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REVIEW ARTICLE

Connecting the dots between inflammatory cascades of obesity and COVID-19 in light of mortal consequences—a review

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Abstract

Obesity is a term that has recently been referred to describe a condition in which a person has become a diseased vessel. Obesity's internal pathology is too mysterious as it has a close resemblance with fatal diseases pathology. Obesity and coronavirus disease 2019 (COVID-19) are simultaneous epidemics declared by many organizations after observing their rampage in the recent world. Oxidative stress, cytokine storm, interleukin, and their contribution to the internal adipocyte environment implicated in the cascades of inflammatory pathology are portrayed here. Major determinants like angiotensin-converting enzyme 2 (ACE2) and renin–angiotensin–aldosterone system (RAAS) axis are highly sensitive molecular factors. Data from various countries suggested a clinical overview of how greater body mass index (BMI) is related to greater COVID-19 risk. It also gives insight into how obese individuals are obligately getting admitted and combating COVID-19 in intensive care unit including children less than 13 years of age under ultimate therapeutic options. There are numerous studies currently taking place for finding a cure for obesity which are mainly focused on natural resources and novel therapies like photobiomodulation (PBM) consisting of laser treatment, infrared treatment, etc. as current pharmacological treatments are reported to have fatal adverse effects. Finally, it is discussed how attenuating obesity will be a solution for future combat strategy. This review gives light on the areas of coagulation, inflammatory parameters, cardiometabolic complications, endothelial dysfunctions, immunological infirmity due to COVID-19 in obese individuals. A conceptual outline about correlation between the inflammatory pathophysiological steps triggering the aggravation of fatal consequences has been drawn in this review.

Keywords Obesity · COVID-19 · Cytokine storm · PBM · ACE2 · D-dimer · WAT

Abbreviations

COVID-19	Coronavirus disease 2019
ACE2	Angiotensin-converting enzyme 2
RAAS	Renin–angiotensin–aldosterone system
IL-6	Interleukin 6
ARDS	Acute respiratory distress syndrome
ANG-1–7	Angiotensin (1–7)
MasR	Mas (mitochondrial assembly) receptor
BMI	Body mass index
WAT	White adipose tissue
BAT	Brown adipose tissue
HFD	High-fat diet
IFN	Interferon
LIF	Lipofibroblast
PFL	Pulmonary fibrosis
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus 2
TMPRSS2	Transmembrane serine protease 2
AT1R	Angiotensin II type 1 receptor
ACE	Angiotensin-converting enzyme
NK	Natural killer cell
ILC	Innate lymphoid cell
MHC	Major histocompatibility complex
ADCC	Antibody-dependent cellular cytotoxicity
MCP1	Monocyte chemoattractant protein-1
TNF-α	Tumor necrosis factor-α
DIC	Disseminated intravascular coagulation
DM2	Type 2 diabetes mellitus
vWF	von Willebrand factor
EAT	Epicardial adipose tissue

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Introduction

Over the past decade, there are numerous strides in understanding the underlying pathophysiology of obesity which is being reported in journals (Schwartz et al. 2017). Obesity is the condition resulting from excess consuming food or hampered energy expenditure and interlinked with various mortal diseases. Pathophysiology is implicated in many diseases like hepatic steatosis, atherosclerosis, various metabolic syndromes, non-alcoholic fatty liver, and insulin resistance precipitating type-2 diabetes mellitus diseases. As per various literatures, obesity is considered not just a risk factor but an initiator of diseases. Hitherto, the established pathophysiology suggests the involvement of oxidative stress and immunological reactions (Shoelson et al. 2007). This review is aimed towards detecting the relationship of coronavirus disease 2019 (COVID-19) pathology with obesity and how it is causing severity in complications for obese individual. As per numerous reports, it is expected that a huge extent of obese patients with a body mass index (BMI) greater than 25 suffered severe COVID complications. It is also reported that mostly the obese individuals were taken to intensive care units with many challenges of management (Bernard 1995). Obese patients have been reported with possessing more adipose tissues in the areas that cover the larynx and segments of the pharynx. Various literatures reported this as the main cause of bronchoconstriction to a greater extent than non-obese COVID individuals. Managing these patients was challenging in terms of intubation. Due to the limited extension of the truncal region in obese patients, airway flow is easily obstructed (Horner et al. 1989; Yu et al. 2021). Clinical literature reported that obese pregnant patients with COVID-19 caused greater resistance towards nursing staff to perform proning positions as a part of respiratory management due to their immobility caused by obesity (Saraya and Balkwill 1993). On the other hand, there is one "obesity paradox" which is observed and reported in COVID-19 cases that patients with acute respiratory distress syndrome (ARDS) reported to have decreased mortality rate in obese people rather than non-obese COVID-19 individuals (Dana et al. 2021). This review is also aimed to give an overview of relationships at the molecular level. From the established mechanism of action, it is reported that severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) enters the host cell and triggers a functional downregulation of angiotensin-converting enzyme 2 (ACE2) (Gheblawi et al. 2020). The whole phenomenon is shifted towards triggering pro-inflammatory cascades due to the lack of ACE2/angiotensin (Ang-1–7)/mitochondrial assembly receptor (MasR) axis. A pro-inflammatory cascade explains the phenomena of cytokine storm and it shows synergistic action when ACE2 is compromised by viral infection. The main knotty factor is the presence of ACE2 in adipose tissue in higher amounts; it implies that the higher the adipose tissue, the higher the viral load. Obesity is familiar to trigger chronic inflammation and increase inflammatory factors like interleukin 6 (IL-6) and cytokines; those are reported to cause severity in COVID-19 complications. As per various reports, COVID-19 and obesity share the same pathology, so both cause huge amplification in the severity of disease (Fager and Freidberg 1980; Petrakis et al. 2020; Sanchis-Gomar et al. 2020). Possessing a higher BMI not only means an increase in the risk of infection and complication but also causes an increase in the chance of the appearance of other virulent viral strains. Obesity may result in a parallel pandemic by COVID-19-induced pneumonia and higher mortality in the future. Endothelial dysfunction is caused by obesity such as microvascular thrombosis; in COVID-19, it is interpreted as an increase in D-dimer which implies blood clot formation (Yan et al. 2021; Popkin et al. 2020; Gómez-Mesa et al. 2021). All the parameters in terms of evidence and how they are related are discussed in a sequential algorithm with some molecular level approach.

