independent risk factor for severe disease, admission, need for invasive mechanical ventilation, and

mortality from COVID-19 in cohorts from China, US, and Europe with an adjusted hazard ratio of 1.92 for COVID-19 related death if BMI > 40 kg/m^{-2} (2, 3). DM is closely linked to obesity, and at least two large retrospective studies identify DM as an independent risk factor for increased mortality with COVID-19 (3, 4). Dissecting the mechanisms by which obesity and DM independently contribute to COVID-19 disease risk is fraught with methodologic challenges (5), and these physiologic modifiers likely participate in complex interactions to potentiate disease.

Interestingly, obesity may be a protective factor for non-COVID-19 associated acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (6). Meta-analyses suggest that while people with obesity have an increased risk for progressing to ALI/ARDS compared to people without obesity, people with obesity also have a reduced risk for mortality from ALI/ARDS. Significant debate persists regarding potential confounders and mechanisms behind these associations (7). Furthermore, there is debate regarding if ARDS associated with COVID-19 is unique and different than non-COVID-19 ARDS (8, 9). Nonetheless, in light of the current pandemic, the links between obesity and COVID-19 severity beg the question, if obesity is a protective factor for non-COVID-related lung disease, why is COVID lung disease different in this respect? In other words, more globally speaking, what are the mechanisms by which obesity increases risk of COVID-19 disease severity and mortality?

In this review, we will summarize current theories regarding the intersection of COVID-19 disease and obesity physiology, with a focus on the pulmonary, metabolic, adipose tissue, and immune aspects of COVID-19 that may interface with obesity to shift the risk curve for mortality and morbidity towards more severe disease. We acknowledge that the rapid accumulation of new information about COVID-19 may clarify some of these mechanisms and refute others over time. However, we hope to broaden the framework for the discussion on obesity and COVID-19 and point out new areas for research.

Clinical Course of COVID-19

Core to understanding why people with obesity are more susceptible to morbidity from SARS-CoV-2 is identifying the keys steps of disease progression that lead to severe COVID-19 (Reviewed in (10, 11)). Coronaviruses are lipid membrane-enveloped, positive-sense, single-strand RNA viruses, named for the crown-like structure of spike proteins surrounding the virion observed under electron microscopy. In the early stages of infection, SARS-CoV-2 binds to nasal and bronchial epithelial cells where viral replication is initiated. SARS-CoV-2 binds the angiotensin converting enzyme 2 (ACE2) on the cell membrane, followed by cleavage of viral capsid spike (S) protein by the host transmembrane serine protease TMPRSS2, followed in turn by viral fusion and release of the viral nucleocapsid into the cell cytoplasm. The virus then utilizes host cell machinery to synthesize the viral replication/transcription complex, which associates with autophagosome-like intracellular double membrane vesicles. This

complex mediates replication, transcription, and translation of viral genomic RNA into structural and accessory proteins in the ER, followed by transport to the Golgi apparatus for virion assembly, budding, and release thru the cell plasma membrane (Figure 1).

Individuals in the early stages of infection (Stage 1) are asymptomatic and may only develop mild symptoms. Some will progress to more severe disease with symptoms of dyspnea (shortness of breath) and decreased oxygen saturation typically one week after symptom onset (Stage 2). This phase of illness is characterized by inflammatory lung infiltrates, pulmonary edema that appears as ground glass opacities on chest CT imaging, and signs of impaired gas exchange. Epidemiologically, severe COVID-19 is defined as dyspnea, tachypnea (respiratory rate >30 breaths per minute), blood oxygen saturation < 93%, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao2:Fio2) < 300 mm Hg, and/or infiltrates in more than 50% of the lung field (11). 14% of individuals present with severe COVID-19 and 5% become critically ill (Stage 3) with organ failure in association with markers of systemic inflammation (12).

A challenge in the field is to understand where in this disease progression from mild to severe disease does obesity leave its mark and shift patients towards severe disease (Figure 1). Are the antiviral responses that prevent progression from Stage 1 to Stage 2 disease impaired in people with obesity? Do differences in the sensation of dyspnea delay people with obesity from seeking care when in Stage 2? Do differences in the inflammatory responses to SARS-CoV-2 in critical illness in Stage 3 increase clinical severity in the context of obesity? And finally, can tailored clinical management for patients with obesity and severe COVID-19 impact outcomes?

Pulmonary Physiology in People with Obesity Relevant to COVID-19

People with obesity have multiple alterations in pulmonary physiology that may contribute to increased COVID-19 severity. Many individuals present in Stage 2 with profound hypoxemia without dyspnea, suggesting that COVID-19 may alter neuronal pathways important in the sensation of dyspnea. People with obesity and diabetes have been shown to have decreased ventilatory responses to hypoxia and hypercarbia (14), and impaired ventilatory drive is linked to increased susceptibility to severe COVID-19 disease (13). Therefore, with decreased sensation of respiratory difficulty, people with obesity may delay care or present with more severe disease.

Changes in pulmonary function in people with obesity include decreased functional residual capacity (FRC), increased pleural pressure, and reduced lung and chest wall compliance (15). Baseline mismatch of ventilation and perfusion (V/Q) is observed in individuals with severe obesity (16) and V/Q mismatch has been shown to be a significant component of the severe hypoxemia seen COVID-19 disease (17) suggesting another mechanism by which obesity may lead to more severe disease. The clinical

progression of lung disease in COVID-19 has been described to progress from an "L" phase with low elastance (high compliance), low V/Q ratio, and low lung weight that progresses to an "H" phase in 20-30% of patients characterized by high elastance (low compliance), right-to-left shunt (decreased perfusion of unventilated areas), and high lung weight (18). In many ways, people with obesity are predisposed to pulmonary mechanics associated with "H" phase characteristics (low compliance, higher V/Q mismatch), potentially making them more susceptible to progression to more severe disease.

Another potential reason for worse outcomes may be due to lack of evidence-based tailored approaches to ventilator management of people with obesity once they progress to ARDS. The NIH NHLBI ARDS Network (ARDSNet) has made a significant impact on ventilator management of patients with ARDS by standardizing protocols based on large randomized clinical trials (19). Unfortunately, severe obesity (BMI >35 kg/m^2) has been an exclusion criterion for many ARDSNet studies, leading to significant gaps in the understanding of how to best manage patients with obesity using evidence-based approaches. Some groups have employed specialized ventilator management teams for individuals with class III obesity and ARDS to titrate care based on more in depth pulmonary measures of compliance and pleural pressures that has been shown decreased mortality compared to standard ventilator management (20). As we learn more about respiratory management in COVID-19, there will likely be need to tailor management to the unique physiology of people with obesity.

