Review Article

Journal of Microbiology and Related Research
Volume 7 Number 2, July - December 2021
DOI: http://dx.doi.org/10.21088/jmrr.2395.6623.7121.5

Corona Virus Disease-19 Obesity & Leptin: A Complex Paradigm

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How to cite this article:

Diksha Rani, Jitender Gairolla, Shikha Mudgal, et. al./Corona Virus Disease-19, Obesity & Leptin: A Complex Paradigm/J Microbiol Relat Res. 2021;7(2): 65–74.

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Received on: 17.02.2022, **Accepted on:** 18.03.2022

Abstract

The global prevalence of obesity is increasing and recognized as a potential risk factor for viral infections including Coronavirus Disease-19. Morbidity and mortality due to COVID-19 are higher in obesity which is considered a constant state of low-grade inflammatory milieu. Emerging data revealed a fatal connection of obesity with COVID-19 however the underlying mechanism is unclear. Leptin, a non-glycosylated peptide hormone derived from white adipose tissue that assists in metabolism, homeostasis, neuroendocrine, and other physiological functions. Additionally, leptin, as an adipocytokine has pro-inflammatory properties and acts as a connecting link between obesity and host immune responses thus, proliferates the secretion of C-reactive protein (CRP), IFN-γ, TNF-α IL-6, IL-4 and IL-2. This paper aims to address the paramount role of leptin as a potential mediator of inflammation that could exaggerate and worsen the prognosis of COVID-19 in obese individuals. Furthermore, the disproportionate efficacy of the COVID-19 vaccine in obese individuals is also highlighted.

Keywords: Leptin, Obesity, COVID-19, SARS-CoV-2, Vaccine

Introduction

Corona Virus Disease-19 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The disease which emerged in the last week of December 2019 has greatly impacted public health worldwide and has brought the world to a standstill.[1] As of 20 February 2022, the number of confirmed cases has exceeded 422 million and resulted in more than 5.8 million deaths globally (https://www.who.int/ accessed on 20 February, 2022). Morbidity and mortality due to SARS-CoV-2 are higher in people with underlying conditions such as obesity, diabetes, hypertension, stroke, cardiovascular, and chronic lung diseases.[2] The global prevalence of obesity is increasing and recognized as a critical factor for viral infections.[3-5] Emerging literature revealed a fatal linkage between obesity and COVID-19 severity.[6,7]

Obesity and overweight increase the risks of SARS-CoV-2 infection, thus requiring hospitalization and aggressive treatment in intensive care units (ICUs).[8,9] The preliminary findings from China and USA suggest that 70–90% of COVID-19 cases admitted to ICUs were overweight.[10] Moreover, the prevalence of acute respiratory distress syndrome (ARDS) was significantly greater among overweight and obese individuals.[11] Due to the variability in nature, obesity contributes to various respiratory diseases, including pulmonary hypertension, ARDS, and pneumonia. These respiratory diseases strike the lungs and turn out to be the most typical cause of mortality in the obese individual affected with SARS-CoV-2.[12]

Obesity is considered a low-grade inflammatory condition that abnormally increases adipose tissue contents which secrete dozens of adipokines mainly leptin, resistin, adiponectin, visfatin, chemerin, tumor necrosis factor (TNF)-α and interleukin (IL)-6.[13-15] Among these adipokines, leptin is widely studied and has shown pro-inflammatory as well as pro-atherothrombotic effects in humans.[16] Recently, a potential connection and underlying mechanism explaining the effect of obesity on the worst outcomes of COVID-19 have been elucidated and leptin as a target molecule has received the most attention.[10,17] However, at present, data on leptin dysregulation in COVID-19 patients are scarce and needs more extensive population-based research studies that would further explore the treatment strategies targeting leptin dysfunction among COVID-19 patients.

