TRANSLATIONAL REVIEW

The Role of Obesity in the Immunopathogenesis of COVID-19 Respiratory Disease and Critical Illness

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Abstract

Coronavirus disease (COVID-19), the clinical syndrome caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is currently a global health pandemic with substantial morbidity and mortality. COVID-19 has cast a shadow on nearly every aspect of society, straining health systems and economies across the world. Although it is widely accepted that a close relationship exists between obesity, cardiovascular disease, and metabolic disorders on infection, we are only beginning to understand ways in which the immunological sequelae of obesity functions as a predisposing factor related to poor clinical outcomes in COVID-19. As both the innate and adaptive immune systems are each primed by obesity, the alteration of key pathways results in both an immunosuppressed and hyperinflammatory state. The present review will discuss the cellular and molecular immunology of obesity in the context of its role as a risk factor for severe COVID-19, discuss the role of cytokine storm, and draw parallels to prior viral epidemics such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and 2009 H1N1.

Keywords: COVID-19; obesity; innate; adaptive; cytokine

The Spanish influenza pandemic of 1918 affected nearly 100,000,000 individuals worldwide (1). Since then, there have been few instances of such a rapidly communicating pandemic affecting millions of victims across six continents. Coronavirus disease (COVID-19), the clinical syndrome resulting from infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as a global threat without precedent in the last century, resulting in substantial morbidity and mortality (2). Obesity, defined as a body mass index of 30 or more, is an epidemic unto itself, affecting more than 1.9 billion persons (3). It is associated with increased incidence and progression of multiple chronic diseases (4), including metabolic syndrome, respiratory infections such as pneumonia (5), pandemic influenza (6), and synergistically worsens cardiovascular disease mortality (7). Obesity was found to have a striking link to mortality in the H1N1 pandemic (8–10). Epidemiological data from COVID-19 hospitalizations (11) suggest that the presence of obesity is associated with more severe disease and greater mortality, with more data substantiating this issue over time (12, 13).

To build on these data, there exists a need to understand the immunological basis of disease development in patients with COVID-19 and comorbid obesity and, in particular, the mechanism of development of the cytokine storm phenotype. Thus, understanding the mechanistic links between obesity, immunomodulation, and disease outcomes is especially crucial in the understanding of COVID-19 and will improve ongoing efforts to prevent COVID-19–related mortality worldwide.

Immunological Changes Because of Adiposity as a Risk Factor for Infection

The role of adiposity in modifying the innate and adaptive immune system is firmly established in the human host response to infection (14, 15). In general, when

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compared with those without obesity, patients with obesity have a greater risk for acquiring severe and nonsevere infections (16). Potentiated interactions between adiposity, insulin resistance, and inflammation (17, 18) underscore this problem because patients with COVID-19 often carry overlapping diagnoses of diabetes, obesity, and metabolic syndrome. Insights from preclinical studies on acute lung injury, inflammation, and obesity (19–22) will be useful to elucidate the complex and multifactorial links between obesity and immune dysregulation in the pathogenesis of COVID-19 lung injury and multiple organ failure (23, 24).

Physiologically, adipose tissue is essential, as it provides the substrate for normal metabolism and fuel storage, and it is considered an organ, possessing paracrine and endocrine functions together with robust immunological activity (25). Excess adiposity is a condition of nutrient imbalance in which the threshold of normal fatty acid storage is exceeded. The resulting stress state, referred to as "metainflammation" (26), is marked by mitochondrial dysfunction, apoptotic signaling and production of reactive oxygen species (ROS) (25, 27). One component of this stress response is the activation of the smooth endoplasmic reticulum (ER) of macrophages, termed the "ER stress response." This response occurs when cholesterol-overloaded macrophages generate ROS mediated by the ER stress sensors PERK and IRE1α (28), and they form proinflammatory "foam cells," leading to TNF-α and IL-6 via NF-κB activation (29) and to mitogen-activated protein kinases (28, 30). The result is a chronic, low-grade inflammatory environment (31) in which circulating cytokines (32) and complement proteins (33) are constitutively activated, including increased concentrations of IL-6 (31). IL-6, which is directly associated with abdominal obesity as it is generated in adipose tissue (31), acts on IL-6 receptors and represents a key cytokine implicated in the hypercytokinemic phase of COVID-19, in which higher circulating concentrations are correlated with severity (34). Excess lipids can directly affect intracellular signaling pathways by activating PKC isoforms. Lipids also act as a damage-associated molecular patterns and directly engage pattern recognition receptors (pathogen-associated molecular patterns). For example, saturated fat, palmitate, and oxidized cholesterol can activate Toll-like receptor (TLR) signaling via TLR4, resulting in activation of the inflammasome and proinflammatory gene expression (26). This stimulates hepatic CRP, fibrinogen, and marrow leukocyte and platelet release, together with endothelial activation, which may result in the "primed" immune responses seen in patients with obesity and SARS-CoV-2 infection and could further predispose the host to immunosuppression and excessive cytokine activation.

