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REVIEW ARTICLE

Obesity and COVID-19: A Fatal Alliance

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Abstract Most people infected with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV2) are mildly symptomatic while few progress to critical illness and succumb to the infection. The disease severity is seen to be associated with increasing age and underlying comorbid conditions. Obesity, responsible for various metabolic disorders, appears to be a risk factor in determining the severity of infection despite any age group. Though this association is clinically relevant, the mechanisms underlying are not fully elucidated. SARS CoV2 enters host cell via Angiotensin Converting Enzyme 2 receptor, expression of which is upregulated in visceral fat tissue in obese people, underscoring the fact that adipose tissue is a potential reservoir for virus. Adipose tissue is also a source of many proinflammatory mediators and adipokines. High baseline C-Reactive Protein, interleukin 6, hyperleptinemia with Leptin resistance and hypoadiponectinemia associated with obesity explains the preexisting inflammatory state in obese individuals which predisposes them to worse outcomes and fatality.

Keywords COVID-19 · Obesity · Interleukin-6 · C-reactive protein · ACE 2 · Leptin

Abbreviations

SARS	Severe acute respiratory syndrome
CoV2	coronavirus 2
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
IL-6	Interleukin-6
TNF-α	Tumor necrosis factor alpha
BMI	Basal metabolic index
IMV	Invasive mechanical ventilation
ARDS	Acute respiratory distress syndrome
RAS	Renin angiotensin system
ACE 2	Angiotensin converting enzyme 2
AT1R	Angiotensin II type 1 receptor
TMPRSS2	Trans membrane serine protease 2
CRP	C-reactive protein
hs-CRP	High sensitivity C-reactive protein
IL-6R	Interleukin-6 receptor
sIL-6R	Soluble form of IL-6R
ADAM	A disintegrin and metalloproteinase

Introduction

Large, enveloped, roughly spherical, positive sense RNA coronavirus (CoV) were known causative agents of mild respiratory and gastrointestinal diseases until the SARS outbreak of 2002. It was then discovered that this virus has great potential for causing highly lethal epidemic outbreaks as witnessed during Severe Acute Respiratory Syndrome (SARS)-CoV and Middle East Respiratory Syndrome (MERS)-CoV eruptions. The latest addition to pathogenicity of coronaviruses is the current pandemic of SARS-CoV2 responsible for COVID-19, coronavirus disease 2019 [1–4]. As on 31st May 2020, the disease has already infected 6.2 million cases worldwide with a record case fatality of 3.72 lakhs. India, with a total of 1.86 lakh cases and 5200 deaths, is standing at 8th position amongst

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215 countries affected globally [5, 6]. The increasing hospitalization and mortality linked to COVID-19 are seen to be associated with a number of underlying conditions such as obesity, hypertension, diabetes, advancing age, history of cardiovascular and chronic lung diseases [7–10].

Obesity is a chronic disease with complex pathophysiology that is characterized by hypertrophy and hyperplasia of adipose tissue resulting in an imbalanced energy state. Obesity is a fast growing, non-communicable pandemic with a global prevalence of 39%. According to 2016 WHO Global Health Observatory data, it can be seen more predominantly in developed nations such as European countries and United States in comparison to South East Asian countries with a prevalence of 58.7% and 62.5% vs 21.9% respectively [11]. Adipocytes and non-adipocytic immune cells together constitute adipose tissue. Besides being a storage site, adipose tissue is also responsible for secretion of various hormones (leptin, adiponectin etc.) and cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). Adipocyte is no longer considered to be an inert cell, but they are considered as an active endocrine organ [12]. Increased production of these substances establishes a state of chronic low-grade inflammation which in turn results in various metabolic disturbances.

KEY CONCEPT 1: Adipocyte—an active endocrine organ

Adipose tissue secretes various hormones, cytokines, chemokines, complement components, proteins of renin angiotensin system etc. and maintains an organism's metabolic homeostasis

The metabolic disorders most significantly related to obesity are insulin resistance and type 2 diabetes mellitus; hypertriglyceridemia, atherosclerosis, hypertension and cardiovascular diseases; many forms of cancer and various other inflammation related diseases [13–16]. All these disorders frequently related to obesity are also found to be associated with patients at increased risk of developing COVID-19 infection. Moreover, a strong correlation of obesity with influenza and other respiratory viral infections has already been established earlier [17, 18]. These factors suggest the importance of studying the role of obesity in present SARS CoV2 infection and its role in disease progression.