Dysregulated Pulmonary Responses To Infection In Obesity

While the mechanisms underlying the association between ARDS and obesity are unknown, multiple studies have identified molecular characteristics of the lungs of individuals with obesity relevant to COVID-19. Lungs from patients who died from COVID-19 ARDS demonstrate pulmonary thrombosis and vascular angiogenesis that are unique compared to ARDS without COVID-19, suggesting that pulmonary small vessel disease may be a key contributor to mortality (21). Supporting this, COVID-19 individuals with elevated D-Dimers, a marker of thrombosis, and poor lung compliance have a higher mortality rate than those with low D-Dimers and normal lung compliance. This suggests an interaction between pulmonary physiology and thrombosis that contributes to COVID-19 mortality. (22) The link between obesity and endothelial dysfunction is well recognized, but gaps exist in our understanding of the effect of obesity on pulmonary vascular biology.

Rodent models of obesity and diabetes demonstrate that hyperglycemia increases pulmonary vascular permeability, inflammation, and remodeling that may exacerbate COVID-19 lung inflammation (23). Mouse models suggests that circulating factors from obese mice and free fatty acids upregulate endothelial cell adhesion molecules and worsening LPS induced acute lung injury potentially through ER stress (24). Mouse models of MERS-CoV infection reveal altered kinetics of perivascular inflammation in

high fat diet and diabetic mice that ultimately results in a more severe inflammatory response in the lungs of obese mice (25). Early stages of infection are associated with a decrease in lung monocytes and T cells. In the later stages of illness, pulmonary inflammation persists longer after infection in diabetic mice compared to non-diabetic independent of viral load. These findings suggest that obesity blunts early host inflammatory responses to MERS-CoV infection in the lung, ultimately impairing resolution of inflammation and thus leading to severe disease.

Interactions between infected pulmonary epithelial cells and inflammatory leukocytes control the degree and nature of the pulmonary inflammatory response. Single cell RNA sequencing studies comparing mild and severe disease demonstrate that COVID-19 is associated with induction of ACE2 expression in bronchial epithelial cells that correlates with interferon responses (26). Bioinformatic evaluation of chemokine ligand-receptor networks suggested that COVID severity was associated with increased epithelial-macrophage communication. Obesity is associated with increased ACE2 expression on bronchial epithelial cells patients with COPD, suggesting that obesity may potentiate SARS-CoV-2 entry and inflammation (27).

Glucose Metabolism and COVID-19

Viral infection has diverse effects on host cellular metabolism. Decades ago it was observed that influenza virus infection induces a shift in cellular metabolism towards a glycolytic phenotype (28); more recent data demonstrate that inhibition of glycolysis reduces influenza virus infection in *in vitro* cell culture models and in human bronchial epithelial cells *in vivo* and *in vitro* (29). The effects of viral infection on glucose metabolism are complex, and include maladaptive responses that enhance viral replication, along with adaptive responses that potentiate host immunity. For example, in a murine model of acute cytomegalovirus (CMV) infection, lean animals maintained glycemic control due to compensatory hyperinsulinemia that directly potentiated $CD8^+$ T cell-mediated antiviral immunity. Pre-diabetic obese animals, in contrast, responded to viral infection with loss of glycemic control, demonstrating that similar responses in the context of pre-diabetes can tip systemic metabolism towards frank diabetes with attendant adverse effects (30). Human data support these observations, with acute viral infection inducing systemic skeletal muscle insulin resistance in healthy humans without resulting in hyperglycemia (30), while in contrast, persons with obesity and/or diabetes are at risk for loss of glycemic control and DM complications in response to influenza infection (31).

Poor glycemic control has been identified as a risk factor for mortality with COVID-19 (4). Obesity and DM may contribute to COVID-19 risk by placing patients at increased risk for loss of hyperglycemic control and DM complications in response to viral disease. SARS-CoV-2 also appears to have direct effects on cell metabolism that may enhance infection or promote inflammation. SARS-CoV-

2 infection of monocytes induces a shift towards a glycolytic cellular metabolic phenotype that promotes viral replication, enhances inflammatory cytokine release from monocytes, and impairs T-cell function (32). SARS-CoV-2 therefore appears to have multiple effects on glucose metabolism at both cellular and systemic levels that act to potentiate disease. Given data implicating dysregulation of glucose metabolism in COVID-19 and increased disease severity in DM patients, tight glucose control has been recommended for DM patients with COVID-19, although certain hypoglycemic drugs, such as metformin and SGLT2 inhibitors may be contraindicated due to risks of acidosis (33). Nonetheless, metformin has been linked to reduced mortality in COVID-19 infections in three large observational studies to date (34, 35). Multiple mechanisms have been proposed for these effects, including improvement in glucose control and insulin resistance, activation of AMPK signaling with reduced ROS formation, and anti-inflammatory effects among others (36). PPAR-γ agonists (thiazolidinediones, TZDs) have also been suggested as therapy for COVID, and have been shown to reduce mortality in patients with non-COVID viral lung disease (37). In addition to hypoglycemic effects, TZDs have important anti-inflammatory properties which may reduce cytokine storm.

Lipid Metabolism and COVID-19

Numerous studies provide a snapshot of the metabolic effects of COVID-19, and we are struck by the significant parallels between the dysregulation of metabolites in COVID-19 and in people with obesity independent of viral infection. Such overlap suggests that patients with obesity represent a vulnerable metabolic phenotype with respect to COVID-19 due to specific pre-existing metabolic derangements that predispose to efficient viral infection and replication and are amplified by SARS-CoV-2 infection.
As such, we posit that individuals with pre-existing metabolic derangements related to obesity and diabetes experience a further exacerbation of similar derangements induced by COVID-19. The additive effects of these insults make patients with obesity more likely to reach a threshold beyond which severe disease ensues. Proteomic and metabolomic analysis of sera from patients with or without COVID-19 demonstrated dysregulation of macrophage signaling, platelet degranulation, and complement system pathways, along with decreased levels of glycerophospholipids, sphingolipids, and fatty acids, molecules critical for lipid raft formation required for SARS-CoV-2 cell entry (38). In a separate mass spectrometry study, the plasma lipidome of COVID-19 patients, relative to healthy controls, was characterized by increased levels of monosialodihexosyl ganglioside (GM3) and increased GM3-exosomes, levels of which correlated directly with disease severity and indirectly with $CD4^+$ T-cell counts (39). In addition, reduced levels of acylcarnitines and tricarboxylic acid cycle metabolites, progressive reductions in circulating polyunsaturated phosphatidylcholines (PUFA-PCs),which correlated with increasing COVID-19 disease severity, and increased levels of sphingomyelins were noted in severe COVID-19 disease.