Obesity and COVID-19—crisscrossing pandemics

Obesity has always been a key factor for many chronic diseases like hypertension, diabetes, dyslipidemia, and cardiovascular complications like atherosclerotic block. Obesity is always a prevailing factor for malignancy and the growth of tumors (Pi-Sunyer 2009). It is established that obesity plays with various pathways of immunological response. Thus, it is obvious that it will trigger many forms of severity in COVID-19. As per various reports to date, it was reported that obesity takes part in the pathogenesis and severity of COVID-19 through altering the BMI (Jiang et al. 2016; Gao et al. 2021). Comorbidities are reported which are related to obesity in COVID-19 via aforesaid complications. As per the WHO report, the USA ranks first on the basis of morbidity and mortality due to obesity. Data from a study in New York City large academic hospital stated that 3615 individuals were tested with COVID-19 out of which 775 are having a BMI of 30–34 kg/m^2 and 595 have greater than 35 kg/m^2 (Singh and Misra 2020). Diabetes plays an inducer role along with obesity in the severity of COVID-19 as per reports from Mexico. Reports from France and Italy also revealed that increased BMI is the major risk factor for mortality and morbidity in COVID-19 by aggravating the symptoms (Hernández-Galdamez et al. 2020; Mohammad et al.

Table 1 Data of COVID and BMI relation from many countries

Country name	COVID-positive patients	Patients with BMI values within (30–34 kg/m^2)	Patients with BMI values greater than 35 kg/m^2	References
USA	3615	775 (21%)	595 (16%)	Singh and Misra (2020) Hernández-Galdamez et al. (2020) Mohammad et al. (2021) Goossens et al. (2020)
France	124 (ICU admitted)	Not reported	28.2%	Singh and Misra (2020) Hernández-Galdamez et al. (2020) Mohammad et al. (2021) Goossens et al. (2020)
Spain	48 (ICU admitted)	48%	44% (severe)	Singh and Misra (2020) Hernández-Galdamez et al. (2020) Mohammad et al. (2021) Goossens et al. (2020)
Italy	Not known	Not reported	7.2%	Singh and Misra (2020) Hernández-Galdamez et al. (2020) Mohammad et al. (2021) Goossens et al. (2020)
Korea	28 (hospitalized)	Not reported	17.9% (severe)	Singh and Misra (2020) Hernández-Galdamez et al. (2020) Mohammad et al. (2021) Goossens et al. (2020)

2021). The complete data related to the reports are given in Table 1. Therefore, obesity is considered a major key factor for severity in COVID-19. As per the aforementioned reports, we can outline dependent factors, so this review will deduce the equation of how the severity of COVID-19 is related to obesity factors from adipose tissue biology and metabolic dysfunctions as well as vascular and immunological point of view (Goossens et al. 2020). Associated risks are presented schematically in Fig. 1.

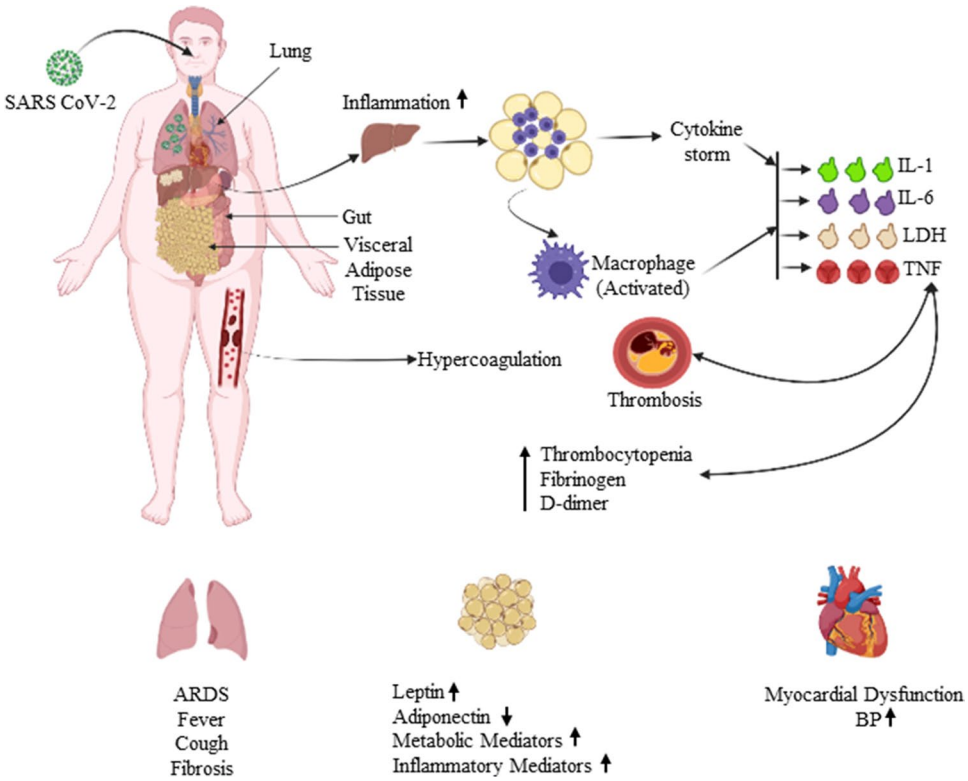

Fig. 1 Schematic representation of the enhancement of complications and risks associated with respiratory and cardiovascular system precipitated in obese COVID-affected patients. TNF, tumor necrosis factor; LDH, lactic acid dehydrogenase; IL-1, interleukin-1; IL-6, interleukin-6; ARDS, acute respiratory distress syndrome; BP, blood pressure; D-dimer, protein fragment and diagnostic marker for blood clot formation