Association of Obesity with COVID-19

Obesity is either directly or indirectly linked to most of the high risk factors for COVID-19 as determined by Center for Disease Control and Prevention [10]. Individuals with diabetes mellitus, hypertension, and severe obesity (Basal Metabolic Index, BMI $\geq$ 40 kg/m^2) are more likely to be infected and are at a higher risk for complications and death from COVID-19 [19]. These chronic low-grade inflammatory conditions characterized by increased levels of several pro-inflammatory cytokines predisposes individuals to increased risk for infection and adverse outcomes [20].

The link of obesity to various comorbidities safely establishes its role as an exponentially important factor in determining the morbidity and mortality risk in SARS CoV2 patients. A case study on 5700 patients with COVID-19 admitted to 12 hospitals in New York City between March 1, 2020, and April 4, 2020 showed that 41.7% patients suffered from obesity, thus being one of the most common comorbidities along with diabetes 33.8% [21]. Similar results were observed by Lille University Center, France which showed that requirement of invasive mechanical ventilation (IMV) was significantly higher in severe obesity (BMI $\geq$ 35) compared with lean patients (81.8% vs. 41.9%) [22]. It has been observed that young people with severe obesity may evolve towards destructive alveolitis with respiratory failure and death [23]. A French study in 124 SARS CoV2 patients also corroborated the fact that severely obese patients were more predisposed to receive IMV and the proportion of patients who require IMV increased with BMI [24].

Data from the UK Intensive Care National Audit and Research Centre, Wuhan and Bronx, New York, the hotbeds of COVID-19, established that 72%, 88% and 35% of those admitted in intensive care units respectively, who developed fatal COVID-19 related complications were either overweight or obese [25]. Thus, establishing that obesity and COVID-19 have a fatal association which is all pervasive, beyond ethnicity and geographical boundaries. On studying clinical characteristics of COVID-19 patients suffering from cardiovascular disease, it was found that BMI of patients in the critical group was much higher when compared to non-critical patients. On further subdivision of critical patients, it was found that non-survivors had significantly higher BMI when compared to survivors (88.24% vs 18.95%) [26].

KEY CONCEPT 2: Obesity and COVID-19 severity

Obese individuals are more prone to developing COVID-19 infection, severity of the disease and the need for mechanical ventilation increases in morbidly obese individuals.

Obesity not only causes fatal outcomes in COVID-19 but also there is increasing evidence that suggests that it is responsible for a more severe form of the disease. Italian National Institute of Health launched a surveillance system to collect information on all COVID-19 cases throughout the country which revealed that 99% of all deaths occurred

in patients with history of preexisting noncommunicable diseases [27, 28]. Data from a hospital in Shenzhen elucidated that those who were overweight had 1.84-fold odds of developing severe COVID-19, while those who were obese were at 3.40-fold odds of developing the severe form of the disease [29]. This buttressed the fact that the relationship between obesity and severity of COVID-19 was a continuum, more the BMI worse would be the disease severity.

In developing South East Asian countries, prevalence of obesity is 21.9% as established from WHO data. A study from Brazil analyzed its general adult population assessing the risk factors associated with COVID-19 infection. In a large household-based survey covering 51,770 individuals it was found that 22% of the population irrespective of any age group was obese and were prone to developing the infection [11, 30]. Extensive data search has yielded that despite having a considerable prevalence of obesity, most of the developing countries, including India, have not yet focused on efforts to correlate COVID-19 severity with BMI.

Obesity, as a risk factor is more prevalent in the United States and other developed countries probably due to increased consumption of the typical western diet consisting of high amounts of carbohydrates, sugars and saturated fat with low levels of fiber, unsaturated essential fats and antioxidants. This type of a diet leads to activation of the innate immune system and inhibition of the adaptive immune system (inhibition of T and B lymphocyte function) potentially via an increase in oxidative stress [31].

Obesity, SARS CoV2 and ACE 2 Receptor

KEY CONCEPT 3: Obesity and COVID-19 pathogenesis

Intracellular invasion of SARS CoV2 is via ACE 2 receptors located on cells. Expression of these are upregulated in obese individuals, leading to increased susceptibility of obese patients to infection.

Emerging evidence suggests that adipocytes and adipocyte-like cells play an important role in the pathogenic response to COVID-19. Human cell receptor for SARS CoV2, Angiotensin converting enzyme 2 receptor (ACE 2) is a component of Renin Angiotensin System (RAS). It allows intracellular invasion of the virus and its expression is found to be upregulated on alveolar epithelial cells in the lung and in adipose tissue due to obesity, smoking and air pollution [32]. Expression of ACE 2 is found to be upregulated in adipocytes of obese and diabetic patients, which could turn adipose tissue into a potential target and viral reservoir. This could explain why obesity and diabetes are potential comorbidities for COVID-19 infections and in conjunction with each other, significantly increase the severity of the local response in the lung [33].