Metabolic Derangements Common to Obesity and COVID-19

While the mechanistic significance of these alterations remains unclear, many serum lipidome and metabolome changes observed in COVID-19 parallel similar observations in other viral diseases and are also independently associated with obesity and DM, suggesting potential mechanisms linking obesity to COVID-19 disease severity. For example, increased GM3-exosome membrane composition is notably also seen in Ebola virus disease (40), and the observed negative correlation between GM3-exosomes and $CD4^+$ T-cell counts in COVID-19 suggests that GM3-exosomes may mediate communication between viral-infected cells and immune cells with immunosuppressive effects on T-cells. Similarly, the observed lower serum levels of acylcarnitines, tricarboxylic acid cycle metabolites, and fatty acids in COVID-19 patients is consistent with decreased entry of fatty acids into mitochondrial β-oxidation pathways and defects in oxidative cellular energy metabolism, pathways well-documented to be impaired in obesity independent of COVID-19 (41). The observed decreased levels of PUFA-PCs in COVID-19, which are associated with HDL synthesis, similarly implicate aberrations in HDL synthesis as a risk factor for severe COVID-19 disease, a pathway also known to be dysregulated in obesity independent of infection (42). Furthermore, decreases in PUFA-PCs are also associated with ARDS mortality independent of COVID-19 and obesity (43). The dysregulation of sphingolipids and sphingomyelins in SARS-CoV-2 infection are of interest, as these lipid moieties, critical to viral entry through lipid rafts, are increased in plasma lipidomic studies in obesity and DM independent of infection (44). Finally lysophosphatidylcholines, which play diverse roles in regulating intracellular trafficking in all cells as well as specific roles in regulating endothelial cell function, inflammation, and cholesterol synthesis (45), are increased in COVID-19 sera (39), and these lipid moieties are also dysregulated in sera from patients with obesity and DM (46).

ACE2 and TMPRSS2 proteins localize to cholesterol- and sphingolipid-rich lipid rafts in the cell plasma membrane, which are required for efficient infection, suggesting targeting these lipid moieties. Cholesterol-depleting agents such as methyl-β-cyclodextrin reduce infection by type I feline coronavirus, parainfluenza virus, and SARS-CoV-1 replication in cell culture models (47). Statins have also been proposed as potential treatment, and while data regarding their use for a wide range of infectious diseases in heterogeneous patient populations are mixed, a number of studies suggest efficacy (48, 49). Other drugs that regulate cholesterol and fatty acid synthesis and trafficking, including amiodarone, haloperidol, Orlistat, and Triacsin C, show promise as off-label antiviral agents in *in vitro* models of coronavirus infection (50). More targeted therapy may result from ongoing lipidomic and metabolomic studies. For example, Yan et al. used UPLC–MS lipidomics to demonstrate perturbed levels of glycerophospholipids and fatty acids including arachidonic acid in an *in vitro* model of HCoV-229E-infection of Huh-7 and

VeroE6 cells, and showed that exogenous supplement of arachidonic acid inhibited viral replication in this model as well as in a similar model of MERS-CoV infection (51). Along similar lines, the FDA-approved "sphingomimetic" drug FTY720 is currently being studied as treatment for COVID-19 in clinical trials (NCT04280588-ClinicalTrials.gov) (52).

Adipose Tissue as a Target For SARS-Cov-2 Infection

Adipose tissue plays a central role in metabolism, immune, and endocrine function, and as such is a prime candidate for regulating metabolic and inflammatory responses to viral infection. Adiposity, specifically visceral adiposity which is strongly linked to metabolic disease, has been identified as a risk factor for COVID-19 disease severity (53), yet underlying mechanisms remain poorly defined. Adipose tissue may serve as a direct target for SARS-CoV-2 and SARS-CoV-2 RNA can be detected in visceral (omental) adipose tissue of humans with COVID-19 (54), but whether infectious virions are present remains unknown. Precedent for direct adipotropy of other viral infection exists: H5N1 targets white adipose tissue and is adipotropic in murine models (55), while CMV, adenovirus, and RSV infect adipocytes *in vitro* (56). Influenza A, while predominantly targeting airway epithelial cells, infects immune and non-immune cells as well, including preadipocytes, in mice (57). Other data demonstrate infection of non-adipocyte adipose tissue resident cells by multiple viruses, including adipose tissue macrophages (ATM) and lymphocytes by influenza, adenovirus, and HIV (56, 58, 59). ACE2 expression is high in adipose relative to other tissues (60), adipocyte expression of ACE2 is upregulated in obesity and DM, and increased expression of ACE2 in adipose tissue has been linked to worse clinical outcomes with COVID-19 (61, 62). In sum, these observations suggest a potential mechanism for SARS-CoV-2 viral adipotropy. If adipose tissue is a reservoir for persistent SARS-CoV-2 infections in people with obesity, anti-viral and vaccine approaches to combat disease may have to be titrated based on adiposity.

A heightened state of inflammation is a dominant feature of adipose tissue as adipocytes, preadipocytes, and adipose tissue leukocytes, most notably ATM, are a source of inflammatory cytokines *in vivo* . Other viral infections increase adipose tissue inflammatory cytokine release. Adenovirus-36, RSV, or CMV infection induces increased adipocyte IL-6 cytokine secretion *in vitro* (56), which is further increased in the presence of co-culture with macrophages, suggesting that adipose tissue resident leukocytes synergize with adipocytes potentiate cytokine expression . Visceral adipose tissue, relative to subcutaneous adipose tissue, secretes higher levels of inflammatory cytokines independent of obesity, including TNF-a, IL-6, and IL-1b (63), all cytokines implicated in COVID-19 cytokine storm. These observations suggest that increased inflammatory cytokine expression from VAT in obesity may contribute to cytokine storm and increased COVID-19 severity.

Viral infection may regulate adipocyte browning as well. Influenza A infection of murine 3T3L1 adipocytes induces browning, with upregulation of *Ucp1*, *Pgc1a*, *Fgf21*, *Apln*, and *Tmem26* (57). Irisin, an adipokine that induces browning, reduces adipocyte expression *in vitro* of a number of genes that are induced in the lung by COVID infection, including *FURIN, ADAM10, TLR3, KDM5B, SIRT1* and *TRIB3* (64). Interferon (IFN) and interferon-response genes play a critical role in viral defense and are specifically implicated in host responses to coronaviruses (65), and have been implicated in browning as well, with some IFN-response genes promoting (Ifi27) (66) while others inhibit (IRF3) (67) adipocyte browning. The directionality of IFN effects on browning thus depends on the specific mediators involved. IL-6, a key mediator of COVID-related cytokine storm (68, 69), is increased in serum and adipose tissue in obesity (70), and also promotes browning in adipocytes (71). Whether adipocyte browning is an adaptive or maladaptive response to viral-induced inflammation remains unclear, but it is possible that browning may be an adaptive response that potentiates IFN and IL-6-mediated immune responses within adipose tissue. Alternatively, browning may potentiate excessive cytokine release (e.g. IL-6, secretion of which from WAT is increased in browning (71), and contribute to disease severity, depending on the phase of infection. Further research will clarify these issues, but these observations suggest that adipocyte browning-inflammation crosstalk plays a role in host response to viral infection.

While much attention focuses on canonical white adipose tissue anatomic depots, including visceral and subcutaneous sites, ectopic adipocytes, which are present in most tissues and increased in obesity, may also be a target for SARS-CoV-2. Epicardial adipose tissue has been suggested as a target for infection and a contributor to COVID-associated myocarditis (72), although data directly demonstrating viral infection of this adipose tissue depot to date is lacking. Excess perinephric adipose tissue and liver steatosis are risk factors for disease severity in young COVID-19 patients (73). De-differentiation of dermal adipocyte-like cells into lipofibroblasts contribute to fibrosis in fibrotic skin disease, and investigators have suggested that similar de-differentiation of pulmonary adipocyte-like cells may contribute to COVID-19 disease severity by promoting pulmonary fibrosis (74). Interestingly, in a separate study, leptin has been shown to promote fibrosis in a murine model of ARDS (75), suggesting a role for fibrosis in mediating lung disease in obesity. While direct evidence implicating pulmonary lipofibroblasts or leptin in COVID-lung disease is so far lacking, ectopic adipocytes are increased in multiple tissues in obesity, and may contribute to disease severity through multiple mechanisms including but not limited to fibrosis.