Impact of adipose tissue in SARS-CoV-2 infection

It is reported that the patients with increased white adipose tissue (WAT) and decreased brown adipose tissue (BAT) are diagnosed with chronically activated RAAS which explains a set of dysfunctions in various systems like the heart and kidney. Molecularly, it is explained as increased reactive oxygen species which is the main culprit not only in vascular dysfunctions as well as insulin resistance followed by diabetes (type 2) (Pahlavani et al. 2017). ROS is responsible for the immune system's unregulated firing and thus inflammatory action over the pancreas and the death of beta cells. So, obesity indirectly implements cytotoxic activity in the body (Zorov et al. 2014; Echtay et al. 2002). Abnormal activation of RAAS pathway due to aforesaid reasons which is also induced by Ang II and aldosterone leads to cascades of vascular pathogenesis (Ma et al. 2010). Progression of metabolic disorders and immunological disorders is the major outcome of obesity as reported. COVID-19 is chiefly related to the activation and intrinsic activity of ACE2 receptors. So hampered RAAS pathway implies hampered ACE2 activity, which is in turn related to comorbidities. From the reports, it is concluded that increased WAT and decreased BAT (brown adipose tissue) result in severity of symptoms in COVID-19 (Iannelli et al. 2020; Vaduganathan et al. 2020). RAAS component ACE2 is well expressed in adipocytes and plays a major role in the metabolism of glucose and lipid as per many studies performed in vivo obese mice which were on high-fat diet (HFD) (Gupte et al. 2008). Apart from that, it is also reported some drugs which are used to treat obesity-induced complications like antihypertensives, statins, and fenofibrate can upregulate the activity of ACE2 consequently resulting in increased viral load. One of the most important factors is the cytokine storm of various anomalies in COVID-19 progression (Kaur et al. 2020; Ritter et al. 2020). And as per the report, it is stated that white adipocytes are responsible for pro-inflammatory cytokine release (Coppack 2001). Obesity also results in decreased type 1 interferon (IFN) release which is important for antiviral immunity. In a study, it is reported that WAT is responsible for bronchial asthma as it gets deposited on the airway walls and increases thickness so it leads to bronchoconstriction. Apart from that, it also results in increased infiltration of white blood cells (e.g., neutrophil) in the airway. Increased aggregation of immune mediator cells leads to increased cytokine release and increased tissue damage (Teran-Cabanillas et al. 2013; Tian et al. 2019). The whole phenomenon is followed by the incidence of fibrosis and increased comorbidity and severity of COVID-19. Excessive adipose tissue gives rise to a generation of lip fibroblasts which are also called lipofibroblast (LiFs). Lipofibroblast affects lung function and, in the worst-case scenario, it gets transformed and proliferated as myofibroblasts. Myofibroblast triggers collagen deposition and thereby pulmonary fibrosis. Lipofibroblast contains perilipin-2 inside its lipid vesicles at cytoplasm (Kendall and Feghali-Bostwick 2014). Alveolar interstitium-located cells express the excess of ACE2-type 2 epithelial cells. LiFs may produce pulmonary fibrosis (PF) by degeneration of the surfactant-producing cells and collagen deposition. Thus, obesity has a close relation with the severity of COVID-19 in this way (Engin et al. 2020; Hung et al. 2016). Furthermore, it has been revealed that LiFs express ACE2, implying that in the case of COVID-19, it may promote viral load. The extracellular homolog of ACE2 (angiotensin-converting enzyme 2) is anticipated to be the SARS-CoV-2 receptor, which will be coupled through the use of the spike (S) protein. SARS-CoV-2 entrance is dependent on the receptors transmembrane serine protease 2 (TMPRSS2) and ACE2. TMPRSS2 is a transmembrane protease that is triggered by androgens (Gkogkou et al. 2020). The RAS system (renin-angiotensin system), which consists of a cascade of enzymatic events leading up to the generation of many angiotensin peptides, has been linked to obesity in several investigations. Renin promotes proteolytic cleavage of angiotensinogen to form angiotensin-1, which is then transformed to angiotensin-2 by angiotensin-converting enzyme (ACE). Angiotensin-2 attaches to two types of receptors: angiotensin type 1 receptor (AT1R) and angiotensin type 2 receptor (AT2R). However, there are two types of ACEs: ACE1 and ACE2 (Fountain and Lappin 2021; Sztechman et al. 2018). The action of ACE1 leads to inflammation, vasoconstriction, fibrosis, and proliferation; meanwhile, the action of ACE2 causes dilatation functions as an anti-fibrotic agent, and anti-inflammatory even protects against sepsis by stimulating Mas receptors. ACE2 is widely distributed in human bodies and expressed broadly in adipocytes; its expression is upregulated in mice with obesity caused by a high-fat diet. The ACE/Ang II/AT1 receptor (AT1R) axis is downregulated by the ACE2/Ang-1–7/MasR axis (Sztechman et al. 2018). In both human and experimental animal models, mature adipocytes express angiotensinogen and release it intermittently from fat tissue. The angiotensin type 1 (AT1R) and type 2 (AT2R) receptors may mediate the impact of Ang II, causing an increase in adipose tissue lipogenesis (mediated by AT2R) and a decrease in lipolysis (mediated by AT1R) (mediated via AT1R). The RAS pathways were downregulated in obese patients with hypertension. Obesity can cause a condition of moderate chronic inflammation, with TNF and IL-6 levels persistently increased in obese human and mice models (Del Valle et al. 2020; Caci et al. 2020; Hernández-Galdamez et al. (2020)). Obese human subjects and mice had elevated amounts of angiotensinogen and ACE1. Different studies highlight the importance of angiotensin

