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Review Article

Obesity and SARS-CoV-2 Infection a Multifaceted Interplay - Adipose Tissue Inflammation, Adipokine Disbalance and Immunity

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Abstract

Overweight and obesity are the most common comorbidities in SARS-CoV-2 patients, requiring hospitalization in intensive care units. The multifaceted nature of obesity including its effects on respiratory mechanics and immunity can fundamentally alter the pathogenesis of acute respiratory distress syndrome and pneumonia, which are the major causes of death due to SARS-CoV-2 infection. Most coronaviruses overcome host antiviral defense, and the pathogenicity of the virus is related to its capacity to suppress host immunity. Hyperleptinemia, insulin resistance and adipose tissue inflammation are hallmarks of obesity, which is associated with a leptin and insulin resistant state. Leptin regulates appetite and metabolism and through the Jak/STAT and Akt pathways modulates T cell number and function; insulin receptor signaling is closely engaged in T cell proliferation, whereas low garde adipose tissue inflammation provokes aberrant inflammasome activation. The review discusses these phenomena. It presents the reasons for susceptibility to respiratory viral infections in obese patients, as well as, the immunomodulatory effects of obesity to the outcome.

Keywords: Obesity; Adipose tissue inflammation; Adipokine disbalance; SARS-CoV-2; Immunity

Introduction

In the last fifty years, obesity has tripled. In 2016, more than 1.9 billion adults were with abnormal body mass index [1]. More than 300,000 deaths annually in USA are due to obesity, it reduces the average lifespan with 9-13 years [2,3]. SARS-CoV-2 is a novel Coronavirus (CoV) that has spread through Europe and USA causing pressure to the healthcare system. Advanced age and comorbidities are risk factors for severe forms of the disease [4]. Obesity predisposes patients with SARS-CoV2 infection to higher risk of complications and mortality [5]. In France, 47.6% of patients admitted to the Intensive Care Unit (ICU) had a Body Mass Index (BMI) >30kg/m^2 and 28.2% had a BMI >35kg/m^2 [6]. In Spain 48% of the admissions due to SARS-CoV-2 in ICUs were with obese patients [7]. In the ICU in USA there was a significant inverse relationship between BMI and age - advanced age increases the risk of severity of the diseases, but in younger patients, those with severe forms of the infection were more likely to have obesity [8].

Coronavirus Infection

In humans, the viral Spike protein (S) of SARS-CoV-2 binds to the receptor prior to activation and initial entry into the primary target cells. Angiotensin-Converting Enzyme 2 (ACE2) is the receptor for SARS-CoV-2. After viral entry, Pathogen-Associated Molecular Patterns (PAMP) are secreted. These are biomolecules derived from the surface of the viruses or generated during their life cycle [9]. They are recognized by the Toll like receptors. Upon PAMP recognition inflammatory cytokines and antiviral Interferons (IFNs) are secreted - type I IFNs (IFN-α and IFN-β), type II IFNs (IFN-γ), and type III IFNs (IFN-λ) [10]. Type 1 interferon is a key component of the host antiviral defense against SARS-CoV-2 [11]. Gene analyses of cell culture studies of SARS-CoV-2 infection in human airway epithelial cells illustrate a diminished IFN-I and IFN-III expression. This was validated in post mortem lung samples, as well as, serum from SARS-CoV-2 positive patients. SARS-CoV-2 provokes gene signature and transcriptional response characterized by cell death and leukocyte activation. Thus, despite the reduced IFN-1 and IFN-III response to SARS-CoV-2 there is a robust chemotactic and inflammatory response [12].

