The Collision of Meta-Inflammation and SARS-CoV-2 Pandemic Infection

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Abstract

The COVID-19 pandemic has forced us to consider the physiologic role of obesity in the response to infectious disease. There are significant disparities in morbidity and mortality by sex, weight and diabetes status. Numerous endocrine changes might drive these varied responses to SARS-CoV-2 infection including hormone and immune mediators, hyperglycemia, leukocyte responses, cytokine secretion, and tissue dysfunction. Studies of patients with severe COVID-19 disease have revealed the importance of innate immune responses in driving immunopathology and tissue injury. In this review we will describe the impact of the metabolically induced inflammation (meta-inflammation) that characterizes obesity on innate immunity. We consider that obesity-driven dysregulation of innate immune responses may drive organ injury in development of severe COVID-19 and impair viral clearance.
Introduction

The chronic obesity-induced inflammation characterized by increased tissue and circulating myeloid cells has been termed metabolic inflammation or meta-inflammation. The coronavirus disease 2019 (COVID-19) pandemic has highlighted the endocrine manifestations of obesity and impact of diabetes and obesity on immune responses to infectious disease. Obesity and metabolic syndrome have been identified as risk factors for severe manifestations of SARS-CoV-2 infection. Prior studies of the epidemiology of sepsis, the acute respiratory distress syndrome (ARDS), and other acute illnesses have raised the question of whether obesity is associated with lower mortality in critical illness – the “obesity paradox”. However, the COVID-19 pandemic has forced reconsideration of the impact of obesity and diabetes on disease outcomes. While obesity and diabetes may complicate the delivery of supportive care in critical illness regardless of the underlying disease, lessons learned from the interaction of obesity with other systemic inflammatory syndromes suggest that obesity modifies biologic factors related to SARS-CoV-2 infection and the COVID-19 syndrome.

COVID-19 was first reported in Wuhan, China in December 2019 and first made its appearance in the United States in Washington State on January 31, 2020. Outbreaks quickly spread throughout Washington and California before spreading to the rest of the US. Obesity was not studied in the early SARS-CoV-2 studies coming from Wuhan, China, likely because so little of the population is obese. However, pre-existing type 2 diabetes was demonstrated to be a risk factor for illness severity. In the US, obesity, hypertension, and diabetes are commonly reported among the most common comorbidities for patients hospitalized with COVID-19 across several metropolitan disease outbreaks. When considering the obesity epidemic in the US, this is not surprising, as approximately 35% of men and 40% of women in the United States are obese by body mass index (BMI > 30 kg/m2). However, obesity is independently associated with odds of hospital or intensive care admission among patients presenting for medical care. Several studies suggest that...
obesity is an independent predictor of hypoxic respiratory failure and death among hospitalized patients, even among young patients with fewer comorbidities. Decisions about hospital admission, and thus the characteristics of hospitalized patients, may be confounded by the expectation that obese patients require closer monitoring. Population-based estimates of COVID-19 mortality, however, also show a 2.6-fold increase in risk for patients with BMI > 40.

Prior meta-analyses of both ARDS and sepsis have found either no harm or reduction in mortality among obese adults. However, severity of illness and organ damage has been demonstrated to increase based on obesity in pediatric patients. While changes in critical care practice during a pandemic could explain differences in mortality or ICU admission, the association of obesity with physiologically defined hypoxic respiratory failure suggests a biologic interaction of obesity with SARS-CoV-2 infection. Obesity as a risk factor for severe infectious disease is not a new concept and is not limited to coronavirus infections. During the 2009 influenza A/H1N1 pandemic, it was noted that obese patients were more likely to experience more severe disease requiring hospitalization than normal weight patients. Additionally, even when both groups were vaccinated, obese individuals were more likely to become infected with the influenza virus. Along with viral infections, obesity alters the course of bacterial infections. All of this clinical evidence emphasizes the importance of further understanding the mechanisms by which obesity influences immune responses.