(Ang)-1–7 in metabolic control since Ang-1–7 is likely to play an important role in obesity prevention (Takahashi et al. 2007). Through the synthesis of Ang-1–7 and the Mas receptor, ACE2 has an anti-obesity impact. As evidenced by the following evidence, Ang-(1–7) has an anti-obesity impact. (i) Transgenic rats with elevated levels of Ang-(1–7) are slimmer and do not exhibit diet-induced obesity. (ii) Ang-(1–7) is given orally putting down weight and fat mass in mice. (iii) Hypercholesterolemia, abdominal fat accumulation, glucose intolerance, and decreased insulin sensitivity were all detected in Mas-deficient animals. In ACE2 knockout mice, insulin resistance and inflammation are increased, as well as there is an increase in pro-inflammatory profile in macrophages and lung disease. Natural killer (NK) cells are innate immune system effector lymphocytes that belong to the innate lymphoid cell (ILC) family. They are obligated for the elimination of cells with low or undetectable levels of high expression of stress ligands or major histocompatibility complex (MHC I), both of which are associated with viral infections. Obese patients have a considerable reduction in NK cell cytotoxic activity, which has been linked to increased virus transmission in human and animal models (Kawabe et al. 2019; Cantoni et al. 2020; Kosaraju et al. 2017). In vitro, antibody-dependent cellular cytotoxicity (ADCC) in NK cells was reduced in overweight and obese patients. COVID-19 patients, particularly those who required intensive care (ICU), had smaller percentages of circulating T CD8 + cells and T CD4 +, as well as a decreased capacity to produce antiviral cytokines. Increased blood IL-6 levels were also seen in these obese COVID-affected ICU patients, which was associated with a lower frequency of granzyme-expressing NK cells and a lower cytotoxic capacity. Tocilizumab, which is an anti-IL-6 monoclonal antibody, was used off-label to restore the cytotoxic activity of NK cells. Obesity causes a decrease in T-cell receptors and has also been linked to a reduction in lymph node size. As a result, the immunological response is compromised. In obese people, adipocytes suppress the anti-inflammatory response. T-cell fatigue and persistent inflammation are eventually precipitated by this cascade of downregulated pathways (Mazzoni et al. 2020; Magnuson et al. 2017; Smith et al. 2009). As a result, we now have a foundation to establish a relationship between obesity and worsening inflammatory and immunological severity in COVID patient infection, and the relation with adipose tissue is depicted in Fig. 2.

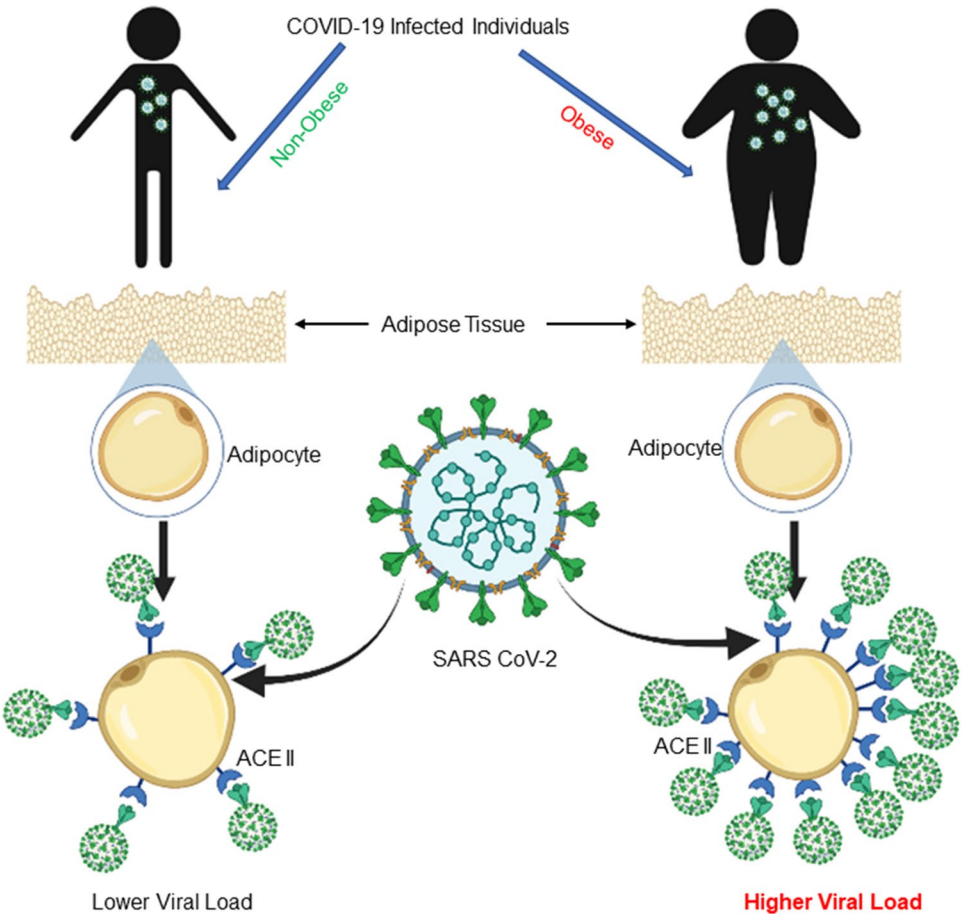

Fig. 2 Schematic depiction of obesity being a cause of increment of viral load due to possessing higher expression of ACE2. ACE2 receptor, angiotensin-converting enzyme 2 receptor

