Mechanisms contributing to adverse outcomes of COVID-19 in obesity

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Abstract

A growing amount of epidemiological data from multiple countries indicate an increased prevalence of obesity, more importantly central obesity, among hospitalized subjects with COVID-19. This suggests that obesity is a major factor contributing to adverse outcome of the disease. As it is a metabolic disorder with dysregulated immune and endocrine function, it is logical that dysfunctional metabolism contributes to the mechanisms behind obesity being a risk factor for adverse outcome in COVID-19. Emerging data suggest that in obese subjects, (a) the molecular mechanisms of viral entry and spread mediated through ACE2 receptor, a multifunctional host cell protein which links to cellular homeostasis mechanisms, are affected. This includes perturbation of the physiological renin-angiotensin system pathway causing pro-inflammatory and pro-thrombotic challenges (b) existent metabolic overload and ER stress-induced UPR pathway make obese subjects vulnerable to severe COVID-19, (c) host cell response is altered involving reprogramming of metabolism and epigenetic mechanisms involving microRNAs in line with changes in obesity, and (d) adiposopathy with altered endocrine, adipokine, and cytokine profile contributes to altered immune cell metabolism, systemic inflammation, and vascular endothelial dysfunction, exacerbating COVID-19 pathology. In this review, we have examined the available literature on the underlying mechanisms contributing to obesity being a risk for adverse outcome in COVID-19.

Introduction

There has been a substantial rise in the prevalence of obesity and associated metabolic disorders worldwide during recent years. The World Health Organization has reported over a billion overweight adults worldwide, and over 300 million of these individuals are clinically obese [1]. Being a complex metabolic disorder, obesity is linked to development of several human diseases including cardiovascular diseases (CVD), Type 2 Diabetes (T2D), hypertension, stroke, hepatic steatosis, endometriosis, and certain type of cancers. It is becoming increasingly evident that obesity is also associated with infectious diseases though mechanisms underlying their possible association are not well understood. While the association between obesity and the risk for contracting hospital-borne nosocomial and surgery-site infection is well known, adequate data in support of susceptibility to community-based infections are lacking. In many of the bacterial or viral infections, data on the link between obesity and susceptibility to infection and the outcome of the disease is either limited or controversial [2]. An exception to this is perhaps the H1N1 influenza pandemic in

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2009, when a series of epidemiological studies showed that obesity was independently associated with risk for severe disease [3]. Although several studies revealed that obesity was linked with poor outcome in H1N1 infection in terms of hospitalization, Intensive Care Unit (ICU) admission, and death, the relevant pathophysiological mechanisms are not well understood. Some of the obesity-related factors that can affect the course and outcome of the disease may include obesity-related immune dysregulation and impaired immune response, respiratory dysfunction, comorbidities such as diabetes, hypertension, and vascular endothelial dysfunction, and disrupted micro and macrovascular circulation. Unlike bacterial or other microbial infections, viral infection involves taking over of host cell machinery for their multiplication and evasion of host cell immune surveillance, thus, causing havoc to host cell function and leading to disease.

COVID-19 is a viral infectious disease of zoonotic origin, caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV2). Coronaviruses (CoVs) are enveloped, positive-sense, single-stranded RNA viruses. They belong to the family Coronaviridae within the order Nidoviridae and sub-order Coronavirinae. The family is further divided into the sub-family Orthocoronavirinae made up of four genera—alpha, beta, gamma, and delta coronavirus. There are seven Human corona viruses (HCoVs) that cause illness in humans and the first of these were discovered in 1966 and 1967. Four of the HCoVs—HCoV-229E, HCoV-OC43, HCoV-NL63, and HKU1—cause mild seasonal respiratory infections. The other three, Severe acute respiratory syndrome coronavirus (SARS-CoV), the Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV2, which are beta-coronaviruses, can infect bronchial epithelial cells, pneumocytes, and cells of the upper respiratory tract. They cause more serious infections which can progress into severe life-threatening disease [4]. SARS-CoV was responsible for an outbreak in Guangdong in 2003 in which 800 out of around 8,000 people died. MERS-CoV caused an outbreak, mainly in Middle Eastern countries in 2012 that affected more than 2500 people killing close to 900 [5].