Adiposity and Adipokines

The two major types of adipose tissue—white and brown—are located in visceral and subcutaneous compartments (35). Visceral white adipose tissue is essential for energy storage, glucose homeostasis, and glucose, metabolism, and endocrine functions (36). In patients with obesity, particularly those with insulin resistance, excess deposition of fatty acids in visceral adipose tissue is associated with a chronic proinflammatory state, also referred to as "metainflammation" (26), in which circulating immune cells, particularly macrophages, are abundant (37). Adipose tissue undergoes remodeling in obesity via an increase in size and number of adipocytes, but an infiltration of immune cells also occurs within the tissue itself. In the obese state, macrophage activation and production of proinflammatory transcription factors, such as NF-κB and JNK, occurs in activated in adipose tissue as well as liver and muscle tissue (25, 38). In visceral adipose tissue, both adipocytes and surrounding stromal cells are the site of production of proinflammatory cytokines and polypeptides, such as TNF-α, IL-6, resistin, MCP-1, and angiotensinogen (39, 40). Adipocytokines are adipocyte-derived cytokine-like proteins typically engaged in energy homeostasis, fat metabolism, and tissue remodeling (41–43). Dysfunctional regulation of adipokines has been implicated in the development of inflammation, insulin resistance, and metabolic syndrome. Adiponectin is a key adipokine with predominantly antiinflammatory actions and is deficient in obesity (42). It is expressed in the endothelium as well as adipocytes and skeletal muscle cells, binding to cellular receptors ADIPOR-1 and ADIPOR-2, stimulating PPAR-α (peroxisome proliferator–activated receptor α), AMP-kinase and p38 mitogen–activated protein kinase, yielding multiple downstream antiinflammatory effects, including the attenuation of TNF-α (42). Adiponectin deficiency in obesity presents a mechanistically important role in COVID-19, especially in the context of numerous preclinical studies revealing obesity as a risk factor for the development and severity of respiratory failure (19). In a murine model, Shah and colleagues (44) demonstrated a protective effect of adiponectin on the pulmonary endothelium, such that deficiency was associated with excess permeability via modification of junctional adherens proteins and the development acute lung injury and acute respiratory distress syndrome (ARDS).

Leptin is a 16Kd protein with immune and neuroendocrine properties produced in adipocytes in proportion to body fat mass. It serves diverse homeostatic and immunoregulatory roles (36, 45, 46), including weight regulation, stress responses, and satiety (4, 45, 47), in addition to robust effects on the innate and adaptive immune systems, exerting activity on neutrophils, natural killer (NK) cells, monocytes, and macrophages as well as CD4 cells (45). Increased leptin concentrations in excess adipose tissue may be associated with leptin resistance and the development of diabetes and metabolic syndrome (48). A key role is to modify T-cell responses (49) by promoting Th1 differentiation (45). Immunosuppression due to hyperleptinemic states is also significant in that patients with obesity have defects in neutrophil function and impaired cytokine signaling and chemotaxis, suggesting that leptin at high concentrations can suppress the innate immune response (50).

Van der Voort and colleagues (51) demonstrated that critically ill patients with SARS-CoV-2 infection had higher baseline leptin concentrations than matched control subjects, supporting findings from a prior study in which Ubags and colleagues (50) found an association between elevated leptin concentrations and the progression of respiratory failure, ARDS, and mortality. Finally, leptin exhibits structural parallels to IL-6, IL-12, and G-CSF (granulocyte colony-stimulating factor) (45) and promotes the release of Il-6, IL-1β, and ROS, which, taken together, may be crucial in the pathogenesis of COVID-19 cytokine storm.