The current SARS-CoV-2 pandemic has highlighted the increased need for research to understand the mechanisms behind severity of pandemic infection in different risk groups.
With the prevalence of obesity rising without an end in sight, it is important to understand the endocrine, metabolic, and inflammatory shifts that occur in obesity may drive increased pathogen-driven morbidity and mortality.

**Monocytes and macrophage activation at the intersection between chronic metabolic inflammation and acute infection**

High levels of circulating chemokines and cytokines are associated with severe COVID-19 disease and mortality. SARS-CoV-2 infection, like many other coronavirus infections, has the ability to generate a cytokine storm\(^{27}\), caused by the release of large amounts of cytokines and chemokines by effector cells of the immune system. The cytokines most associated with the cytokine storm generated by SARS-CoV-2 are IL-1\(\beta\), IL-6, IL-12, and TNF-\(\alpha\). IL-6 seems to be the most predictive cytokine, as patients with increased IL-6 above 80 pg/mL was associated with a 22-fold increased risk of respiratory failure\(^{28}\).

Early studies of leukocyte heterogeneity utilizing single-cell RNAseq in samples from patients with COVID-19 indicate a shift in monocyte populations. These studies have identified increased cytokine and chemokine expression which are associated with markers of classical, pro-inflammatory monocytes in circulation\(^{29}\). Similarly, leukocytes in the bronchoalveolar lavage fluid of patients with COVID-19 shift from homeostatic alveolar macrophage signatures to chemokine expressing classical monocytes with cell surface markers such as CD14, FCN1, and S100A8\(^{30}\). Given the association of high cytokine and chemokine expression and innate-immune mediated tissue injury, these pro-inflammatory immune subsets have been viewed as drivers of pathology in SARS-CoV2 infection\(^{31}\).
Pro-inflammatory circulating monocyte and macrophage populations are associated with a number of chronic diseases, including obesity. A striking feature of obesity in both clinical and animal studies is the chronic low-grade inflammation tied with metabolic diseases, meta-inflammation. Increased BMI correlates with an increase of several cytokines including IL-6, IL-8, IL-1β, and TNF-α and obesity also correlates with an increase in chemokines such as CCL14 and MCP-1 furthering the overall inflammatory tone.

Hyperglycemia alone may lead to significant changes in macrophage function and inflammation. In patients with diabetes, increased glucose levels and glycolysis promoted Sars-CoV-2 replication in monocytes via ROS/HIFα pathway activation leading to secondary T-cell dysfunction. Patients with well controlled blood glucose levels were less likely to experience serious complications and death from COVID-19 compared to diabetic patients with poorly controlled blood glucose levels. The well-controlled patients had lower IL-6, C Reactive Protein, and LDH levels, as well as only a 1.1% mortality rate, which is significantly lower than the 11% mortality rate seen in the poorly controlled group. This association of diabetes diagnosis with COVID-19 mortality is also observed on the population level as well. While one cannot directly say the hyperglycemia causes this enhanced mortality, there is abundant evidence that obesity leads to long-term reprogramming of the innate immune system.

Macrophages from obese animals and humans have been described as metabolically active, M1 polarized, and pro-inflammatory with both regulatory and detrimental activity. These macrophages produce cytokines, chemokines, reactive oxygen species, and factors regulating fibrosis and metabolism. Overall, our understanding is that these metabolic macrophages have a similar profile to those stimulated with lipopolysaccharide (LPS), an abundant bacterial derived
molecular pattern molecule and ligand of the Toll-like receptor 4 (TLR4). More recently it has become clear that while the inflammatory phenotype of these macrophages is closest to what is seen with LPS stimulation, traditional M1 macrophages, the added activation by fatty acids creates a unique phenotype that has characterized these obesity myeloid cells as metabolically active macrophages 41.