Obesity and Leptin Functions in Humans

Obesity is defined as a complex, multifactorial disease that represents the excessive accumulation of white adipose tissue that impairs human health to a greater extent.[18] Obesity is now becoming a global health problem as its worldwide prevalence has nearly doubled for the last 3 decades.[19] This rising prevalence of obesity has reduced the quality of life, and is found to be associated with the leading cause of mortality and extrapolating health care costs globally.[20,21] The aggregation of fat in adipose tissues especially in white adipose tissue (WAT) in obesity favours the secretion of high levels of leptin levels and lowers the secretion of adiponectin thus influence energy intake and insulin sensitivity.[22] Moreover, WAT also stimulates the secretion of inflammatory mediators especially TNF-α and IL-6 that predispose obese individuals to a pro-inflammatory state.[23] Thus the possible causal for adipose tissue dysfunction may include inflammation and altered secretion of adipokines.[24]

Leptin is a non-glycosylated peptide hormone derived from WAT constitutes a 16-kD protein encoded by ob (lep) gene.[25,26] Functionally, food intake and energy balance in humans is regulated by leptin which mediates its action through neuroendocrine signaling by binding to specific leptin receptors (ObRs) present in the brain predominantly in the hypothalamus.[27] Additionally, leptin has manifold effects on human biology as it has receptors that are expressed ubiquitously on various organs including heart, lungs, kidneys, and pancreas.[28] Its signaling is mediated primarily through activation of Janus kinase 2/signal transducer and activation of transcription 3 (JAK2/STAT3) pathways.[28-31] JAK2 and STAT3 pathways are involved in the transcription of various genes that affect cellular and biochemical processes.[32] Other than a hormone, it has been suggested that leptin as a cytokine could acts as an important link between obesity and non-communicable diseases (NCDs) such as cardiovascular[33,34] and cerebrovascular disease[35]. The underlying mechanism is potentially mediated through its various effects on the vascular inflammatory response, blood pressure[36,37], platelet aggregation[38], and atherosclerosis[39] and is thus considered a pro-atherogenic, pro-inflammatory, and pro-thrombotic adipocytokines.[40,41] In general, leptin enhances the secretion of pro-inflammatory cytokines (IL-6, TNF-α & IL-2), Th1 cells function, and activation of antigen-presenting cells (APCs).[29,42,43] Interestingly, the high levels of pro-inflammatory cytokines have been correlated with increased leptin levels in obese individuals.[44]

Role of Obesity & Leptin in Viral Infections

Throughout the world, obesity arising as a new class of disease contributes as a co-morbid factor in various life-threatening conditions. Obesity association with pathogenic viruses is well -established example of adenovirus infection where obesity is linked in over 10, 000 subjects.[45] Emerging literature on dysregulation of adipocytokines especially leptin is now considered as a significant determinant of the severity of viral infection in obese patients.[46, 47] Additionally, obesity serves as a link between metabolic control and immune tolerance.[48] There are reports in the literature suggest that circulating leptin levels in plasma are significantly regulated by the body mass index and metabolic condition.[49] The main function of plasma leptin is metabolic homeostasis. It acts as a secondary messenger to pass information about body mass to the hypothalamus, which regulates energy balance by insulin metabolism.[50] Simultaneously, leptin also regulates immune modulators and

various pro-inflammatory cytokine-like interleukin (IL)-6, and tumor necrosis factor-α (TNF-α).[51] It has also been investigated that leptin increases susceptibility towards infection both in vitro and in vivo conditions. In a study, obese mice with leptin resistance increase their susceptibility towards influenza infection, the main mechanisms lie with decreased IFN-α, IFN-β, and IFN-γ and suppressed T-cell response and IFN-α, IFN-β, and IFN-γ levels leading to more viral infiltration.[52]

Leptin significantly upregulates the functionality of Th17 immune arm and suppresses the Th2 differentiation, ERK1/2 phosphorylation, and is the most plausible mechanism in respiratory syncytial virus infection.[53] HIV-infected patients have an enhanced leptin receptor expression on peripheral blood mononuclear cells (PBMCs), whereas low leptin levels in circulation are strongly associated with immune response deficiency in these patients.[54,55] Recently, leptin therapy showed a beneficial role in HIV patients.[56] However, published studies have shown the contrary nature of leptin in perspective of its deficiency. A decrease in leptin levels increases the susceptibility of acquiring other infections.[43,51,52] Significantly reduced leptin levels in malnourished individuals are strongly associated with dysregulated immune response and atrophy of the thymus.[57,58] In addition, leptin deficiency is linked with various infectious diseases like viral infection[59,60] and bacterial infections, namely sepsis[61], tuberculosis[62] and leishmaniasis[63] as there is defective cytokine production.[64] Leptin receptor deficiency in mice results in slow viral clearance, and reduced levels of IFNγ levels in the lungs lead to a low survival rate when infected with influenza-A.[65] These all studies imply that the obesity and leptin axis plays an important role in viral-specific immune defense failure, and it needs further investigation for diseases like COVID-19.