Resistin is a cysteine-rich protein first described in adipose tissue (52) that has been implicated in the development of obesity. Resistin concentrations are elevated in

patients with obesity and are decreased in the setting of weight loss. The pathogenesis of insulin resistance is believed to be mediated, in part, by resistin (41), and, in fact, the expression of resistin is induced in inflammatory states by TNF-α and NF-κB (53). Key proinflammatory cytokines TNF-α, IL-6, and IL-1β; CCL-2; and leptin are generated in excess in white adipose tissue, where adipose tissue–derived macrophages are a primary source of cytokine production. IL-6 has a myriad of proinflammatory actions, as reviewed extensively by Ellullu and colleagues (31). This is pertinent in COVID-19–associated viral pneumonia because serum IL-6 concentrations are increased under hypoxic conditions (54), and thus elevated baseline concentrations in patients with obesity may be a pivotal mechanistic link between obesity and disease severity in COVID-19.

Innate Immunity and Obesity

The innate immune response is an essential early response to viral pathogens. Numerous murine models have been established to evaluate pathological alterations of cell immunological mechanisms in obesity, allowing the investigation of diverse respiratory diseases, including ARDS, pneumonia, and asthma (19). The chronic inflammatory state generated by obesity, termed "metainflammation" (39), impairs the immune response to an infectious insult. In essence, bioactive proteins and cytokines are produced from activated adipocytes, which are more often located in visceral fat (40). This process commences with dysregulated lipid and glucose metabolism, which is normally coordinated by the gut, liver, and pancreas, and may be potentiated by inflammatory signals from the hypothalamus. In the overfed state, this leads to lipid accumulation, insulin resistance, and adiposity development. Lipid accumulation also results in pathologic alterations to phagocytic cells such as macrophages and NK cells. In the innate immune response, recognition of pathogens, pathogen-associated molecular patterns, and damage-associated molecular patterns, including free fatty acids and high glucose concentrations, occurs by pathogen recognition receptors, including TLRs (39). TLRs as well as RIG-like and NOD-like receptors are components of immunologically active multiprotein complexes or "inflammasomes," which, when activated, can lead to caspase activation and NF-κB–mediated IL-1β synthesis (55) and release. Both resident and peripheral macrophages play a central role in pathogen recognition, and, ultimately, the macrophages serve as "signal amplifiers" of the inflammatory process started in the adipocyte (18). Macrophages are not only increased in number via signaling by CCL-2 in the peripheral circulation but also become highly activated to a proinflammatory M1 phenotype (56), in which M1 gene expression leads to robust cytokine production, including ROS, IL-2, TNF-α, IL-6, IL-1β, and MCP-1, within adipose tissue (25, 57–59). This results in increased neutrophil sequestration and impaired migration into the alveolar space during times of infectious insult, as well as M1 polarization of resident alveolar macrophages. In an LPS model of bacterial sepsis, the obese state promoted switching to the M1 (proinflammatory) phenotype, increasing alveolar TNF-α/IL-10 ratio, and reprogramming of adipose tissue macrophages to a state of increased responsiveness (60, 61). NK cells are a subset of lymphocytes that respond swiftly to infected host cells with lytic substances such as perforins and granzymes (62). NK cells can also shape subsequent immune responses through their rapid production of cytokines (IFN-γ, TNF-α, IL-6, and GM-CSF [granulocyte-macrophage colony-stimulating factor]). One on hand, in adipose tissue, NK cells may activate macrophages to a proinflammatory phenotype, and, on the other, NK cell function is defective in the obese state (62).