While changes to macrophage phenotype in obesity were originally characterized in the adipose tissue36,42, it is now evident that obesity has significant effects on hematopoiesis, circulating monocytes, and macrophages in multiple organs. Elevated BMI and obesity has been shown to enhance hematopoiesis and expand myeloid cell production43,44 but it has also been shown to impair immune responses in a TLR4 dependent manner 45. High fat diet increases the number of monocytes in circulation and expands bone marrow macrophages, neutrophils and their progenitors 43. Expansion of these progenitors leads to increased macrophage production, but also skews the resulting macrophage population to a pro-inflammatory phenotype43,44,46.

During obesity there is an overall increase in chemokines, which play a role in metabolic inflammation by recruiting monocytes into adipose tissue. Additionally, during obesity and type 2 diabetes (T2D), there is an increase in circulation of free fatty acids (FFAs), including palmitate (PA). PA induces CCL4 release from monocytes and macrophages by interacting with TLR4 47. Obese individuals, regardless of diabetes status, also have higher circulating levels of LPS 48,49 which binds to TLR4. This binding increases the production of the chemokine CCL2 in monocytes and macrophages 50. This further leads to enhanced tissue macrophages that have the potential to lead to dysfunctional cytokine production and tissue damage if triggered.
While the phenotype of these macrophages in driving impaired metabolism is well described there are several other implications of these metabolically activated macrophages. In pulmonary viral infections such as influenza, macrophages from obese mice exhibit enhanced and likely injurious pro-inflammatory cytokine production but impaired production of antiviral type-I interferons. Obese mice suffer increased interstitial inflammation, alveolar permeability, and lung injury even in the absence of increased viral load. Chronic systemic inflammation is accompanied by impaired induction of pathogen-induced and lung-specific responses to influenza across a variety of obesity models. Pro-inflammatory activation of macrophages in obesity impairs their function in other domains, as well. For example, in obese diabetic mice, macrophages recruited to diabetic wounds as a result of epigenetic alterations have a pro-inflammatory phenotype and have elevated levels of prostaglandin E2 (PGE2) production. PGE2 signaling can impair macrophage innate immune functions as well as alter production of pro-inflammatory cytokines. This activated state causes delayed wound healing but may also have further implications in responses to infection, which is a major physiologic function of macrophages. PGE2 signaling instructs macrophages to secrete IL-10 and influences naïve T cells to shift from a Th1 to a Th2 phenotype. This Th2 phenotype causes a decreased ability to clear intracellular pathogens, such as viruses.

**Impact of Obesity in Response to Infection**

Immune system activation in obesity is not confined to adipose tissue or organ dysfunction related to metabolic disease, such as the liver or vasculature, but also has a negative effect on the immune system on the whole, leading to an increase risk of infection. It is well recognized clinically that diabetes negatively impacts the body’s response to infection. Hyperglycemia stemming from T2D caused by obesity has proven to reduce control of invading pathogens. Hyperglycemia can increase glucose concentrations in the lung and respiratory system, allowing for greater bacterial colonization and replication and can further directly affect intestinal barrier dysfunction enhancing risk for
infection\textsuperscript{66}. On top of the direct effects that obesity may have on macrophage function in infection, diaphragm excursion is also inhibited due to obesity, which restricts ventilation and can inhibit the clearance of pulmonary pathogens\textsuperscript{10}.