ACE 2 receptors play a central role in the pathogenesis of SARS CoV2 infection. This receptor has a peptidase in its N terminal and a collectrin (collecting duct specific transmembrane glycoprotein) in its C terminal. The peptidase has a key role in the function of RAS [34]. ACE 2 receptors are expressed mostly in apical surfaces of well differentiated ciliated cells hence there is a preponderance of these receptors in the lungs and gastrointestinal cells. These receptors are also expressed in the endothelial cells, kidneys, pancreas, adrenals, and adipocytes. The spike protein "S" of the virus is cleaved into two parts i.e. S1 and S2. The S1 domain attaches to ACE 2 receptor and is thus internalized into the host cell. The S2 is cleaved further by host cell serine protease termed TMPRSS2 (Trans Membrane Serine Protease 2) which is instrumental in causing membrane fusion and further dissemination of the virus into the host [35] (Fig. 1).

It has been observed in animal models that SARS CoV2 infusion results in a decrease in the ACE 2 levels. Once the ACE 2 levels are decreased the Ang (1–7) levels decrease and proinflammatory pathways override the anti-inflammatory pathway. In the lung, after the entry of the virus, ACE levels increase and ACE 2 levels decrease. Action of ACE causes proinflammatory, pro fibrotic and hyperresponsive airway which propels the patient towards ARDS. ACE 2 is also expressed in visceral adipose tissue more than subcutaneous adipose tissue. In visceral adipose tissue the quantum of viral load is large due to expression of ACE 2. ACE 2 has anti-obesity actions in adipose tissue. It causes stimulation of brown adipose tissue and browning of existing yellow adipose tissue [40, 41].

KEY CONCEPT 4: RAS pathways and ARDS

A tenuous balance between Ang (1–7) and ACE-Ang II-ATR1 which are anti inflammatory and pro inflammatory pathways eventually tilts the balance between recovery and progression to ARDS.

Therapeutic Implications

Strategies to treat SARS CoV-2 virus infection with ACE 2 inhibitors are being evaluated. It has been theorized that since SARS CoV2 gains entry through ACE 2 receptors, hence blocking of ACE 2 will help in spreading the infection to the lung. Since convalescent plasma containing neutralizing antibodies decreases the severity of the infection, one approach surmised was to saturate the SARS CoV 2 "S" protein with recombinant ACE 2 [42, 43].