Inflammatory alterations in obesity and COVID-19

The inflammatory response is one of the important determinants in the progression of COVID complications. Complications lead to chronic disease progress and death of COVID-affected patients. Inflammatory pathogenesis starts with the activation of IL-17, IL-1, IL-6, C-reactive protein, IL-18, and interferon (Tanaka et al. 2014; Gleeson et al. 2021). COVID-19 is associated with multiple forms of inflammatory reactions. All the mortality and morbidity were observed for these inflammatory responses. Various immunological parameters that have been seen in patients with COVID have much more similarities with the immunological parameters seen in obesity (Albashir 2020). From this point of view, COVID-19 and obesity can be correlated with each other. Unlike COVID-19, obesity shows low-grade inflammation; furthermore, this will lead to aggravated immunological cascade and metabolic disorders in chronic disorders. White adipose tissues (WAT) are the significant indicator that orchestrates obesity; it contains adipocytes, immune, and epithelial cells. WAT is also a production hub for cytokines; thus, unregulated entries in the number and contents of WAT lead to cellular necrosis, activating the local cellular immune response, and hypoxia. On the other hand, IL6 and TNF-alpha are the triggering factors of inflammation linked to COVID-19 comorbidities (Longo et al. 2019; Gubernatorova et al. 2020). Macrophages are attracted by monocyte chemoattractant protein-1 (MCP-1) towards the inflammatory sites due to an abundance of IL6 and TNF-alpha. Studies have been shown that there is infirmity of interferon production in obese individuals. IFN is the most important combating factor for viral infection. It implies that the complication in obese individuals will be severe and there will be a higher risk of comorbidities and mortality (Deshmane et al. 2009; García-Sastre 2017). Molecularly, it is shown in the following diagram (Fig. 3).

Coagulation alterations in obesity and COVID-19

Blood coagulation parameters have been reported to be altered increasingly which implies COVID-19 severity. As per recent studies, it is concluded that COVID-19 complication is linked with coagulation disorders and thrombus

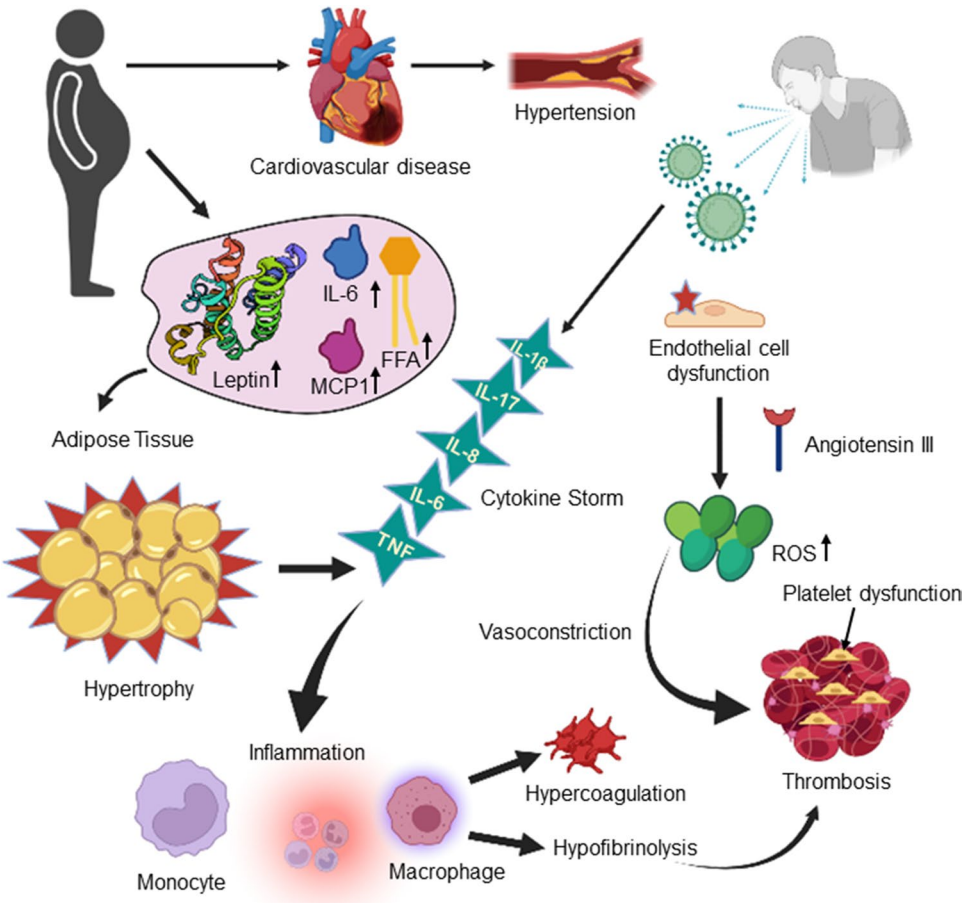

Fig. 3 Pictorial illustration of altered inflammatory cascades and outcomes causing severity in obese COVID-affected individuals. ROS, reactive oxygen species; MCP-1, monocyte chemoattractant protein-1; IL, interleukin; TNF, tumor necrosis factor; FFA, free fatty acids

or embolus formation which is called disseminated intravascular coagulation (DIC). Obese COVID-19 patients who are hospitalized frequently have higher D-dimer levels than non-obese COVID-19 patients, followed by fibrin/fibrinogen disintegration, partial thromboplastin time, anomalies of prothrombin time, and atherosclerotic pathologies (Tang et al. 2020). Likely in the obesity scenario, there is a close similarity of hypercoagulopathy seen in COVID. The reason is that excess body weight, especially abdominal fat that leads to vascular dysfunction, releases adipokines which result in pro-inflammatory, prothrombotic, and embolization states. Hypertension, dyslipidemia, insulin resistance, cellular necrosis, thrombocytopenia, DM-II, and systemic oxidative stress are the contributions of obesity which in turn contributes to the severity of COVID complications (Abou-Ismail et al. 2020; Redinger 2007; Hayden 2020). Adipokines/inflammatory factors such as IL6, IL8, and TNF-alpha lead to the secretion of von Willebrand factor (vWF) from the endothelium layer followed by the activation of platelet adherence and aggregation which leads to thrombotic events. As per various reports, it is stated that shear stress produced by excess fat increases the expression ACE-II which promotes the production of NO to increase vascular permeation. As a consequence, SARS-CoV2 has greater access to increase viral load (Bernardo et al. 2004; Rajendran et al. 2013). Therefore, to prevent thromboembolic events, anticoagulation drugs such as heparin and enoxaparin are reported to have a preference for treating typically ill hospitalized obese COVID-19 patients (Barnes et al. 2020). Coagulation hamperment is depicted in Fig. 3.