Obesity & Leptin in COVID-19

COVID-19 encompasses a wide spectrum of manifestations, and cases experience mild to moderate illness of the upper respiratory tract.[66,67] Acute respiratory distress syndrome (ARDS) was found to be associated with 42% of COVID-19 cases.[68,69] Substantial evidence from the available literature suggests that obesity is a major risk factor for SARS-COV-2 infection to enhance disease progression and mortality.[70,71] A systematic review published by Popkin et al showed that overweight and obesity increase the risk of hospitalization(>46.0%), ICU admission (113%), mortality (74%), and death in COVID-19 cases (48%).[8]

Another study by Stefan et al. reported that 70–90% of ICU admission cases were overweight and, concluded that individuals with obesity are at increased risk of COVID-19[72]. Similar findings were observed in a case study of 12 hospitals in New York that revealed that among 5700 COVID-19 patients, 41.7% of patients were obese, 56.6 % hypertension, and 33.8 % diabetes.[2] The probability to develop ARDS is significantly high among individuals with obesity.[11] Obesity physically compresses the lungs, decreases the residual capacity, and tidal volume resulting in shortening of the inner diameter of the airway that leads to airway resistance.[73] It is proposed that these respiratory physiological changes in obese individuals may worsen respiratory infections and are associated with the severity of COVID-19. Of concern, a systemic review and meta-analysis were conducted to observe the association of obese H1N1 patients and the risk of Intensive care unit (ICU) admission. They reviewed 53 articles and six cross-sectional studies and observed that among 3,059 individuals who were infected with H1N1, 804 (26.2%) were markedly obese with body mass index ≥40 kg/m2, and were more likely to be admitted to ICU compared to non-obese H1N1 patients.[74] Obesity is a low-grade chronic inflammatory state that shows dysregulation of various adipocyte-derived cytokines (Leptin, resistin, adiponectin, visfatin, chemerin, IL-6, &TNF-α).[75,76] Indeed, the high body mass index (BMI) in obese people interactively impairs the immune responses to NCDs and viral diseases.[12,15,77] The multifaceted nature of obesity can profoundly alter the pathogenesis of ARDS which is the utmost cause of death in COVID-19 cases.[12,47] However, the underlying cause is unclear. It is well known that white adipose tissue (WAT) is the major source of cytokines, chemokines, and metabolically active inflammatory mediators.[78] Moreover, macrophages derived from adipose cytokines secret cytokines like TNF-α, IL-1β, and IL-6 affect potential impacts in inflammatory processes.[78,79] Interestingly, the cross-talks between pro-inflammatory cytokines (TNF-a, IL-1β, and IL-6) and adipocytokines such as leptin, adiponectin, visfatin, chemerin probably interconnect obesity and related inflammatory disorders.[79] In lean people, anti-inflammatory cytokines like interleukin (IL)-10, 13, and 4 are produced by Th2, regulatory- T cells and eosinophils, in turn stimulating M2 macrophage activation. Cytokines secreted by M2 macrophages help to regulate insulin sensitivity in slender people. On the other hand, in people with obesity, high amount of Th1 cells, regulatory T cells,

eosinophils, mast cell, cytotoxic T- cells, B- cells and immunoglobulins are found that cause insulin resistance.[80]