Suppression of Host Antiviral Response

Viruses encode products that mimic cellular components of the IFN signal transduction pathway. They suppress host interferon production and impair the development of an antiviral state [13]. In addition, Corona Viruses (CoV) can synthesize molecules that either suppress, or induce cell death. The molecules that suppress apoptosis extend the production of new virions in the infected cells. Those that function as inducers of apoptosis facilitate the release and dissemination of progeny virions [13]. Pyroptosis is cell death that results from an exuberant proinflammatory cytokine release [14]. The severe forms of SARS-CoV infection are associated with high levels of proinflammatory cytokines [11]. PAMPS generated during viral replication stimulate the NLRP3 antiviral immune response. NLRP3 inflammasome (NACHT, LRR, and PYD domains-containing protein 3) is an oligomeric complex that is critical in host antiviral response. Viruses either evade NLRP3 activation and facilitate viral replication, or trigger NLRP3 activation for pathological inflammatory response. Aberrant NLRP3 activation or chronic systemic inflammation lead

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to severe pathological injury. The pathogenicity of the virus is related to its capacity to suppress host immunity [14]. CoVs have evolved features that suppress the human IFN pathway [15-18]. Sets of tissues that harbor SARS-CoV-2 show that in human airway epithelial cells, IFN-I, and IFN II, upregulate ACE2 expression [19]. Angiotensin-Converting Enzyme (ACE) cleaves angiotensin I to angiotensin II, whereas ACE2 inactivates angiotensin II and is a negative regulator of the system. Angiotensin II drives acute lung injury through various mechanisms - plasma leakage, increased vascular permeability [20]. ACE2 is critical for early tissue tolerance to respiratory infection [19]. In influenza angiotensin, II levels rise and ACE2 provides protection to tissues reducing it [21]. SARS-CoV-S binds to ACE2 and reduces ACE2 expression causing acid-aspiration - induced lung failure [22]. Low levels of IFN-I are produced in response to SARS-CoV-2 infection, which blunts the protective effect of ACE2.

Adipose Tissue Inflammation

Adipose tissue inflammation is a hallmark of obesity [23]. Macrophages and dendritic cells, infiltrating adipose tissue provoke the production of the proinflammatory cytokines closely related to the metabolic consequences of obesity [24]. $CD8^+$ T-cell infiltration precedes macrophage accumulation and is essential for their differentiation, activation, and migration. Adipose tissue itself activates the $CD8^+$ T-cells without the need for a systemic increase in T-cells. The activated $CD8^+$ T-cells create a local proinflammatory milleu. In obesity, $CD4^+$ T-cells and Treg also contribute to adipose tissue inflammation. $CD4^+$ T-cells, balance the immune response, but are reduced in obesity. Treg cells mitigate the effects on the adaptive immune responses, [25]. In humans with obesity, adipose tissue depots contain ~40% macrophages [24]. They are primary mediators of the innate immune response and have an important role in the adaptive immune response. What is reasonably expected is that individuals with obesity would have increased mortality when afflicted with ARDS. In contrast, inflammatory cytokine milieu in obesity is not associated with mortality in mechanically ventilated patients with acute lung injury - obesity paradox in ARDS [26,27].

Obesity and Mortality in SARS-CoV-2

The high mortality rate among SARS-CoV-2 patients with obesity has however prompted against obesity paradox in ARDS [28]. During an infection, T-cell activation is accompanied by high-energy requirements to support biosynthesis of intracellular components. From an evolutionary perspective, downregulation of non-essential, energy-consuming pathways such as immune cell activation is pragmatic [29]. As leptin is the link between metabolism and the immune response, it seems reasonable that its dysregulation would have serious consequences during an infection. In SARS-CoV-2 infections, Lymphopenia occurs in almost 80% of patients. Patients with infection demonstrate low levels of circulating $CD4^+$ and $CD8^+$ T lymphocytes. In contrast, in lungs there is accumulation of mononuclear cells and macrophages [30,31]. Peripheral Lymphopenia and macrophage predominance in SARS-CoV infection reflect the suppression of host antiviral response [32]. Immune evasion may increase viral replication and hinder its clearance. This causes tissue damage and further stimulation of macrophages. The enhanced secretion of cytokines results in cytokine-storm syndrome and precipitates multi-organ failure [33]. It is assumed that hyperleptinemia and insulin resistance in obesity disrupts additionally disrupts T-cell function and suppresses T-cell response to infection [34,35].