Obesity and therapeutics against COVID-19

Obesity-related disorders enhance the probability of SARS-CoV-2 infection severity. The administration of multiple medications daily is required to regulate such illnesses, and their impact on the body's ability to respond to infections is being widely debated around the world. Studies on this interaction have led to the development of prospective therapeutic targets aimed at reducing or preventing the severity of the symptoms. In the absence of a COVID-19 vaccine, research into existing potential medications is critical for battling COVID-19 and lowering the high mortality rate associated with obesity. As previously mentioned, chronic inflammation in the lungs caused by obesity triggers a cytokine storm by overexpressing pro-inflammatory mediators like TNF-alpha and IL-6. This is one of the mechanisms by which imbalanced inflammation in the host worsens the prognosis of COVID-19-affected persons with obesity. As a result, anti-inflammatory medications may play an essential role in safeguarding patients with obesity, particularly those with COVID-19 multi-organ damage, because inflammation is a common feature of COVID-19 and obesity aggravation. However, this must be carefully considered because lowering the pan-inflammatory response might also lengthen the time it takes for successful viral clearance. Anti-inflammatory medicines that are effective against COVID-19 are a concern. The use of non-steroidal anti-inflammatory medicines (NSAIDs) and corticosteroids has been linked to an increased risk of developing severe COVID-19. Corticosteroids are the ultimate option for COVID treatment to give a jerk in the body's combat mechanism as we have seen in ICU patients. COVID with obesity has proven to have more steroidal drugs in a prescription for disease management; as a result, it leads to transient immune compromisation in those patients followed by a second opportunity for the viral manifestation and superinfections (Woods et al. 2020; Moore et al. 2020; Costela-Ruiz et al. 2020). On the other hand, this type of medication has the potential to synergize the diabetes precipitation action. Schematically, how steroidal medications are affecting immune response is shown in Fig. 4.

COVID-19 severity associated with cardiometabolic complications in obese individuals

In endangered individuals, the causal agent of COVID-19 triggers a significant reaction, resulting in hyper-inflammation, cytokine storm syndrome, and acute heart damage, all of which are linked to disease severity and outcome. According to the literature, different cardiometabolic risk factors are associated with increasing the severity of COVID-19 leading to a high mortality rate (Costela-Ruiz et al. 2020; Moazzami et al. 2020). According to recent observational data, visceral adipose tissue, rather than total body mass, may play a role in predicting COVID-19 severity. In between the myocardial and the visceral layer of the pericardium, the heart's visceral adipose tissue is a possible source of inflammatory mediators, i.e., interleukin (IL)-1β, tumor necrosis factor (TNF)-a, and IL-6. Epicardial adipose tissue (EAT) has recently been suggested as a major causative agent for myocardial inflammation in association with COVID-19 (Iacobellis and Bianco 2011). Cardiometabolic complications and linking other parameters are reproduced in Fig. 5.

Post-hoc study—analyzing the epicardia adipose tissue

A cohort study was performed between the 25th of February and the 19th of April in the year 2020 among 652 COVID-19 patients, aimed to analyze the characteristics of EAT in obese individuals. The current study comprised a total of

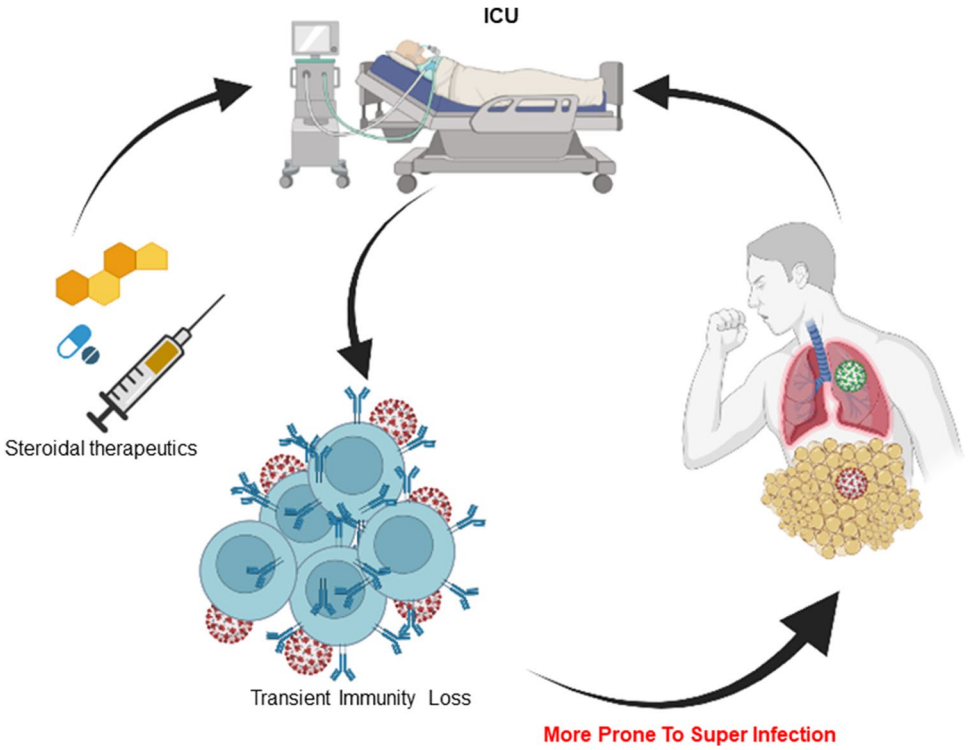

Fig. 4 Therapeutics and drawbacks in ICU-admitted obese COVID individual with the chances of having superinfection; ICU, intensive care unit