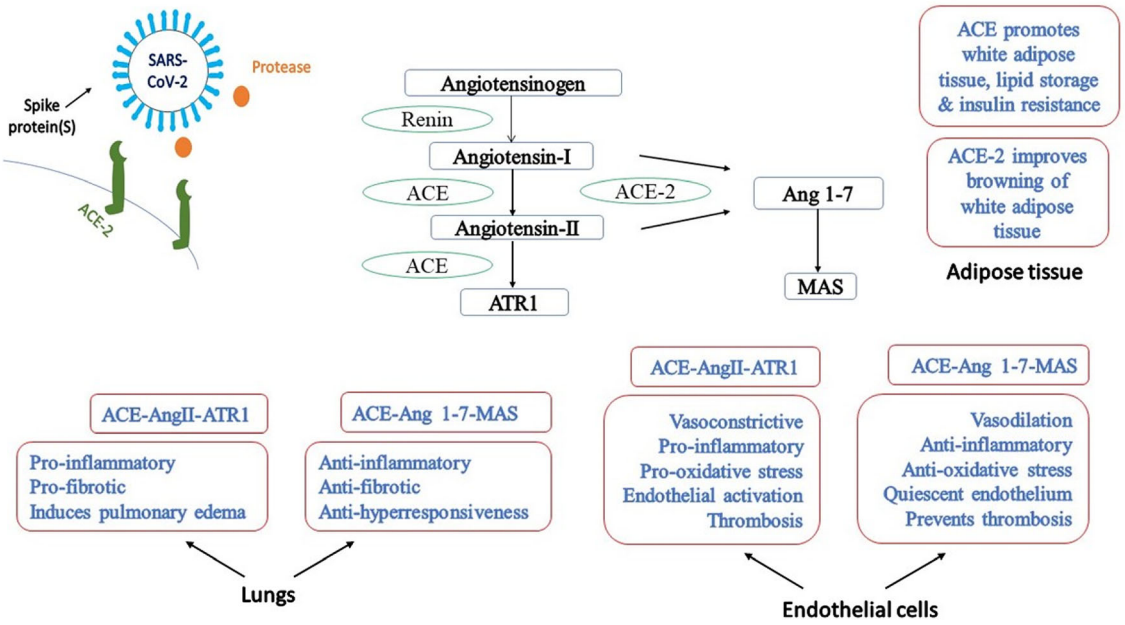

Fig. 1 *Renin Angiotensin System*—Angiotensinogen is produced mainly in the liver. In addition, it is also found in the kidneys, heart, adipose tissue, adrenals, brain and blood vessels. This peptide is converted into inactive Angiotensin I by Renin. Angiotensin I is acted upon by Angiotensin Converting Enzyme (ACE) to Angiotensin II. Angiotensin II when acted upon by ACE 2 converts into Ang (1–7) which has an anti-inflammatory, vasorelaxatory action. Ang (1–7) acts thru the Mas receptors. Angiotensin II on the other hand when acted upon by ACE acts on the AT1R (Angiotensin II type 1 receptor) to produce pro inflammatory effects. The balance between these two inflammatory pathways tilts the balance towards either proinflammatory or anti-inflammatory pathways based on whether there is excessive amounts of Angiotensin II or Ang (1–7) [35–39]

ACE2 is already available as an experimental drug for the treatment of ARDS (41). It has shown improvement in ARDS in mice and pigs. Unfortunately, humans have not shown any effect on mitigation of lung injury in ARDS by ACE 2 [41, 44–46]. In a Japanese study TMPRSS2 inhibitor, Camostat mesylate, was used to decrease pancreatic inflammation. The patient showed decrease in viral infection [47]. This anti TMPRSS2 approach could be developed as a strategy to decrease viral infection.

ACE and ATR1 receptor blockade leads to ACE 2 upregulation. Blockade of ACE 2 and ATR1 could lead to decreased proinflammatory pathway and enhanced ACE 2 would tilt the balance towards Ang (1–7) through Mas receptors [48]. However, upregulation of ACE 2 might increase the severity of infection. Clearly then ACE blocking is a double-edged sword. In the absence of clear-cut data as to the potential risks and benefits of ACE blockade, AHA has issued instructions to all patients on ACE inhibitors to continue their treatment [49].

KEY CONCEPT 5: Effects of ACE 2 and ATR-1 blockade

ACE and ATR-1 blockade could be a double-edged sword. Increased ACE 2 could lead to increased Ang (1–7) activity or it could facilitate the dissemination of the virus in the body leading to a more severe course

Obesity and Inflammatory Mediators

Subclinical chronic low-grade systemic inflammation is responsible for underlying pathological condition of obesity and its complications. Adipose tissue not only contains adipocytes but also other cells like fibroblasts, preadipocytes, macrophages and vascular components. Macrophages are as such important contributors to inflammation and it has also been documented that adipocytes also contribute to significant intrinsic inflammatory properties. Adipocytes express many receptors that are sensitized by infectious disease agents just like macrophages. On stimulation of these receptors, cytokine-mediated inflammatory signal transduction cascades are activated and a number of potent inflammatory cytokines and acute phase reactants are secreted [50].

C-Reactive Protein (CRP) is named so because it has the capacity of precipitating somatic C-polysaccharide of Streptococcus pneumoniae. Human CRP is a pentameric calcium dependant ligand binding plasma protein, weighing 115 kDa and consists of five identical polypeptide subunits. CRP is an acute phase reactant that binds to a variety of autologous and extrinsic ligands. The pentameric form dissociates into a physiologically active and pro-inflammatory monomeric form which further binds to cell

surface receptors and thus is implicated in the pathogenesis of many inflammatory diseases [51–53]. High baseline CRP in overweight individuals has been observed in number of studies that establishes the chronic low-grade inflammatory state in obese individuals [54–58].

In a large multicentric study in South Korea, the association between hs-CRP (high sensitivity-CRP) and sarcopenic obesity was studied. After all the demographic variables were adjusted, it was found that hs-CRP was significantly elevated in obese individuals when compared to normal control group. These findings can be corroborated further with support of many studies where baseline CRP is found to be elevated in obese individuals [57].