Adipose tissue-based therapy for COVID-19 is an active area of research. Specifically, adipose tissue stem cells, aka preadipocytes, are a type of mesenchymal stem cell (MSC) with diverse immunomodulatory, anti-inflammatory, and regenerative properties. MSC therapy for COVID is under active study. Over 30 clinical trials are currently in progress studying MSC therapy for COVID-19 (76,

77), of which at least 5 study adipose tissue MSC (NCT04313647, NCT04276987). To date, clinical efficacy has not been demonstrated, but trials have yet to mature. Any putative therapeutic effects of adipose tissue MSC may not be adipose tissue-specific, as multiple data suggest that MSC from other tissues have diverse therapeutic potential. Further research will be necessary to clarify this issue in COVID-19 disease. Nonetheless, adipose tissue represents a readily available source of expandable MSC that has potential as a therapeutic tool.

Obesity-Induced Inflammation as a Potentiator of COVID-19 Disease

The biphasic clinical course of severe COVID-19 from initial mild symptoms to progression toward ARDS suggests dysregulation of the immune response to viral infection. IFN responses are crucial to antiviral responses and impaired production of type 1 interferons is a feature of severe COVID-19 (78). Further emphasizing the importance of proper IFN production, patients with severe COVID-19 have been found to harbor neutralizing auto-antibodies to IFN and to be enriched for loss of function mutations in genes critical for proper IFN signaling (79, 80). Estimates suggest that innate defects in IFN production may account for up to 14% of individuals with severe COVID-19. The importance of IFN in COVID-19 intersects with the observations of impaired IFN responses to immunologic stimuli seen in people with obesity that is believed to contribute to inability to mount proper antiviral immunity.(81) Leptin has been shown to impair IFN responses via SOCS3, suggesting a potential mechanism by which obesity and dysfunction IFN responses are linked (82).

Broad evidence indicates that severe COVID-19 disease is associated with amplified inflammatory responses in both innate and adaptive immunity that contributes to disease severity. Single cell profiling of bronchoalveolar lavage fluid (BALF) from patients with COVID-19 indicate an abundance of monocyte-derived macrophages and neutrophils in severe disease and an association of clonal $CD8^{+}$ T cells in BALF with moderate disease (83). In serial analysis of blood samples from a range of COVID-19 severity, severe COVID-19 was characterized by a disappearance of non-classical $CD14^{Low}CD16^{High}$ monocytes, accumulation of $HLA\text{-}DR^{Low}$ classical monocytes, the generation of immature neutrophils, and the upregulation of calprotectins (S100A8/S100A9) (84). Early COVID-19 disease is associated with exaggerated myeloid activation in the blood identified by an elevated neutrophil/lymphocyte ratio at presentation for those who progress to severe disease with evidence of emergency hematopoiesis, elevated number of $Ki\text{-}67^{+}$ monocytes (85). Therefore it is clear that severe COVID-19 is associated with both qualitative and quantitative alterations in peripheral blood monocytes and neutrophils that may represent exaggerated inflammatory responses and contribute to disease severity. These observations align with the longstanding association between myeloid cell activation, myelopoiesis, and obesity and diabetes (86).

Independent single cell analysis of blood samples also has demonstrated specific derangements in adaptive immune cells that are associated with COVID-19 disease severity (87). While moderate disease is associated with a vigorous immune response with expansion of CD4 and CD8 effector T cells, severe COVID-19 is associated with evidence of exhausted T cell responses, dysregulated interferon signatures, and evidence of broader T cell expansion. The importance of adequate T cell responses in preventing severe COVID-19 disease was emphasized in independent studies that evaluated T cells in conjunction with SARS-CoV-2 neutralizing antibodies in acute and convalescent patients (88). Coordinated $CD4^+$ and $CD8^+$ T cell responses were associated with mild disease, while discoordinated T cell responses and a loss of naïve T cells were observed in the elderly and those with poor COVID outcomes. Peripheral blood naïve T cells decrease with age and are believed to be a marker of a reduced capacity of the thymus to maintain a T cell pool capable of generating robust immunity to infection (89). Importantly obesity has been associated with a loss of naïve T cells in adults and children suggesting that impairment in adaptive immunity in individuals with obesity may contribute to COVID-19 susceptibility (90).

Adipokines such as leptin and adiponectin have been shown to modulate pulmonary inflammation. Elevated leptin levels are associated with increased mortality in patients with ARDS (91). Leptin has also been shown to induce an inflammatory phenotype in murine alveolar macrophages suggesting that increased leptin in obesity may potentiate pulmonary inflammation in COVID-19 (92). Adiponectin inhibits IL-6 expression by murine pulmonary endothelial cells *in vitro* and reduces lung inflammation in murine ARDS models *in vivo* (93). While the potential for adipokines to potentiate pulmonary inflammation in COVID-19 is attractive, data directly implicating leptin, adiponectin, and other adipokines in COVID-19 is lacking so far, which may suggest a dominant effect of other unique features of pulmonary physiology in people with obesity.

Treatment Considerations for COVID-19 for People with Obesity

One important unanswered question is whether weight loss might attenuate risk of severe COVID-19 disease. Weight loss has been shown to reduce expression of ACE 2 receptor in SAT (94), suggesting a mechanism by which weight loss may decrease viral burden in COVID-19 assuming adipose tissue is a reservoir for viral replication. In contrast, despite weight loss, inflammation persists within adipose tissue in formerly obese mice and humans (95, 96), a finding which might be expected to attenuate beneficial effects of weight loss on COVID-19. A single study has examined predictors of COVID-19 infection and disease severity in a cohort of patients who had undergone bariatric surgery and found that COVID-19 correlated with persistent DM and greater weight loss after surgery and that ICU admission correlated with persistent DM after surgery (97). These data suggest that DM remission may be more important than weight loss per se in modifying COVID-19 severity.

In terms of existing treatment options for COVD-19, currently dexamethasone treatment has been the most consistently supported to reduce mortality (98) and is broadly used as an anti-inflammatory approach. The effect of dexamethasone on attenuating IL-6 production from monocytes is impaired in people with obesity, suggesting that this strategy may have to be modified based on BMI (99).