The influence of immunosuppression and hyperactivation of cytokine pathways underlie the severity and lethality caused by COVID-19. Under homeostatic conditions, the type I IFN pathway is activated when presented with a viral pathogen. JAK–STAT signaling and nuclear transposition results in increased expression of nuclear IFN-stimulated response elements (63, 64) (Figure 1). Tian and colleagues (65) found that obesity leads to inefficient antiviral response by predisposing patients with obesity to an attenuated type 1 IFN–mediated defense. Teran-Cabanillas and colleagues (66) showed that IFN responses to influenza are attenuated in patients with obesity, and, in similar fashion, alteration and evasion of IFN responses by SARS-CoV-2 are likely culprits of severe disease and worsening cytokinemia (67). A proposed mechanism of obesity in viral infections is described by Almond and colleagues (68), in which elevated leptin concentrations and consequent leptin resistance in obesity could attenuate the IFN response via SOC-3 (suppressor of cytokine signaling 3), which is upregulated in obesity (68). Antimicrobial peptides, such as defensins and cathelicidins, play a role in host defense and are present in respiratory endothelium (69). Defensins are commonly induced in the setting of viral infection with effector functions ranging from inactivating virions to regulating chemokine production, depending on the type of defensin and the type of virus (70). Cathelicidins concentrations are correlated with elevated body mass index (BMI) (71). These peptides are chemotactic for neutrophils and T cells in viral infection and have been demonstrated to reduce proinflammatory cytokine release by macrophages (69). It has been demonstrated that individuals with obesity and asthma have decreased concentrations of surfactant protein, an essential finding, as decreased concentrations are associated with impaired clearance against both bacterial and viral pathogens (72, 73). Surfactant D is a soluble protein in the collectin family located in mucosal secretions of the respiratory epithelium, and it plays an important role in the innate response to viral infection (74). The full impact of obesity on cathelicidins, defensins, and surfactant is largely unknown; however, disrupted surfactant concentrations are considered to be important in the pathogenesis of inflammation in the obese and insulin-resistant state (75).

Obesity in the Adaptive Immune System

COVID-19 impairs adaptive immune responses, with significant lymphopenia and altered T-cell responses (76). These actions may be exaggerated in obesity, in which the influence of B cells on T cells generates a proinflammatory T-cell phenotype (77). Patients with obesity have an increased frequency of CD4 TH1 cells, whereas $CD4^+$ TH2 cells progressively decrease with the development of obesity (78). Despite elevated $CD8^+$ T-cell numbers, there is decreased $CD8^+$ T-cell activation and expression of functional proteins (79). Misumi and colleagues (16) assessed the effects of obesity on T-cell responses to viral infection in