Considering the pathogenesis of COVID-19, ACE2 receptors are the target for SARS-CoV-2 expressed abundantly on lungs, heart, blood vessels, and adipocytes facilitate the virus entry and replication.[81,82] Consequently, SARS-CoV-2 infection activates the alveolar macrophages, which further trigger cytokine release and subsequent activation of T-cell and neutrophils.[83] Looking at the immunological triggers, elevated levels of pro-inflammatory cytokines viz. IL-2, IL-10, IL-7, TNFα, MCP-1, and G-CSF were detected in severe cases of COVID-19 patients.[84] Growing evidence shows that these cytokines and growth factors play a crucial role in developing the 'cytokine storming' which reflects the characteristics of the severe form of COVID-19 and develops ARDS that may disrupt multiple cellular processes, cause organ collapse, shock, and eventually death.[85,86] Previously, a study by Ibrahim et al showed that the reduction in ACE2 is allied with increased levels of ATII and Leptin.[87] Moreover, high leptin levels were also found to be associated with decreased alveolar fluid clearance, and an increased inflammatory response to ARDS. [88] Further, the higher leptin levels were also estimated in ventilated patients when compared to the control group and this hyperproduction of leptin increases pulmonary infection in ventilated patients. This cross-sectional study revealed that the mean BMI of SARS-CoV-2 ventilated patients was 31 Kg/m2 with 21.2 mean leptin levels when compared with control patients of SARS-CoV-2 having the mean BMI of 26 Kg/m2 and mean leptin level was 5.6Kg/m2.[10] In a recently published study, coagulopathy had also been reported to be associated with poor prognosis in patients with COVID-19.[89] A resilient link between obesity and thrombosis-promoting molecules such as plasminogen activator inhibitor-1(PAI-1) also has been studied.[89] Notably, leptin increases the PAI-1 in obese subjects were also demonstrated, and it seems leptin plays a crucial part in the pathophysiology of SARS-CoV-2 infection, however, the mechanism is partially explained and needs further studies to ascertain the role of leptin that may increase the susceptibility of acquiring COVID-19 in obese individuals (Figure1).

Obesity & Therapeutic implications

Ample evidence shows that obesity alone and related comorbidities such as hypertension, type 2 diabetes, CVD and renal diseases deteriorate the conditions of COVID-19 patients and have been associated with the worst outcomes in these patients.[90-93] This insight suggests the inflammatory cytokines secreted by adipose tissue including leptin could act as the target molecule(s) for effective treatment in COVID-19, especially in a hyper-inflammatory response. In obesity, excessive adipose tissue releases high leptin levels since this can be postulated that dysregulated leptin levels could worsen the illnesses and slow down the prognosis of COVID-19 and finally lead to severe respiratory condition.[10,17] Wang et al explored the underlying pathway through

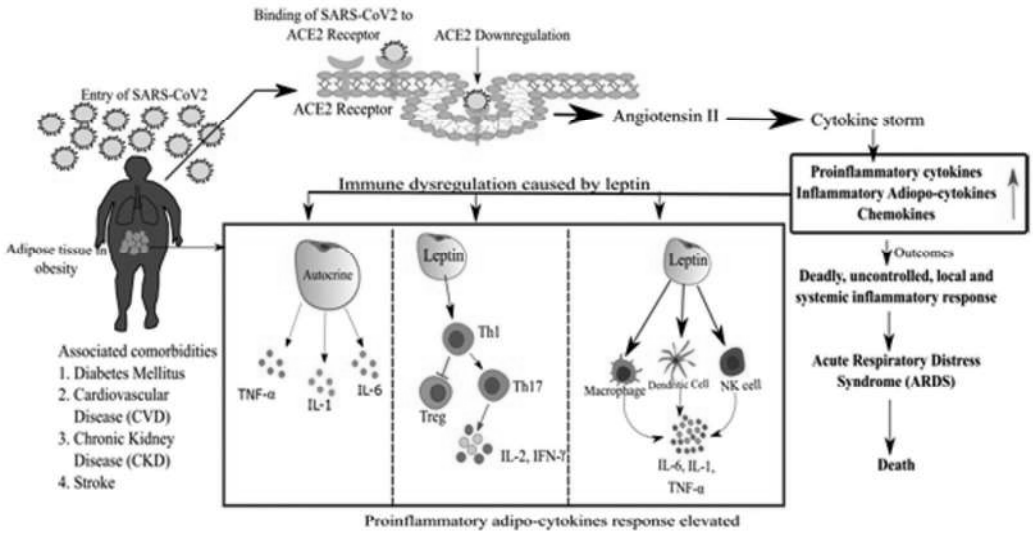

Fig. 1: Depicts the possible mechanism through obesity and associated comorbidities lead to fatal outcomes in COVID-19 patients.