The pursuit of a vaccine as a public health measure is crucial in prevention of SARS-CoV-2 infection and spread. Since the preparation of this review, several vaccines have shown high efficacy in prevention of COVID-19 disease and applications for FDA emergency use authorization are pending. Distribution of vaccines may start as early as late 2020. However a reduction in response to vaccination to other viral illnesses such as influenza is well documented in people with obesity due to impairments in T cell memory responses (100). Impaired T cell immunity is related to abnormal T cell metabolism and generation of an exhausted/senescent T cell phenotype in people with obesity and diabetes similar to other states of chronic immune activation (101). The decrease in naïve T cells for people with obesity, which is linked to poor vaccine responses, suggests that the wide range of SARS-CoV-2 vaccine strategies under investigation may be less robust in people with obesity and that vaccine regimens may have to be modified based on BMI.

Future Directions and Opportunities

The constantly shifting impact of SARS-CoV-2 on the health of individuals, communities, and society cannot be overstated. Unfortunately, social distancing and increased time at home needed to address the public health threat of SARS-CoV-2 may only worsen the prevalence of obesity, as 22% survey respondents report weight gain and increased eating (103). Therefore, we may note an increase in the prevalence of people with obesity as a risk group for severe COVID-19. In addition, we are just beginning to understand the long-term implications of COVID-19 on health and how mild, moderate, and severe COVID-19 may impact people with obesity. Therefore, the need to improve COVID-19 outcomes in people with obesity spans prevention, early symptom management, and acute intensive care settings and provides opportunities for research at many stages that the obesity research community is uniquely positioned to address.

FIGURE LEGENDS

Figure 1. Clinical Progression of COVID-19. SARS-CoV-2 infection progresses through stages starting with initial asymptomatic or mild symptoms associated with active viral replication (Stage 1). Some individuals progress to Stage 2 with increased pulmonary involvement with symptoms of dyspnea and hypoxemia and opacities observed with chest imaging that often has to be managed with hospitalization. A subset of individuals in Stage 2 progress to more severe disease (Stage 3) associated with respiratory failure, elevated markers of systemic inflammation, and multisystem organ failure. Relative to normal weight individuals (black line), people with obesity (red line) have a higher risk of progressing to Stage 2 and 3 and have more severe disease at each stage. Abbreviations: ARDS – Acute Respiratory Distress Syndrome.

Figure 2. Obesity-associated alterations in physiology and immunity that amplify responses to SARS-CoV-2. Obesity has broad effects on pulmonary physiology, adipose tissue biology, metabolism, and immune system function. COVID-19 exploits these impairments in normal homeostasis leading to more severe disease and/or requiring different clinical management approaches (e.g. ventilator management) compared to people without obesity. Abbreviations: V/Q – Lung Ventilation/Perfusion; FRC – Function Residual Capacity; IFN – Interferon; FA – Fatty acid; EC – Endothelial Cells.

References

1. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A*, et al.* High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. *Obesity (Silver Spring)* 2020;28:1195-1199.

2. Seidu S, Gillies C, Zaccardi F, Kunutsor SK, Hartmann-Boyce J, Yates T*, et al.* The impact of obesity on severe disease and mortality in people with SARS-CoV-2: A systematic review and meta-analysis. *Endocrinol Diabetes Metab* 2020:e00176.

3. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE*, et al.* Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;584:430-436.

4. Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J*, et al.* Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metab* 2020;31:1068-1077 e1063.

5. Muniyappa R, Wilkins KJ. Diabetes, Obesity, and Risk Prediction of Severe COVID-19. *J Clin Endocrinol Metab* 2020;105.

6. Ni YN, Luo J, Yu H, Wang YW, Hu YH, Liu D*, et al.* Can body mass index predict clinical outcomes for patients with acute lung injury/acute respiratory distress syndrome? A meta-analysis. *Crit Care* 2017;21:36.

7. Wang H, Lee CC, Chou EH, Hsu WT, Robinson RD, Su KY*, et al.* Mortality association between obesity and pneumonia using a dual restricted cohort model. *Obes Res Clin Pract* 2019;13:561-570.

8. Fan E, Beitler JR, Brochard L, Calfee CS, Ferguson ND, Slutsky AS*, et al.* COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted? *Lancet Respir Med* 2020;8:816-821.

9. Li X, Ma X. Acute respiratory failure in COVID-19: is it "typical" ARDS? *Crit Care* 2020;24:198.

10. Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. *N Engl J Med* 2020;383:1757-1766.

11. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. *N Engl J Med* 2020.

12. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020;323:1239-1242.

13. Tobin MJ, Laghi F, Jubran A. Why COVID-19 Silent Hypoxemia Is Baffling to Physicians. *Am J Respir Crit Care Med* 2020;202:356-360.

14. Zwillich CW, Sutton FD, Pierson DJ, Greagh EM, Weil JV. Decreased hypoxic ventilatory drive in the obesity-hypoventilation syndrome. *Am J Med* 1975;59:343-348.

15. Dixon AE, Peters U. The effect of obesity on lung function. *Expert Rev Respir Med* 2018;12:755-767.

16. Rivas E, Arismendi E, Agusti A, Sanchez M, Delgado S, Gistau C*, et al.* Ventilation/Perfusion distribution abnormalities in morbidly obese subjects before and after bariatric surgery. *Chest* 2015;147:1127-1134.

17. Lang M, Som A, Mendoza DP, Flores EJ, Reid N, Carey D*, et al.* Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. *Lancet Infect Dis* 2020.

18. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L*, et al.* COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med* 2020;46:1099-1102.

19. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M*, et al.* Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;351:327-336.

20. Florio G, Ferrari M, Bittner EA, De Santis Santiago R, Pirrone M, Fumagalli J*, et al.* A lung rescue team improves survival in obesity with acute respiratory distress syndrome. *Crit Care* 2020;24:4.

21. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F*, et al.* Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med* 2020;383:120-128.

22. Grasselli G, Tonetti T, Protti A, Langer T, Girardis M, Bellani G*, et al.* Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. *Lancet Respir Med* 2020.

23. Willson C, Watanabe M, Tsuji-Hosokawa A, Makino A. Pulmonary vascular dysfunction in metabolic syndrome. *J Physiol* 2019;597:1121-1141.

24. Shah D, Romero F, Guo Z, Sun J, Li J, Kallen CB*, et al.* Obesity-Induced Endoplasmic Reticulum Stress Causes Lung Endothelial Dysfunction and Promotes Acute Lung Injury. *Am J Respir Cell Mol Biol* 2017;57:204-215.

25. Kulcsar KA, Coleman CM, Beck SE, Frieman MB. Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection. *JCI Insight* 2019;4:e131774.

26. Chua RL, Lukassen S, Trump S, Hennig BP, Wendisch D, Pott F*, et al.* COVID-19 severity correlates with airway epithelium-immune cell interactions identified by single-cell analysis. *Nat Biotechnol* 2020;38:970-979.

27. Higham A, Singh D. Increased ACE2 Expression in Bronchial Epithelium of COPD Patients who are Overweight. *Obesity (Silver Spring)* 2020;28:1586-1589.

28. Klemperer H. Glucose breakdown in chick embryo cells infected with influenza virus. *Virology* 1961;13:68-77.

29. Smallwood HS, Duan S, Morfouace M, Rezinciuc S, Shulkin BL, Shelat A*, et al.* Targeting Metabolic Reprogramming by Influenza Infection for Therapeutic Intervention. *Cell Rep* 2017;19:1640-1653.