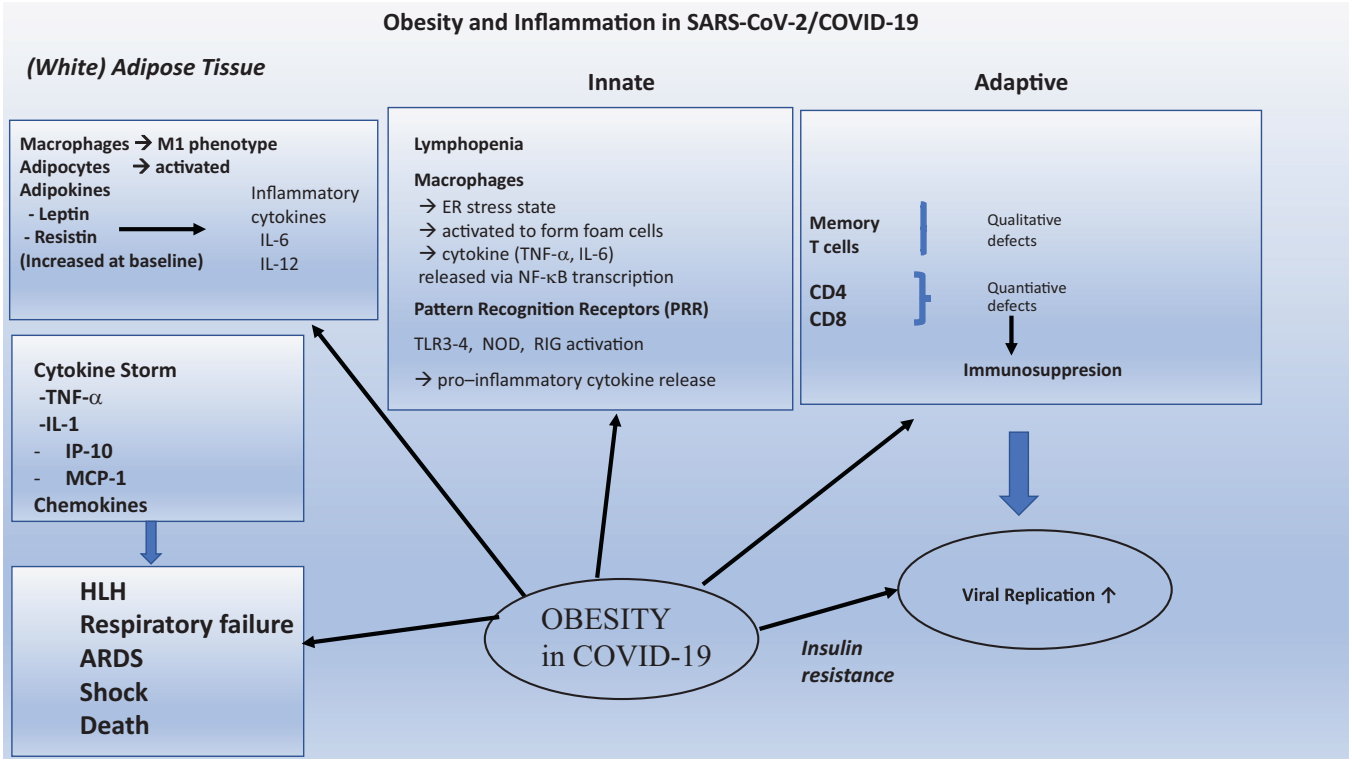

Figure 1. Proposed mechanism of obesity-mediated priming and inflammation in coronavirus disease (COVID-19). ARDS = acute respiratory distress syndrome; ER = endoplasmic reticulum; HLH = hemophagocytic lymphohistiocytosis; MCP-1 = monocyte chemoattractant protein-1; NOD = nucleotide-binding and oligomerization domain; RIG-I = retinoic acid-inducible gene I; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TLR = Toll-like receptor.

murine models and observed increased memory T-cell numbers in white adipose tissue and spleen, with memory T cells rapidly causing severe pathogenesis upon rechallenge with infection. Patients with COVID-19 have higher coexpression of CD38 and HLA-DR on $CD8^+$ T cells. PD-1 expression on CD8+ T cells was significantly lower in patients with COVID-19, with PD-1 being crucial in the reinvigoration of exhausted T cells (76). In murine models, obese mice were found to have T-cell dysfunction, which was partly mediated by the PD-1 axis and driven by leptin (80). T-cell dysfunction is largely characterized by decreased T-cell proliferation, decreased effector function, decreased naive:memory T-cell ratio and shift to TH1/TH17 phenotype from TH2/Treg phenotype (81). Antiinflammatory regulatory T cells, which typically aim to maintain immunologic balance by secreting IL-10 and TGF-β, are reduced (82). Greater concentrations of TH1 phenotype T cells are observed in obese adipose tissue (83). Obesity causes a reduction in thymopoiesis and constricts TCR diversity and thus is associated with impaired T cell–mediated immune monitoring (84). Although CD8 T-cell numbers may be increased in obesity (85), obesity has been shown to impair memory T-cell responses to viral infection (21). This may result in lower leukocyte counts and decreased CD4 and CD8 subsets, resulting in altered monocyte oxidative burst functions in individuals with obesity (14, 15) and potentiating immunosuppression. Frasca and colleagues (86) suggest that B cells within visceral adipose tissue express higher NF-κB and have reduced antibody responses. This may be especially pertinent because an animal model of SARS-CoV-1 (87) infection demonstrated that intranuclear IL-6 expression was activated via NF-κB, indicating the need for further study in SARS-CoV-2 with respect to B cell–induced transcriptional activity.