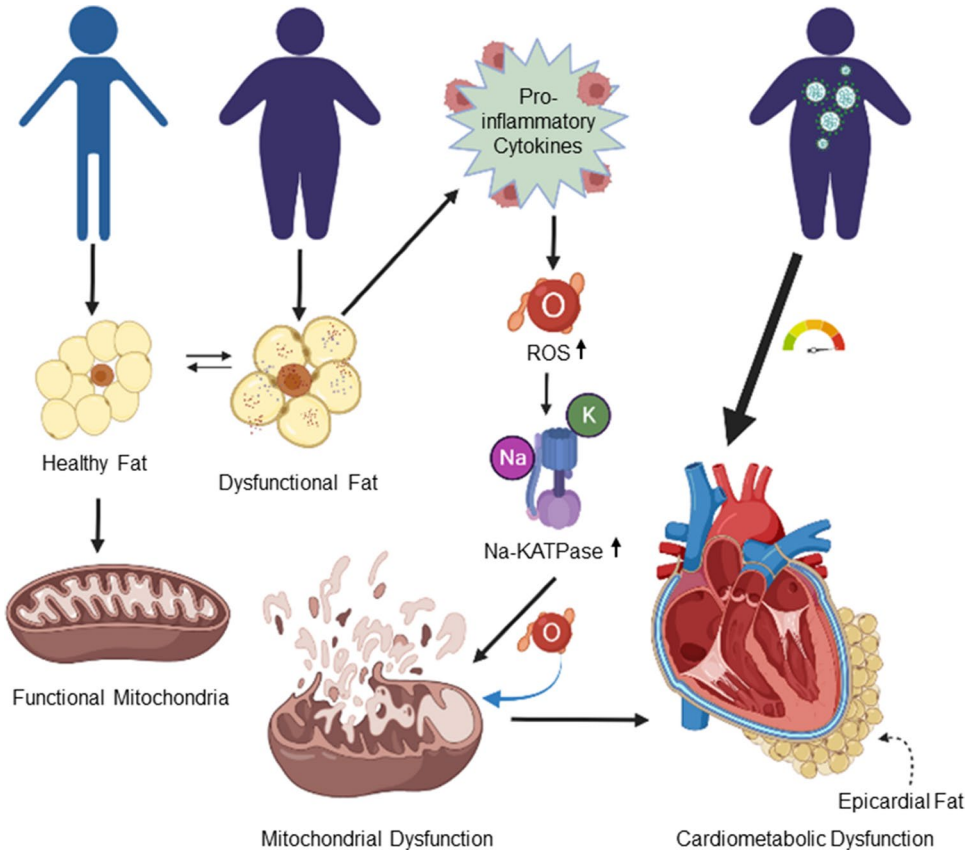

Fig. 5 Pictorial demonstration of cardiometabolic complication that arises from mitochondrial degeneration in molecular overview. ROS, reactive oxygen species; Na-KATPase, sodium–potassium ATPase enzyme; ATP, adenosine triphosphate

192 patients with specific characteristics. The median age of the patients was 60 years of which 76% were men. This study comprised of the patients where overall 70% were obese. The total group's median EAT volume was 2510 (1561; 3539) mm^3 followed by 95.8 (99.1; 93.0) HU median EAT-At. EAT volume was found to be linked with BMI and EAT-At with systemic inflammation. The two groups had identical BMI and EAT volume, but EAT-At was much higher in patients with severe illness (Calder et al. 2011; Ellulu et al. 2017). It can be established that on a chest CT, increased EAT attenuation was a sign of EAT inflammation. The first and most important event that leads to whole-body metabolic disorders is visceral adipose tissue inflammation which can further lead to coronary microvascular inflammation and its dysfunctions. Infection with SARS-CoV-2 may cause EAT inflammation. The angiotensin-converting enzyme 2 (ACE2) receptor, which is abundantly expressed throughout the circulatory system, including EAT, allows SARS-CoV-2 to enter cells. SARS-CoV-2 binding to ACE2 lowers ACE2 expression on the surface, perhaps leading to EAT inflammation (Camici et al. 2020; Fontana et al. 2007). Although EAT-derived inflammatory mediators may have systemic consequences, EAT is more likely to act as a "fuel for cardiac inflammation" during COVID-19, boosting the release of cytokines like leptin, IL-1, IL-6, and TNF-alpha as well as free fatty acids. As we know, in obese individuals, there are high chances of leptin resistance and it acts as a cytokine itself; hence, it may induce lipotoxicity in obese COVID-19 individuals (Fain 2006). Therefore, in the population of this particular study, systemic inflammation, hyperglycemia, and impaired respiratory function were all significantly linked to the likelihood of ICU admission of the COVID-19 patients, invasive ventilation, or mortality (Shang et al. 2020). Future research should look into factors linked to an increased risk of SARS-CoV-2 infection in obese people, the role of ectopic fat deposition, and the mechanisms driving EAT inflammation and heart damage in COVID-19.