30. Sestan M, Marinovic S, Kavazovic I, Cekinovic D, Wueest S, Turk Wensveen T*, et al.* Virus-Induced Interferon-gamma Causes Insulin Resistance in Skeletal Muscle and Derails Glycemic Control in Obesity. *Immunity* 2018;49:164-177 e166.

31. Harper SA, Bradley JS, Englund JA, File TM, Gravenstein S, Hayden FG*, et al.* Seasonal influenza in adults and children--diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2009;48:1003-1032.

32. Codo AC, Davanzo GG, Monteiro LB, de Souza GF, Muraro SP, Virgilio-da-Silva JV*, et al.* Elevated Glucose Levels Favor SARS-CoV-2 Infection and Monocyte Response through a HIF-1alpha/Glycolysis-Dependent Axis. *Cell Metab* 2020;32:437-446 e435.

33. Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL*, et al.* Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol* 2020;8:546-550.

34. Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I*, et al.* Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia* 2020;63:1500-1515.

35. Singh AK, Singh R. Is metformin ahead in the race as a repurposed host-directed therapy for patients with diabetes and COVID-19? *Diabetes Res Clin Pract* 2020;165:108268.

36. Bramante C, Ingraham N, Murray T, Marmor S, Hoversten S, Gronski J*, et al.* Observational Study of Metformin and Risk of Mortality in Patients Hospitalized with Covid-19. *medRxiv* 2020.

37. Ciavarella C, Motta I, Valente S, Pasquinelli G. Pharmacological (or Synthetic) and Nutritional Agonists of PPAR-gamma as Candidates for Cytokine Storm Modulation in COVID-19 Disease. *Molecules* 2020;25.

38. Shen B, Yi X, Sun Y, Bi X, Du J, Zhang C*, et al.* Proteomic and Metabolomic Characterization of COVID-19 Patient Sera. *Cell* 2020;182:59-72 e15.

39. Song JW, Lam SM, Fan X, Cao WJ, Wang SY, Tian H*, et al.* Omics-Driven Systems Interrogation of Metabolic Dysregulation in COVID-19 Pathogenesis. *Cell Metab* 2020;32:188-202 e185.

40. Kyle JE, Burnum-Johnson KE, Wendler JP, Eisfeld AJ, Halfmann PJ, Watanabe T*, et al.* Plasma lipidome reveals critical illness and recovery from human Ebola virus disease. *Proc Natl Acad Sci U S A* 2019;116:3919-3928.

41. Gomez-Serrano M, Camafeita E, Lopez JA, Rubio MA, Breton I, Garcia-Consuegra I*, et al.* Differential proteomic and oxidative profiles unveil dysfunctional protein import to adipocyte mitochondria in obesity-associated aging and diabetes. *Redox Biol* 2017;11:415-428.

42. Weiler Miralles CS, Wollinger LM, Marin D, Genro JP, Contini V, Morelo Dal Bosco S. Waist-to-height ratio (WHtR) and triglyceride to HDL-C ratio (TG/HDL-c) as predictors of cardiometabolic risk. *Nutr Hosp* 2015;31:2115-2121.

43. Maile MD, Standiford TJ, Engoren MC, Stringer KA, Jewell ES, Rajendiran TM*, et al.* Associations of the plasma lipidome with mortality in the acute respiratory distress syndrome: a longitudinal cohort study. *Respir Res* 2018;19:60.

44. Chew WS, Torta F, Ji S, Choi H, Begum H, Sim X*, et al.* Large-scale lipidomics identifies associations between plasma sphingolipids and T2DM incidence. *JCI Insight* 2019;5.

45. Law SH, Chan ML, Marathe GK, Parveen F, Chen CH, Ke LY. An Updated Review of Lysophosphatidylcholine Metabolism in Human Diseases. *Int J Mol Sci* 2019;20.

46. Kim M, Yoo HJ, Ko J, Lee JH. Metabolically unhealthy overweight individuals have high lysophosphatide levels, phospholipase activity, and oxidative stress. *Clin Nutr* 2020;39:1137-1145.

47. Li L, Yu L, Hou X. Cholesterol-rich lipid rafts play a critical role in bovine parainfluenza virus type 3 (BPIV3) infection. *Res Vet Sci* 2017;114:341-347.

48. Douglas I, Evans S, Smeeth L. Effect of statin treatment on short term mortality after pneumonia episode: cohort study. *BMJ* 2011;342:d1642.

49. Katsiki N, Banach M, Mikhailidis DP. Lipid-lowering therapy and renin-angiotensin-aldosterone system inhibitors in the era of the COVID-19 pandemic. *Arch Med Sci* 2020;16:485-489.

50. Sturley SL, Rajakumar T, Hammond N, Higaki K, Marka Z, Marka S*, et al.* Potential COVID-19 therapeutics from a rare disease: weaponizing lipid dysregulation to combat viral infectivity. *J Lipid Res* 2020;61:972-982.

51. Yan B, Chu H, Yang D, Sze KH, Lai PM, Yuan S*, et al.* Characterization of the Lipidomic Profile of Human Coronavirus-Infected Cells: Implications for Lipid Metabolism Remodeling upon Coronavirus Replication. *Viruses* 2019;11.

52. Lythgoe MP, Middleton P. Ongoing Clinical Trials for the Management of the COVID-19 Pandemic. *Trends Pharmacol Sci* 2020;41:363-382.

53. Iacobellis G, Malavazos AE, Ferreira T. COVID-19 Rise in Younger Adults with Obesity: Visceral Adiposity Can Predict the Risk. *Obesity (Silver Spring)* 2020;28:1795.

54. Safari S, Keyvani H, Alamdari NM, Dehghanian A, Hashemi MR, Honar BN*, et al.* Abdominal Surgery in Patients with COVID-19: Detection of SARS-CoV-2 in Abdominal and Adipose Tissues. *Ann Surg* 2020.

55. Nishimura H, Itamura S, Iwasaki T, Kurata T, Tashiro M. Characterization of human influenza A (H5N1) virus infection in mice: neuro-, pneumo- and adipotropic infection. *J Gen Virol* 2000;81:2503-2510.

56. Bouwman JJ, Visseren FL, Bouter KP, Diepersloot RJ. Infection-induced inflammatory response of adipocytes in vitro. *Int J Obes (Lond)* 2008;32:892-901.

57. Ayari A, Rosa-Calatrava M, Lancel S, Barthelemy J, Pizzorno AA-O, Mayeuf-Louchart A*, et al.* Influenza infection rewires energy metabolism and induces browning features in adipose cells and tissues

The Role of Adipocytes and Adipocyte-Like Cells in the Severity of COVID-19 Infections

Ifi27 is indispensable for mitochondrial function and browning in adipocytes

HIV Persistence in Adipose Tissue Reservoirs.

58. Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. *Am J Pathol* 2007;170:1136-1147.

59. Zwezdaryk KJ, Ferris MB, Strong AL, Morris CA, Bunnell BA, Dhurandhar NV*, et al.* Human cytomegalovirus infection of human adipose-derived stromal/stem cells restricts differentiation along the adipogenic lineage. *Adipocyte* 2016;5:53-64.

60. Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect Dis Poverty* 2020;9:45.

61. Al-Benna S. Association of high level gene expression of ACE2 in adipose tissue with mortality of COVID-19 infection in obese patients. *Obes Med* 2020;19:100283.

62. El-Sayed Moustafa JS, Jackson AU, Brotman SM, Guan L, Villicana S, Roberts AL*, et al.* ACE2 expression in adipose tissue is associated with COVID-19 cardio-metabolic risk factors and cell type composition. *medRxiv* 2020.

63. Fain JN, Madan AK, Hiler ML, Cheema P, Bahouth SW. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. *Endocrinology* 2004;145:2273-2282.

64. de Oliveira M, De Sibio MT, Mathias LS, Rodrigues BM, Sakalem ME, Nogueira CR. Irisin modulates genes associated with severe coronavirus disease (COVID-19) outcome in human subcutaneous adipocytes cell culture. *Mol Cell Endocrinol* 2020;515:110917.

65. Bergallo M, Ferrari L, Faolotto G, Balbo PE, Montanari P, Patrucco F*, et al.* Interferon signature in immunosuppressed patients with lower respiratory tract infections: dosage on bronchoalveolar lavage. *Minerva Med* 2020;111:245-253.

66. Jin W, Jin W, Pan D. Ifi27 is indispensable for mitochondrial function and browning in adipocytes. *Biochem Biophys Res Commun* 2018;501:273-279.

67. Kumari M, Wang X, Lantier L, Lyubetskaya A, Eguchi J, Kang S*, et al.* IRF3 promotes adipose inflammation and insulin resistance and represses browning. *J Clin Invest* 2016;126:2839-2854.

68. Chen X, Zhao B, Qu Y, Chen Y, Xiong J, Feng Y*, et al.* Detectable Serum Severe Acute Respiratory Syndrome Coronavirus 2 Viral Load (RNAemia) Is Closely Correlated With Drastically Elevated Interleukin 6 Level in Critically Ill Patients With Coronavirus Disease 2019. *Clin Infect Dis* 2020;71:1937-1942.

69. Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, von Bergwelt-Baildon M*, et al.* Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol* 2020;146:128-136 e124.

70. Park HS, Park JY, Yu R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6. *Diabetes Res Clin Pract* 2005;69:29-35.

71. Kristof E, Klusoczki A, Veress R, Shaw A, Combi ZS, Varga K*, et al.* Interleukin-6 released from differentiating human beige adipocytes improves browning. *Exp Cell Res* 2019;377:47-55.

72. Kim IC, Han S. Epicardial adipose tissue: fuel for COVID-19-induced cardiac injury? *Eur Heart J* 2020;41:2334-2335.

73. Deng M, Qi YA-O, Deng L, Wang H, Xu Y, Li Z*, et al.* Obesity as a Potential Predictor of Disease Severity in Young COVID-19 Patients: A Retrospective Study. LID - 10.1002/oby.22943 [doi].

74. Kruglikov IL, Scherer PE. The Role of Adipocytes and Adipocyte-Like Cells in the Severity of COVID-19 Infections. *Obesity (Silver Spring)* 2020;28:1187-1190.

75. Jain M, Budinger GR, Lo A, Urich D, Rivera SE, Ghosh AK*, et al.* Leptin promotes fibroproliferative acute respiratory distress syndrome by inhibiting peroxisome proliferator-activated receptor-gamma. *Am J Respir Crit Care Med* 2011;183:1490-1498.

76. Pinky, Gupta S, Krishnakumar V, Sharma Y, Dinda AK, Mohanty S. Mesenchymal Stem Cell Derived Exosomes: a Nano Platform for Therapeutics and Drug Delivery in Combating COVID-19. *Stem Cell Rev Rep* 2020:1-11.

77. Tsuchiya A, Takeuchi S, Iwasawa T, Kumagai M, Sato T, Motegi S*, et al.* Therapeutic potential of mesenchymal stem cells and their exosomes in severe novel coronavirus disease 2019 (COVID-19) cases. *Inflamm Regen* 2020;40:14.

78. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N*, et al.* Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* 2020;369:718-724.

79. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y*, et al.* Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 2020;370:eabd4585.

80. Zhang Q, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, Chen J*, et al.* Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science* 2020;370.

81. Teran-Cabanillas E, Montalvo-Corral M, Caire-Juvera G, Moya-Camarena SY, Hernandez J. Decreased interferon-alpha and interferon-beta production in obesity and expression of suppressor of cytokine signaling. *Nutrition* 2013;29:207-212.

82. Teran-Cabanillas E, Hernandez J. Role of Leptin and SOCS3 in Inhibiting the Type I Interferon Response During Obesity. *Inflammation* 2017;40:58-67.

83. Liao M, Liu Y, Yuan J, Wen Y, Xu G, Zhao J*, et al.* Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. *Nat Med* 2020;26:842-844.

84. Silvin A, Chapuis N, Dunsmore G, Goubet AG, Dubuisson A, Derosa L*, et al.* Elevated Calprotectin and Abnormal Myeloid Cell Subsets Discriminate Severe from Mild COVID-19. *Cell* 2020;182:1401-1418 e1418.

85. Mann ER, Menon M, Knight SB, Konkel JE, Jagger C, Shaw TN*, et al.* Longitudinal immune profiling reveals key myeloid signatures associated with COVID-19. *Sci Immunol* 2020;5.

86. Singer K, DelProposto J, Morris DL, Zamarron B, Mergian T, Maley N*, et al.* Diet-induced obesity promotes myelopoiesis in hematopoietic stem cells. *Mol Metab* 2014;3:664-675.

87. Zhang JY, Wang XM, Xing X, Xu Z, Zhang C, Song JW*, et al.* Single-cell landscape of immunological responses in patients with COVID-19. *Nat Immunol* 2020;21:1107-1118.

88. Rydyznski Moderbacher C, Ramirez SI, Dan JM, Grifoni A, Hastie KM, Weiskopf D*, et al.* Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity. *Cell* 2020.

89. Goronzy JJ, Fang F, Cavanagh MM, Qi Q, Weyand CM. Naive T cell maintenance and function in human aging. *J Immunol* 2015;194:4073-4080.

90. Mauro C, Smith J, Cucchi D, Coe D, Fu H, Bonacina F*, et al.* Obesity-Induced Metabolic Stress Leads to Biased Effector Memory CD4(+) T Cell Differentiation via PI3K p110delta-Akt-Mediated Signals. *Cell Metab* 2017;25:593-609.

91. Ubags ND, Stapleton RD, Vernooy JH, Burg E, Bement J, Hayes CM*, et al.* Hyperleptinemia is associated with impaired pulmonary host defense. *JCI Insight* 2016;1.

92. Mancuso P, Canetti C, Gottschalk A, Tithof PK, Peters-Golden M. Leptin augments alveolar macrophage leukotriene synthesis by increasing phospholipase activity and enhancing group IVC iPLA2 (cPLA2gamma) protein expression. *Am J Physiol Lung Cell Mol Physiol* 2004;287:L497-502.