Obesity, Viral Pneumonia, and Hyperinflammation: A Focus on Human Studies

Evidence is mounting that obesity correlates with morbidity and mortality in COVID-19 (88). Simonnet and colleagues (89) reported a positive correlation between BMI and mortality in COVID-19, finding that 47% of patients admitted to the ICU had obesity. In a series of 32 patients hospitalized with H1N1, Hagau and colleagues (90) demonstrated that obesity was more common in those developing ARDS, suggesting that obesity was an independent risk factor for admission to the ICU. Mechanical impairments in individuals with obesity contribute to this finding, including decreased expiratory reserve volume, total lung capacity, functional residual capacity, and vital capacity and changes in pleural pressure (91, 92) in addition to anatomic factors, such as airway narrowing due to redundant oropharyngeal tissue, and large neck circumference. Potentiating this problem are the proinflammatory cytokine concentrations, which are increased in patients with obesity, particularly in those with obstructive sleep apnea (93, 94), in which IL-6 and TNF-α have been shown to circulate at higher concentrations. The amplified cytokine response to viral respiratory infection is a well-known feature of influenza (95), in which infected resident epithelial cells and circulating immune cells

Table 1. Comprehensive List of Cytokines Implicated in Obesity and Severe COVID-19

Cytokine/ Chemokine	Concentration in Obesity	Concentration in Severe COVID-19
TNF-α (TH1; adipokine, cytotoxic)	Increased TNF-α	Increased TNF-α
TNF-β (TH1; cytotoxic)		
IL-1	Increased IL-1β	Increased IL-1β Increased IL-1RA (antiinflammatory)
IL-6 (adipokine, cytotoxic)	Increased	Increased
IL-8/CXCL8	Increased	Increased
IL-2 (TH1/TH2; cytotoxic)	Unknown	Increased
IFN-γ (TH1; cytotoxic)	Increased	Unknown
CXCL10/IP-10	Increased	Increased
CXCL9/MIG1	Increased	Unknown
IL-17	Unknown	Increased
IL-7 (cytotoxic)	Unknown	Increased
IL-4 (TH2; cytotoxic)	Unknown	Increased
IL-9 (TH2)	Unknown	Increased
Rantes/CCL5	Increased	Increased
MIP-1α/CCL3	Increased	Increased
MCP-1/CCL2	Increased	Increased
GM-CSF (TH1/TH2)	Unknown	Increased
TGF-β	Increased	Increased
IL-10 (TH1/TH2; cytotoxic; allergic)	Increased	Increased

Definition of abbreviations: COVID-19 = coronavirus disease; GM-CSF = granulocyte-macrophage colony-stimulating factor; MCP-1 = monocyte chemoattractant protein-1; MIP-1α = macrophage inflammatory protein 1α; TGF-β = transforming growth factor-β; TH1 = T-helper cell type 1.

produce IFN's, 1L-1β, TNF-α, and IL-6. Indeed, the cytokine storm phenotype, which is manifested by the profound activation of the immune response, is the clinical hallmark of COVID-19 multiorgan dysfunction and is associated with critical illness and mortality in COVID-19 (96). Robust cytokine responses in COVID-19 involve IL-2, IL-7 MCP-1, TNF-α, and IFN-inducible protein 10 (32). This pattern mirrors ARDS (97) and bacterial pneumonia, which involves IL-6, TNF-α, and IL-1β release. This response, in conjunction with the dysregulated activation of thrombin (98), leads to the multiorgan dysfunction seen in severe COVID-19 (96, 99). Thrombin is not only an essential mediator of *in situ* thrombosis but also exerts a proinflammatory response via protein-activated receptors (98).

Differential cytokine profiles have bolstered our understanding of disease severity and risk for both SARS-CoV-2 (100) and COVID-19 (101) respiratory disease. Notably, IL-10 concentrations were found to be predictors of severe disease in SARS and COVID-19 (102). In addition, in patients with cytokinemia due to COVID-19, IL-1β, IL-6, and IL-10 concentrations are higher than those found in critically ill patients with community-acquired pneumonia, and they are quantitatively correlated with severity of illness (103) Virus replication in airway epithelial cells promotes CD8 stimulation and cytokine release, resulting in local tissue destruction and systemic inflammatory responses (104). IL-6 production has been correlated with mortality in H1N1 in 2009 (105) and was similarly shown to be elevated in patients with SARS from a Wuhan cohort (102) In MERS-CoV and SARS, cytokine production was elevated, and this was found to be due to nuclear translocation of NF-κB (32, 87, 106). Ultimately, numerous proinflammatory cytokines are not only independently implicated in obesity but also correlate to increased concentrations in severe COVID-19 (Table 1).