Along with increased lung glucose and compromised airspace creating a hotspot for pulmonary infections in obesity\textsuperscript{67}, this condition and diabetes impairs bacterial killing\textsuperscript{68}. Several bacterial models have been tested in obese mouse models and have demonstrated impaired bacterial killing and more severe infection outcomes. For example, during infection with \textit{Mycobacterium tuberculosis}, macrophages from diabetic mice show impaired recognition of the bacteria, as well as a decrease in ability to properly phagocytize and clear \textit{M. tuberculosis}\textsuperscript{69}. After adoptive transfer of macrophages from infected diabetic mice into lean mice, defects in macrophages were still noted to lead to impaired T-cell priming, indicating an intrinsic defect in these macrophages separate from their diabetic environment\textsuperscript{70}. The diabetic lung microenvironment has influenced these alveolar macrophages to have impaired recognition and killing. Bacterial loads are also higher in the lungs, liver, and spleen of diabetic mice, with an increase in the number and size of granulomas in the lungs of these animals\textsuperscript{71}. With directed pulmonary infection with \textit{Klebsiella pneumoniae}, obese mice had impaired host defense with defects in macrophage phagocytosis\textsuperscript{72-74}. Similarly, studies with \textit{Staphylococcus aureus} sepsis demonstrated higher bacterial loads in obese mice although numbers of tissue macrophages were higher in obese mice\textsuperscript{73}. Additionally, less virulent strains of \textit{S. aureus} can generate and maintain an infection longer in diabetic hosts compared to normal weight hosts\textsuperscript{75}. Even more broadly in sepsis models, obese animals have been seen to have more severe organ damage and worsened survival\textsuperscript{76,77}. 
Even a short-term high fat diet can impact the reaction to a bacterial infection. Mice fed a high fat diet for 16 days and then orally challenged with *Listeria monocytogenes* had reduced inflammatory responses, and as a result increased bacterial load and increased numbers of goblet cells.

Obese individuals are not only susceptible to severe bacterial infections, but also severe viral infections. Obesity has been shown to be a risk factor for human papilloma virus incident infection, however obesity was not associated with how long the infection persisted. Additionally, in the 2009 H1N1 Influenza pandemic, obesity was a major risk factor for severe infection and death. Adults aged 20 years or older who died from H1N1 infection were more likely to be obese or morbidly obese. When lean and obese mice are infected with H1N1, although the lungs exhibit the same viral titer, the obese mice lost more weight and experienced more pulmonary pathology than lean mice. Additionally, the virus spread to the alveolar epithelial cells in the obese mice. The increased spreading of the virus in obese mice combined with the reduction in local production of several pro-inflammatory cytokines (while still increased in circulation) likely contributed to the increased murine morbidity and mortality due to infection. The same illness severity and poor responsiveness to treatment with obesity has been demonstrated in seasonal influenza infections.

It has been widely speculated that higher ACE-2 expression in adipose tissue may result in higher total body SARS-CoV-2 viral load in obese individuals. Early reports have not demonstrated a correlation among viral load and obesity or initial viral load and disease severity. In seasonal and pandemic influenza, however, obese individuals may be more susceptible to severe viral respiratory disease even if they mount a serologic response to vaccination, likely due to impaired T-cell function despite enhanced expression of typical myeloid-cell derived pro-inflammatory cytokines. The possibility of different vaccine or treatment efficacy in obese patients underscores the importance of adequate representation of obese individuals in clinical trials and a focus on patient-centered, rather than serologic outcomes in evaluating efficacy.
Along with possible impairments in pathogen clearance, obese hosts are more likely to experience the breakdown of respiratory epithelium during a pulmonary infection, which leads to increased fluid in the airway space. This allows the pathogen to have the opportunity to more easily spread throughout the body and leaves the host with reduced lung function\textsuperscript{63}.

**ACE-2 expression and vulnerability to SARS-CoV-2 infection**

The SARS-CoV-2 virus, like other members of the betacoronavirus subfamily\textsuperscript{85}, enters mammalian cells through the interaction of the viral envelope spike glycoprotein and angiotensin converting enzyme 2 (ACE-2) on host cells\textsuperscript{86}. ACE-2 is expressed in many human tissues, including not only the lungs but also kidney, brain, adipose tissue and small intestine, raising the question of which symptoms of COVID-19 are due to direct viral effects versus systemic immune responses, especially in severe disease\textsuperscript{87}. Tropism of SARS-CoV-2 for extrapulmonary tissues is confirmed by detection of viral RNA from samples outside the respiratory tract\textsuperscript{88}. ACE-2 is upregulated in adipocytes in obese and diabetic patients, which allows the virus to target and replicate in adipose tissue and has led to speculation that adipose tissue can serve as a reservoir of SARS-CoV-2, potentially worsening disease severity in obese individuals\textsuperscript{89-91}. A correlation between respiratory tract viral load and obesity, however, has not been confirmed\textsuperscript{83}.