93. Konter JM, Parker JL, Baez E, Li SZ, Ranscht B, Denzel M*, et al.* Adiponectin attenuates lipopolysaccharide-induced acute lung injury through suppression of endothelial cell activation. *J Immunol* 2012;188:854-863.

94. Li L, Spranger L, Soll D, Beer F, Brachs M, Spranger J*, et al.* Metabolic impact of weight loss induced reduction of adipose ACE-2 - Potential implication in COVID-19 infections? *Metabolism* 2020;113:154401.

95. Magkos F, Fraterrigo G, Yoshino J, Luecking C, Kirbach K, Kelly SC*, et al.* Effects of Moderate and Subsequent Progressive Weight Loss on Metabolic Function and Adipose Tissue Biology in Humans with Obesity. *Cell Metab* 2016;23:591-601.

96. Zamarron BF, Mergian TA, Cho KW, Martinez-Santibanez G, Luan D, Singer K*, et al.* Macrophage Proliferation Sustains Adipose Tissue Inflammation in Formerly Obese Mice. *Diabetes* 2017;66:392-406.

97. Bel Lassen P, Poitou C, Genser L, Marchelli F, Aron-Wisnewsky J, Ciangura C*, et al.* COVID-19 and its severity in bariatric surgery operated patients. *Obesity (Silver Spring)* 2020.

98. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL*, et al.* Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med* 2020.

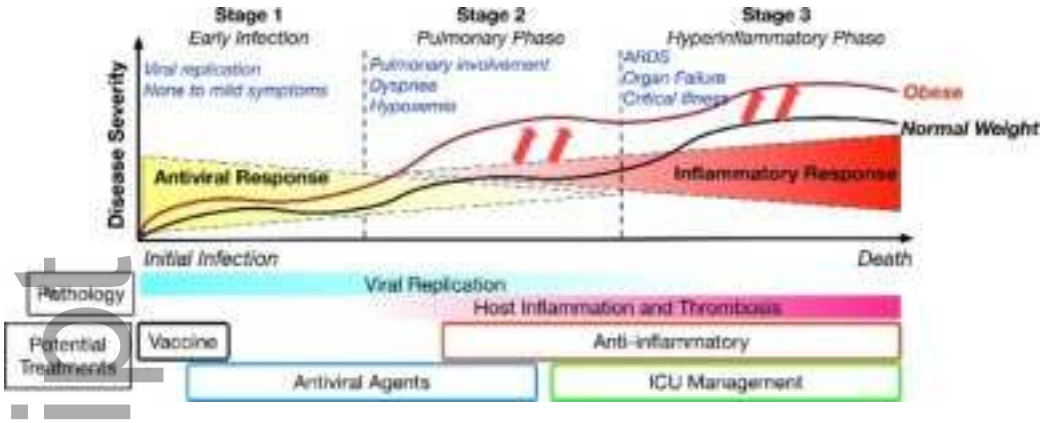
99. Huang CJ, Acevedo EO, Mari DC, Randazzo C, Shibata Y. Glucocorticoid inhibition of leptin- and lipopolysaccharide-induced interleukin-6 production in obesity. *Brain Behav Immun* 2014;35:163-168.

100. Sheridan PA, Paich HA, Handy J, Karlsson EA, Hudgens MG, Sammon AB*, et al.* Obesity is associated with impaired immune response to influenza vaccination in humans. *Int J Obes (Lond)* 2012;36:1072-1077.

101. Yi HS, Kim SY, Kim JT, Lee YS, Moon JS, Kim M*, et al.* T-cell senescence contributes to abnormal glucose homeostasis in humans and mice. *Cell Death Dis* 2019;10:249.

102. Cicin-Sain L, Smyk-Pearson S, Currier N, Byrd L, Koudelka C, Robinson T*, et al.* Loss of naive T cells and repertoire constriction predict poor response to vaccination in old primates. *J Immunol* 2010;184:6739-6745.

103. Zachary Z, Brianna F, Brianna L, Garrett P, Jade W, Alyssa D*, et al.* Self-quarantine and weight gain related risk factors during the COVID-19 pandemic. *Obes Res Clin Pract* 2020;14:210-216.



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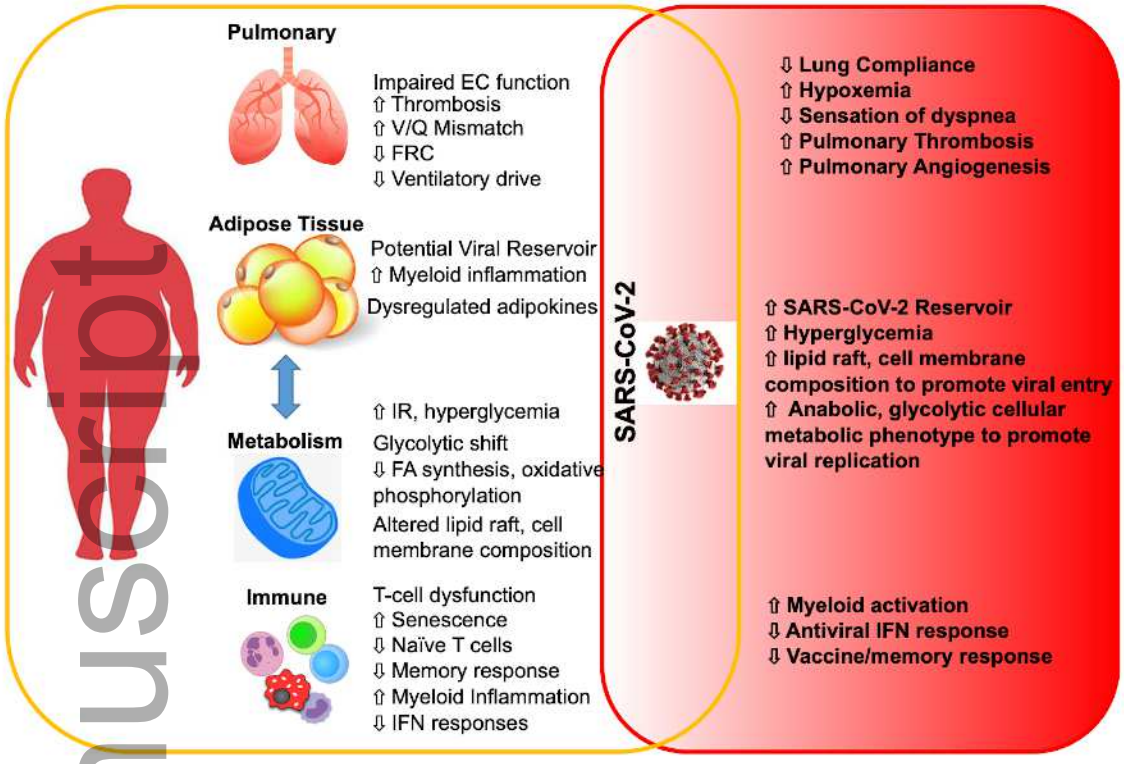

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