Discussion: Clinical Correlation Obesity in SARS-CoV-2 and Cytokine Storm in Patients with Obesity

A comprehensive understanding of the mechanism by which the altered immunologic state of visceral obesity yields predisposition to severe SARS-CoV-2 infection is clearly needed to optimize management strategies. Likewise, the impact of obesity on every aspect of both the innate and adaptive immune systems, including cytokine, chemokine, and adipokine milieu should be assessed. In previous SARS-CoV infections, respiratory ciliated cells were found to abundantly express ACE-2 receptors, and these ciliated cells were the predominant cell type infected by SARS-CoV (107). In obesity, insulin resistance and associated chronically elevated adipokines, including leptin, resistin, and visfatin, promote a constitutive hyperinflammatory response, including cytokine release (108) (Table 2). Resistin may be an important mediator, as it downregulates TRAF-3, which normally impairs TNF, and upregulates VCAM1 and ET-1, which may activate endothelial cells (109). Upon attachment of the virion to antigen-presenting cells such as macrophages, which are overproduced in SARS-CoV-2 (110), recognition receptors such as TLR2–4 (111) lead to the activation of NF-κB, IFN-ɤ, and the type I IFN pathway (112). These TLRs are believed to possibly be activated by saturated fatty acids in the setting of obesity (39), suggesting a baseline activation that is furthered by SARS-CoV-2 viral infection. The downstream effects of these intracellular pattern recognition receptors are a vital portion of the inflammatory response, leading to the production of proinflammatory cytokines TNF, IL-1, IL-6, and IL-8, which are elevated at baseline in obesity (Table 3). In addition, in patients with obesity, there is an elevation in gene expression of chemokines MCP-1, MIP-1α, MIP-1β, MCP-2, MCP-4, MIP-2α, and PARC (pulmonary and activation-regulated chemokine) within adipose tissue (59) that may lead to increased chemokine production.

Table 2. Comparison of Adipokines Implicated in Obesity and Severe COVID-19

Adipokines	Concentration In Obesity	Concentration in Severe COVID-19
Leptin	Increased	Increased
Visfatin	Increased	Unknown
Adiponectin	Decreased	Unknown
Resistin	Increased	Unknown
Omentin (antiinflammatory)	Decreased	Unknown

Table 3. Key Cytokines Elevated in COVID-19 Immune Response and Obesity

Cytokine	Obesity Implicated (+/−/Unknown)
TNF	+
1L-10	+/−
GM-CSF	+
IFN-γ	+
TGF-β	+
MCP	Unknown
MIP-1α	+
IL-2	Unknown
IL-4	Unknown
IP-10/CXCL10	+
Chemokines: CCL-2, CCL-3, CCL-5, CXCL-8, CXCL-9, and CXCL-10	+

Finally, immunologically mediated changes during SARS-CoV-2 infection are especially destructive in patients with obesity, as they are already faced with mechanical disturbances that predispose to hypoxia and hypercapnia, including poor lung compliance, respiratory muscle inefficiency, ventilation–perfusion mismatching, and impaired gas exchange (92). Undoubtedly, patients with ARDS secondary to COVID-19–associated viral pneumonia and hemodynamic compromise due to cytokine storm are at increased risk for poor outcomes because of these mechanical defects. Ongoing studies comparing subsets of patients with obesity with COVID-19 with those having a normal BMI, both with and without cytokine storm, will be crucial in the expansion of our understanding of the role of obesity in COVID-19–related illness.

Conclusions

Early population data from COVID-19 studies, together with conclusions from animal and human studies of prior pandemics, establish the link between obesity, metabolic disease, and the immunological response to respiratory infection. Pathological attenuation of the innate and adaptive immune systems in obesity predispose to infection via dampened response to invading viral pathogens. Concurrently, changes in baseline concentrations of adipokines, leptin, and resistin prime the host to immunodeficiency, coupled with a hyperactivated inflammatory response, cytokine storm, and consequent critical illness that represent the basis of COVID-19 morbidity and mortality. If we are to pave the way for preventive action in the form of vaccine development as well immunologically based treatment strategies for COVID-19, we must combine existing data with these mechanistic links described to devise new translational and clinical studies. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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