Visceral fat accumulation and COVID-19—a cohort study

The renin–angiotensin–aldosterone system (RAAS) includes the angiotensin-converting enzyme (ACE) 2 receptor for the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) (RAAS). It is found in a variety of tissues, including white adipose tissue (WAT). In patients with extreme or morbid obesity, visceral fat (VF) has a higher expression of ACE2 than subcutaneous fat (SCF). The cohort study was aimed to show that visceral fat accumulation, rather than SCF levels or BMI, is a better predictor of COVID-19 severity (Bourgonje et al. 2020; Smith 2015). This cohort included the combined study of 46 patients from Nice and 119 patients from Paris with symptomatic COVID-19. It mainly aimed among the non-obese patients to compare the severity of the disease. The average age of the combined cohort (patients from Paris and Nice) was 64 years and 17 months, with a mean SCF of 152.8 ± 103.4 cm^2, a mean VF of 131.7 ± 101.3 cm^2, and a mean BMI of 26.1 ± 5.4 kg/m^2. The SCF/VF ratio was lower in patients with severe COVID-19 ($p = 0.010$), but there was no difference in subcutaneous fat between patients with mild and severe COVID-19. According to the ROC curve, a VF area of 128.5 cm^2 provided the greatest predictive value for severe COVID-19. A high VF quantity of 128.5 cm^2 was strongly linked with the severity of COVID-19 in each patient cohort (Yordanov et al. 2021; Huang et al. 2020; Kuiken et al. 2003). Because subcutaneous fat is unrelated to COVID-19 severity, the visceral to subcutaneous fat ratio is also irrelevant. Only high VF was linked to COVID-19 severity in a multivariate analysis, but not age or gender. Given that adults and men have more visceral fat than children and women, the amount of VF is likely to account for the link between illness severity, age, and sex. COVID-19 kills men and the elderly more often than it kills women and the young. Excess food consumption limits the ability of white adipose tissue to expand. WAT accepts extra calories above a certain threshold by producing pro-inflammatory adipocytokines in the VF and ectopic fat storage, which leads to insulin resistance. As a result, severe COVID-19 is linked to fatty liver, elevated epicardial adipose tissue, and increased intramuscular fat. Hence, it can be concluded that COVID-19 severity may be influenced by mechanisms other than the RAAS imbalance found in the WAT. ACE inhibitor or angiotensin receptor blocker use to manage hypertension in COVID-19 patients does not reduce the risk of developing severe COVID-19. By this cohort study, it was also believed that constitutive upregulation of ACE2 is the receptor of SARS-CoV-2 for attachment in VF which may contribute to the cytokine storm, although more research into the mechanisms is needed (Savoia et al. 2021; Vincent and Taccone 2020; Phua et al. 2020; Ye et al. 2020).

Future perspectives

As discussed throughout the review, obesity is a familiar, very serious, and expensive chronic disorder that triggers many mortal pathologies or aggravates normal diseases to a fatal one. In this current world, the main scene is played by COVID and its complications (Sanyaolu et al. 2020). As we have seen literature reported the major drawbacks of obesity in the purview of COVID complications those includes increment in a cytokine storm, having the triple risk of hospitalization for obese individuals, triggering impairment in

immunological reactions, obesity reduces lung capacity and reserve volume these leads to respiratory failure followed by a painful death, many studies reported the huge ICU admission, invasive mechanical ventilation, and deaths for the people with higher BMI even in under 65 age (Demeulemeester et al. 2021; Favre et al. 2021). Children were reported to get diagnosed with obesity and COVID and suffered worse outcomes from COVID-19. In a report of COVID-affected cases, in patients of 18 years and younger than those, possessing obesity was 3.07 times more prone for hospitalization and 1.42 times greater risk of severe illness (ICU admission) than that of normal individuals (Kompaniyets et al. 2021; Tsankov et al. 2021; Kim et al. 2020; Alsaied et al. 2020). So, attenuating obesity or staying healthy and maintaining COVID precautions are the keys to avoiding such worse outcomes. As we know, for a healthy human being, COVID can be cured without any complications if it gets diagnosed in the very first place. Numerous researches are going on to attenuate obesity, with major areas focusing on the extraction of agents from natural sources for exploration or looking for a cure by PBM (photobiomodulation) therapies (Liebert et al. 2019). The established drugs for anti-obesity actions are showing severe side effects on long-term use (Cheung et al. 2013), so scientists are looking for promising natural agents which can show the desired action with lesser or no adverse effects (Sun et al. 2016). In this simultaneous epidemic (COVID and obesity), we all have to maintain good physical and mental health.

Conclusion

COVID-19 and its relationship to adiposity are key predictors of severe illness. Endothelial dysfunction, immunological dysregulation, hypercytokinemia, and cardiovascular abnormalities are all possible mechanisms by which an overabundance of adipose tissue can cause the acute hyperinflammatory state that is characteristic of extreme SARS-CoV-2 infections and is responsible for their outcomes. Increased circulating levels of the pro-inflammatory adipokine leptin, combined with lower expression of the anti-inflammatory-acting ACE2 receptors in the lung epithelium of infected individuals, prevent the innate immune response from being cleared, resulting in catastrophic repercussions for the patients. Due to increased cytokine secretion by adipose tissue and associated immune cells, as well as elevated ferritin levels, the immune system can potentially overreact as a consequence of pro-inflammatory "priming," resulting in a cytokine storm. As a result of the immune system's inability to deliver a sufficient immunological response, virus clearance is hampered. Nevertheless, high-risk patients, such as the geriatric and those with obesity, may suffer from a less effective immune response and a lower lasting immunological memory, limiting vaccine effectiveness. The relevance of a healthier life in influencing the trajectory of COVID-19 disease is one of the most significant experiences gained from the catastrophe. There are numerous factors associated with COVID that may be proved to be future drug targets for obesity attenuation followed by reducing the chance of insulin resistance, thereby precipitating diabetes and other immunological and coagulable complications propagated by obesity. In order to create effective prophylactic and therapeutic strategies, future research must understand the sources of severity and complications. The current paper reviews the anatomical, immunological, and molecular alterations linked with obesity, which render obese people more susceptible to COVID-19 infection and make managing its comorbidities more difficult.

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Declarations

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