which leptin is involved in cytokine storming using a large cytokine array study mainly containing inflammatory cytokines in COVID 19 patients.[17] Leptin was found the most commonly up-regulated cytokine along with IL-6, IL-10, IL-12, CXCL-10 and TNF-α. Moreover, leptin was consistently associated with disease progression in COVID19 in overweight patients.[17] Furthermore, the expression of ACE2 expression is not limited to lung tissue and is expressed in adipose tissue at higher levels than that in lung and other tissue.[94,95] Therefore, this makes obese people vulnerable to SARS-CoV-2 by increasing the number of ACE2-targeting sites that allow viruses to enter cells and appear to act as a reservoir of SARS-CoV-2.[96] Based on these observations, this could be postulated that pharmacological perspectives targeting the increased leptin production might be considered a possible treatment of COVID-19. Additionally, merely controlling diet or bodyweight may also mitigate the inflammation of COVID-19 patient.[97] Despite this, large research efforts are inevitable to decipher the impact of obesity and high BMI on the disease progression and mortality of COVID-19 patients. Vaccination against the Sars-Cov2 virus is a safe and effective method to mitigate the risk of infection through the production of antibodies and long-lasting immunity. The influence of overweight and obesity on the efficacy of various vaccines is not well addressed due to the scarcity of data. Previously, poor humoral response to hepatitis B vaccination was reported in obese individuals.[98] Also, children with high BMI showed a considerably lower antibody response to tetanus vaccine compared with lean healthy children.[99] Similarly, the diminishing response of hepatitis A and rabies vaccines has also been observed in people with obesity.[100] Humoral immune response in people with obesity is also found to be low. In a study on H1N1 virus, the viral load and viral incubation time in population with high fatty adipose tissue is more compared to individual with lean adipose tissue. The vaccine efficacy was also found to be low in participants with obesity.[101]

In the context of COVID-19 vaccination, some evidence suggests that patients with high BMIs perhaps suffer from intensified SARS-CoV-2 infection may not respond to a vaccine to the same extent as individuals with normal BMI.[96, 102,103] In a recent study, obese people have shown the widest range in antibody titer after the second dose. Moreover, the efficient antibody response was reported in normal weight and lean individuals in comparison to participants with obesity ($p < 0.0001$).[104] Notably, obesity modifies the immune response by impairing humoral and cell-mediated branches of the immune system, thus researchers have hypothesized that the efficacy of the COVID-19 vaccine may disproportionately vary among obese people.[96,105] It is pertinent to mention that long term follow-up of double-blind placebo-controlled trials is required to determine the long-term effectiveness of vaccine immunogenicity, particularly in high-risk groups.

Conclusion

COVID-19 has impacted the healthcare system in particular and global economies as a whole. Several risk factors have been identified and studied in detail so far. Among those, obesity seems to be one of the most important. The prevalence of obesity is increasing globally, not only in higher-income countries but also in lower and middle-income countries. Accumulating data suggests that obesity provides a gateway to the virus for the initiation, development, and outcomes of COVID-19. Therefore, it is essential to know anthropometric records for patients with COVID-19, and appropriate lifestyle interventions are needed to ameliorate modifiable risk factors on a global scale that could be effective to increase resistance to SARS-CoV-2 infection. Large long term clinical studies will give deeper insights into the subject. Moreover, understanding the mechanism of dysregulation of leptin can help in adopting better and more effective therapeutic interventions, including vaccination in patients against the severe SARS-CoV-2.

Declarations

Funding: None

Conflicts of Interest: None

Author's contribution: Gairolla J, Gupta P, Naithani M, Mathuria P Y conceptualizes the idea and drafts the manuscript. Diksha, Sachdeva K M , Gairolla J, Naithani P, Gupta P, Naithani M, Gupta P, Sahoo B for writing and editing the manuscript. Mudgal S for the diagrammatic representation.

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