SARS-CoV2 was reported for the first time in Wuhan, China in December 2019 [6] and has since developed into a pandemic affecting over 200 nations, infecting over 200 million people (289,293,171) of whom more than four million (5,440,643) have lost their life (downloaded on 2nd January, 2022 from Johns Hopkins University Covid resource center). In contrast to SARS and MERS, SARS-CoV2 is characterized by high infectivity, latency, and asymptomatic transmission [7]. A number of epidemiological studies, although heterogeneous in the nature of the material and the reporting of the data, suggest that obesity does adversely affect the severity and outcome of COVID-19. During the initial viral response phase of infection, most individuals are generally asymptomatic and develop only mild symptoms, whereas some progress to severe pulmonary phase of the disease developing pneumonia with associated symptoms. Some of these patients progress further to a phase of hyper-inflammation and develop acute respiratory distress syndrome (ARDS), sepsis, and multi-organ failure. It is important to understand which of these phases in the progression of the disease is affected in obesity. Does obesity increase susceptibility to infection and its persistence? Does obesity-associated metabolic and immune dysregulation pose risk for progression of the disease and if so, what are the molecular mechanisms? Recent reviews have analyzed the epidemiological data in the context of lessons learnt in previous viral epidemics [8], impact of metabolic and endocrine dysregulation on the susceptibility to serious disease [9, 10], and the impact of SARS-CoV2 infection on organ function relevant in non-communicable diseases and its implications for the obesity epidemic [11]. In this review, we try to analyze the current literature on the role of obesity on COVID-19 pathogenesis focusing on possible mechanisms contributing to the risk for adverse outcome of the infection.

Pathophysiology and clinical course of SARS-CoV2

The SARS-CoV2 genome is about 30 kb long and consists of two flanking, open-reading frames (ORF) and untranslated regions (UTRs) [12]. It encodes at least 27 proteins, including 4 structural proteins (spike (S) protein, envelope (E) protein, membrane (M) protein, and nucleocapsid (N) protein), 16 non-structural proteins (NSP1-11, NSP12-16), and a few accessory proteins (ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF9b, and ORF14). The ORF1ab at the 5′ end, which encodes the polyprotein precursor for NSPs, constitutes more than two third of the SARS-CoV2 genome. The SARS-CoV2 shares a significant amino acid sequence homology with SARS-CoV. The S-protein that is required for binding to the receptor on host cells is encoded by the S-gene. S-protein-RNA-based vaccines have been introduced against SAR-CoV2 [13]. M-protein is another important structural protein that primarily determines the shape of the virus envelope but is also able to bind to other structural proteins [12, 14]. The N-protein binds with the M protein that stabilizes the N-protein-RNA complex by promoting the completion of viral assembly inside the virion. The envelope or E-protein which is crucial for production and maturation of the virus is the smallest protein in the SARS-CoV structure.

The SARS-CoV2 gains entry into the target cell through the receptor protein, angiotensin-converting enzyme-2 (ACE2) which is present in the heart, lungs, kidneys, and gastrointestinal tract. This is initiated by S-protein attaching to ACE2 on the cell surface, its cleavage by the TMPRSS2

serine protease to expose the fusion peptide, and fusion with the host cell plasma membrane [12, 15, 16]. The virus initiates the replication process inside the host cell by releasing the RNA into the cytoplasm. ORF1ab of the viral RNA is translated into the polyproteins, pp1a and pp1ab which produce a variety of non-structural proteins (NSPs) that form the viral replication/transcription complex (RTC) while the rest of the viral RNA is transcribed into a group of nested subgenomic mRNAs. Viral replication and transcription occur with the help of RTC within the double membrane vesicles (DMV) formed by NSP-mediated reorganization of rough endoplasmic reticulum membranes.