Interleukin-6 (IL-6) is a cytokine that has distinct biological activities. It is a hepatic acute phase reactant that helps in regulation of B cell stimulation and in maintaining the balance between regulatory and effector T cells. Apart from involvement in inflammatory and infective responses, it also plays a role in the regulation of metabolic, regenerative, and many neural processes. It acts via two signaling pathways—classic signaling pathway, responsible for mediating anti-inflammatory properties of IL-6 whereas pro-inflammatory activities are mediated by trans-signaling pathway. Biological functioning of IL-6 is mediated by the receptor complex consisting of interleukin-6 receptor (IL-6R)—an IL-6 binding type I glycosylated transmembrane protein, and gp130—a type I signal transducer protein. Unlike IL-6R which is expressed on few cells, gp130 is expressed on all cell surfaces. Cells that express both the components of receptor complex are responsive to IL-6 directly and this constitutes classic signaling pathway, whereas cells that lack IL-6R respond to IL-6 bound to a soluble form of IL-6R (sIL-6R) via trans signaling pathway. sIL-6R is derived by the proteolytic cleavage of membrane bound IL-6R with the help of a disintegrin and metalloproteinase (ADAM) enzyme. Activation of cells by IL-6 through either of the complexes, further activates Janus Kinase (JAK/STAT) signal transduction pathway [59, 60].

Adipose tissue plays a crucial role in mediating inflammatory responses as they are the major source of cytokines, chemokines, and metabolically active mediators named adipokines. Obese people are shown to have higher levels of serum tumor necrosis factor-alpha (TNF-α), interleukin-1 beta and IL-6 among various other cytokines, all of which are produced by macrophages derived from adipose tissue. These pro-inflammatory cytokines regulate the proliferation and apoptosis of adipocytes through various mechanisms. Elevated levels of inflammatory mediators are responsible for long-term effects on glucose homeostasis, food intake regulation and inflammatory responses [61–65].

KEY CONCEPT 6: Obesity—Chronic Inflammatory State

Adipose tissue mediates inflammatory response as it is a source of many proinflammatory mediators such as IL-6, CRP, TNF alpha etc. Their high baseline levels in obese individuals is evident of underlying low grade systemic inflammatory state.

IL-6, TNF alpha and CRP are all found to be substantially elevated in obese individuals positively correlating with BMI, waist circumference and visceral adipose tissue. These studies signify the role of obesity and its association with chronic underlying inflammatory state in body [56, 66, 67]. Further evidential proof to establish their correlation can be documented by studies that observed a significant decrease in levels of these inflammatory mediators on reducing weight/adiposity in obese individuals [11, 58, 68].

Amongst the various adipokines are the hormones secreted by adipose tissue, that have proinflammatory actions such as leptin and anti-inflammatory actions like adiponectin [69]. Leptin is an essential hormone secreted in a pulsatile fashion in body and responsible for maintaining energy homeostasis in an organism besides its role in regulation of neuroendocrine functions. Leptin, an anti-obesity hormone, is found to be responsible for morbid obesity in leptin deficient states in animals as well as humans, reversible on treatment with the hormone [70]. The typical modern diet-induced obesity is characterized by hyperleptinemia (elevated levels of leptin) and resistance to the body weight reducing effects of leptin [71, 72]. Leptin resistance disrupts endothelial leptin signaling pathway further leading to atherogenic state in obese individuals. Thus, high levels of leptin along with leptin resistance in obesity is not only responsible for establishing a proinflammatory state but also makes the individual more prone to cardiovascular complications [73–75].

Adiponectin an exclusive adipokine derived from fat tissue exists in plasma in three major oligomeric forms based on their molecular weight (low, medium, high). It is well established that adiponectin levels correlate negatively with the amount of adipose tissue [69, 76]. Clinical studies have linked low adiponectin levels to many obesity-related metabolic disorders [77–79]. It is an anti-inflammatory hormone that is found to be in negative association with CRP and IL-6 levels in obese individuals (low adiponectin with elevated inflammatory mediators). The findings were further corroborated when bodyweight reduction in obese individuals demonstrated reversal of the adiponectin, CRP and IL-6 levels [80, 81]. This imbalance and reciprocal relationship of proinflammatory and anti-inflammatory adipokines contributes to the

development of obesity related metabolic and cardiovascular disorders.

KEY CONCEPT 7: Obesity and comorbidities

Hyperleptinemia, leptin resistance and hypoadiponectinemia are responsible for increasing the risk of obesity related cardiovascular and other metabolic disorders

In conclusion, obesity is a co morbidity which propels COVID-19 patients into a downhill course. A low grade chronic inflammatory state in obesity as indicated by raised levels of CRP and IL-6, is responsible for initiating the cytokine storm in COVID-19 patients. Upregulation of ACE 2 receptors in adipocytes is another reason why obese individuals are more prone to infection with COVID-19 and progressing into more severe forms of the disease. A vast window of opportunity lies ahead for exploiting recombinant ACE2 and ACE/ATR1 blockade in the treatment of SARS COVID-19.

Authors' Contribution MB: conceptualization, manuscript reviewing, SG: literature search, original rough draft, and manuscript preparation, PS: supervision, JK: proof reading, KG: proof reading

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