Leptin and Immune Cell Function

In a mouse model of diet-induced obesity, Hyperleptinemia was associated with increased mortality, viral spread, and lung levels of proinflammatory cytokines including Interleukin 6 (IL-6) and IL-1β, following infection with influenza (H1N1) in a mouse model of diet-induced obesity. Administration of anti-leptin antibody led to a decrease in the proinflammatory response and improved lung pathology and survival rate [36]. In patients with diabetes and ARDS, elevated leptin levels in bronchoalveolar fluid are associated with increased mortality [37]. Obesity is marked by persistent hyperleptinemia and is a state of leptin resistance. Excess leptin secretion from adipocytes may have paracrine effects on T-cells and promote the development of systemic inflammation [38]. Leptin is a mediator of pulmonary immunity and its chronically elevated levels impair host defenses [39,40]. Leptin is produced by adipocytes, bronchial epithelial cells, type II pneumocytes, and lung macrophages [41]. In addition to satiety, leptin regulates immune cell number and function [42-45]. It is secreted by adipocytes in proportion to fat mass and is essential to upregulate glucose metabolism in activated T-cells [46]. Leptin deficiency reduces T-cell numbers, decreases $CD4^+$ helper T-cells, increases proliferation of regulatory T-cells (Treg, suppressor of effector T-cells activation and excessive inflammatory responses) and provokes aberrant cytokine production [42-45]. Leptin induces Th cells toward the Th1 subset, which has a more proinflammatory response than the Th2 subset that has predominantly regulatory functions [47]. The metabolic derangements that occur when the immune system is activated is regulated by leptin. It inhibits the apoptosis of immune cells and its deficits contribute to the defective immune response. Leptin administration inhibits baseline thymic apoptosis in young rats by 15-30%. [48]. Leptin has an important role in the metabolic regulation of Treg cells. These cells expressed high amounts of both Leptin and its Receptor (LepR). High leptin levels can promote hyporesponsiveness of Treg cells, whereas leptin neutralization rescued Treg cells from their hyporesponsiveness [49]. High circulating leptin have a detrimental effect on intracellular signaling and the response to an infection.

Insulin Resistance, Obesity and Immune Activation

After activation, T-cells use glycolysis to produce the biosynthetic precursors required for rapid cell growth and proliferation. If glucose metabolism is insufficient, T-cells become hyporesponsive or non-responsive [38]. The activation of the PI3K/Akt/mTOR pathway in T-cells facilitates their differentiation and primarily occurs through triggering of the T-cell receptor and CD28 co-receptor. The insulin receptor has also been shown to have a role in PI3K/Akt/mTOR pathway. Signaling downstream of the insulin receptor is reduced in $CD4^+$ T-cells from insulin receptor knock-down transgenic rats [50,51]. Insulin resistance commonly co-exists with obesity. In these subjects, impaired insulin receptor signaling may contribute to insufficient energy supply for effector T-cells to mount an effective response to infection.

Obesity, Pulmonary Mechanics and ARDS

Another feature of ARDS associated with SARS-CoV-2 is that it presents in an atypical form of preserved lung mechanics and severe hypoxemia. The accumulation of fat in the mediastinum and in the abdominal and thoracic cavities decreases functional residual capacity in patients with obesity. This alters the mechanical properties of the chest wall. The diaphragm is elevated and its downward pressure is limited, which elevates pleural pressure. In supine patients with abdominal obesity, diaphragmatic excursion is perturbed, making ventilation difficult. That is why prone positioning is recommended to improve oxygenation in patients with refractory hypoxemia due to SARS-CoV-2 ARDS [26-28].

Conclusion

Obesity predispose patients to morbidity and mortality from the SARS-CoV-2 infection through a compromised immune response. The diminished immune response fails to limit the viral replication and provokes a series of events culminating in heightened cytokine release that can cause ARDS and multiorgan failure. The high mortality rates from SARS-CoV-2 infection in individuals with obesity suggests that the metabolic consequences of obesity compromise host antiviral defenses. Hyperleptinemia is a common feature of obesity and links the regulation of metabolism and immunity. Leptin and insulin resistance (commonly encountered in obesity) are closely associated with T cell activation. His high pathogenicity of the virus in obesity is the result of: 1) Suppressed host interferon production; 2) Proinflammatory state of adipose tissue that contributes to low grade protracted activation of T-cells and their premature senescence; 3) Monocyte-macrophage overstimulation and cytokine oversecretion. Finally yet importantly, obesity hinders respiratory mechanics proturbating respiratory systems.

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