Intestinal involvement in SARS-CoV-2 infection may interact with obesity associated meta-inflammation. While meta-inflammation in obesity is a systemic, multifactorial process\textsuperscript{92}, the gut microbiome is known to have a bidirectional relationship to meta-inflammation\textsuperscript{93} influencing intestinal inflammation\textsuperscript{94}. SARS-CoV-2 infection has been associated with shifts in gut microbiota to more pathogenic taxa, as have other states of critical illness\textsuperscript{96}. These shifts may encourage a state of
systemic inflammation. Both dysbiosis and the direct enteropathic effect of SARS-CoV-2 infection may promote gut barrier permeability and increase metabolic endotoxemia, a potential mediator of metabolic disease and meta-inflammation in obesity\textsuperscript{96}. Establishing a connection between gut dysfunction and meta-inflammation in COVID-19 survivors will require long-term studies.

While considerable speculation has focused on how ACE-2 levels are driven by either polymorphisms, comorbidity, or environmental factors, other genetic factors may also play a role in susceptibility to severe COVID-19 disease, as well\textsuperscript{97}. The first genome-wide association study of COVID-19 severity identified two loci – one containing the ABO blood group locus and another at 3p21.31\textsuperscript{98}. The latter locus contains several chemokine genes, the expression of which may plausibly be altered in meta-inflammation. An ongoing multinational effort continues to examine how host genetics may inform susceptibility to severe COVID19 and may reveal factors that interact with gene expression obesity\textsuperscript{99}. While genetic factors explain a small part of the risk for developing diabetes, diabetes risk genes typically do not include those related to antiviral immunity\textsuperscript{100}, emphasizing that susceptibility to SARS-CoV-2 infection or development of severe COVID19 disease is likely due to environmental exposure and pathophysiology that develops through the life course, rather than a common predisposing genotype.

**Females are protected both from COVID-19 disease and meta-inflammation**

In addition to obesity and comorbidity, male sex confers a significantly increased risk of severe COVID-19 disease and death\textsuperscript{14}. Differences in myeloid inflammation among males and females may play a protective role in the immunopathology of COVID-19, especially in the setting of obesity.
Not all obese individuals are at risk for metabolic and cardiovascular disease\textsuperscript{102} and not all obese develop obesity induced inflammation to the same degree\textsuperscript{103}. Increased androgen concentration in males is also thought to lead to increased IL-10 production when peripheral blood mononuclear cells are stimulated by viral antigens, leading to a delayed and diminished pro-inflammatory response which may also explain disease severity\textsuperscript{104}. Additionally, males tend to have increased levels of pro-inflammatory cytokines and chemokines after stimulation with LPS intraperitoneally \textit{in vivo} and \textit{in vitro} assays\textsuperscript{105,106}. Hence, this difference by sex and due to sex hormones could lead to a possible increased cytokine storm in males with obesity\textsuperscript{107}, and explain the pathologic response and enhanced morbidity described clinically.

Pre-menopausal females are relatively protected from obesity induced inflammation, macrophage activation, and expansion of myeloid progenitors and are relatively protected from metabolic and cardiovascular disease\textsuperscript{108}. In pre-clinical models, females are protected from meta-inflammation\textsuperscript{108-111}. One explanation for this is that females generally handle the expansion of adipocytes with resident macrophage proliferation without recruitment of pro-inflammatory macrophages\textsuperscript{109}. This finding that all macrophages are not the same in responsiveness to obesity but that the overall trend is pro-inflammatory in nature requires further investigation into the overall macrophage phenotype with obesity. In the context of infection though, those with pro-inflammatory macrophages can produce an enhanced cytokine environment leading to severity of illness in obese individuals via both systemic and local lung effects\textsuperscript{112,113}.

While the interaction of sex and diet induced obesity has been most elucidated in the setting of innate immune cell populations, sex hormone receptors are present on cells of the adaptive immune system as well, and sexual dimorphism in autoimmunity and humoral responses has been noted for
decades\textsuperscript{114}. These differences may also be critical in favoring antiviral immunity in females. Of particular note, female mice expand the population of regulatory T-cells significantly compared to male mice in obesity\textsuperscript{115}. This cell population is noted to be deficient in obese male mice during influenza infection\textsuperscript{54} and may play a role in limiting lung injury in the setting of viral infection.

\textbf{Influence of age on COVID-19—does increased BMI and age shift disease burden?}

Individuals of all ages are at risk for obesity, but it is not clear if weight status influences what has been seen with age related risk for COVID severity. Of patients aged 19-64 years admitted to the hospital, those with co-morbidities caused by high BMI were more likely to be admitted to the ICU\textsuperscript{63} and this is true regardless of sex\textsuperscript{10}. As humans age, the immune system changes\textsuperscript{116}, with a decreased number of lymphocytes, which are important cells for fighting viruses. This has proved to be a significant disadvantage during past epidemics, such as SARS\textsuperscript{117}. While elderly individuals are at increased risk for severe COVID-19, the obesity epidemic is shifting to the most targeted demographic to a younger age group. Younger COVID patients are likely to have a higher BMI than older patients while this same trend did not exist in non-COVID admissions\textsuperscript{118}. Age related changes in metabolic inflammation are still being understood regardless of infection\textsuperscript{119} and the impact of this on COVID-19 needs to be further examined.

On the other extreme, young children have fared better than adults during this pandemic. Many viruses, including respiratory syncytial virus and influenza virus, infect children at particularly high rates compared to adults aged 30-65. However, children appear to be less susceptible to SARS, MERS, and SARS-CoV-2 infection\textsuperscript{120}. Additionally, few children present with common co-morbidities seen in adults, such as hypertension, T2D, cancers, and pulmonary diseases. The absence of these diseases may allow children to only have a mild case of the virus\textsuperscript{122}. More recently some children
who have recovered from SARS-CoV-2 infection are presenting with post-infectious cytokine release syndrome, indicative by a fever, GI symptoms, and a rash. Consistent with early life meta-inflammation with obesity it appears that obese children are at higher risk for severe disease. Does hyperglycemia worsen COVID-19 or does COVID-19 lead to immune pancreatic damage leading to hyperglycemia?

COVID-19 patients have been found to have elevated blood sugars during hospitalization and those with uncontrolled diabetes had a higher mortality. However, SARS-CoV-2 virus can also damage the pancreas by infecting the α and β cells, which function to regulate blood sugar levels. In severe COVID-19 cases, 17% of patients were diagnosed with pancreatic injury, compared to only 1-2% in non-severe cases. One possible explanation is that the virus can also increase pro-inflammatory cytokines that destroy these cells. This could possibly lead to an autoimmune disease and development of type 1 diabetes (T1D). Prior studies have demonstrated that SARS coronavirus itself can directly damage islets, further research will be needed to see if T1D or beta cell failures were caused by COVID-19 and if this has happened to other individuals. Given ACE-2 expression in the pancreas it has been hypothesized that this may be a mechanism for pancreatic damage specifically in SARS-CoV2 infection.

Conclusion

Obesity is a significant risk factor for severe COVID-19 illness. Patients with obesity and metabolic disease frequently experience a state of low-grade chronic meta-inflammation. Prior studies of vaccine efficacy and response to viral and bacterial infection show that meta-inflammation may significantly alter the response to pathogens. While this has not been directly established in SARS-CoV-2 infection, emerging evidence indicates that disordered myeloid inflammatory responses are a
significant driver of COVID-19 severity. While the understanding of possible therapies and vaccines continues to rapidly evolve,

understanding the mechanisms and pathways altered by enhanced adiposity and metabolic inflammation in COVID-19 severity is critical to understanding disease severity and the possible treatment mechanisms.
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