Clinical course of COVID-19

COVID-19 presents with a variety of symptoms such as fever, cough, sore throat, fatigue, headache, myalgia, impaired sense of taste and smell, conjunctivitis, and diarrhea [17, 18]. Severe conditions are associated with pneumonia, fever, and cough and dyspnea. The signs and symptoms of illness associated with COVID-19 vary from person to person and with the severity of the disease. Incubation period is generally for 14 days after exposure though symptoms usually start to develop within 4–5 days [19–22].

COVID-19 infection can either be asymptomatic, a mild and self-limiting disease or lead to a critical and fatal illness. It is classified into three stages of increasing severity [23]. During the initial viral phase referred to as stage I, predominant symptoms are that of upper respiratory tract infection. Stage II refers to the pulmonary phase of infection characterized by pneumonia and associated symptoms and can be classified into subgroups of pneumonia patients without hypoxia (Stage II A) and those with hypoxia (Stage II B) requiring hospitalization and oxygen supplementation. Stage III refers to the hyper-inflammation phase when patients worsen rapidly and develop Acute Respiratory Distress Syndrome (ARDS) and sepsis, leading to multi-organ failure. It involves inflammation and fluid build-up in the lungs, which limits air-to-blood transfer of oxygen. Such patients generally need invasive mechanical ventilation (IMV) in the intensive care unit (ICU).

Not much information is available on the frequency of asymptomatic infection; it could be as high as 30–40% [24, 25]. Subjects could be symptom-free at diagnosis but turn symptomatic later (pre-symptomatic). Though similar viral loads have been documented in the upper respiratory tract of both symptomatic and asymptomatic cases [26] and in the pre-symptomatic phase, the risk of transmission of virus by asymptomatic people has not been quantified. However, observational and modeling reports suggest that up to 12% of transmission occurs before an index case develops symptoms [27]. It is also observed that while about 80% cases develop only mild disease, about 14% cases have severe disease; 5%

of cases become critical and seriously ill and 2 to 3% are fatal. Symptomatic infection predominates in adults with underlying comorbidities [28]. Subjects with underlying comorbidities have been reported to be at increased risk of developing severe disease following Covid-19 infection. They include individuals with type 1 and type 2 diabetes, hypertension, cancer, chronic lung disease, tuberculosis, chronic renal disease, chronic liver disease and HIV infection. Also at a higher risk are pregnant women and individuals on immunosuppressant therapy [29].

Acute hypoxemic respiratory failure from ARDS is a major finding [25, 30, 31] and the requirement for IMV is high in critically ill patients. Common complications of COVID-related ARDS include acute kidney injury, hepatic injury, cardiac injury including cardiomyopathy, pericarditis, arrhythmia, and sudden cardiac death [28].

Diagnosis and prognosis of the disease have been mostly based on clinical evaluation of the symptoms and radiological imaging and confirmed by laboratory-based RT-PCR tests. CT scan revealed bilateral lung involvement mostly during the intermediate and late stage of the disease and in severe condition revealed 'white lung' appearances showing the possible effect of the infection on lung functions [32].

Several of the observational studies have only partially described laboratory findings. The common findings among the hospitalized COVID-19 patients include lymphopenia, elevated plasma amino transferase and LDH levels, higher levels of inflammatory markers such as serum ferritin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and abnormalities in coagulatory tests [33, 34]. High D-dimer levels and severe lymphopenia are associated with critical illness or mortality. In a retrospective cohort study of 799 patients in Wuhan, serum concentrations of enzymes such as alanine aminotransferase, aspartate aminotransferase, creatine kinase, LDH, and the levels of creatinine, cardiac troponin-I, N-terminal pro-brain natriuretic peptide, and D-dimer were much higher in patients who died when compared to recovered patients [35]. A systematic review of 28 studies in blood/serum of COVID-19 patients revealed increased CRP, decreased albumin, increased ESR, decreased eosinophils, increased interleukin-6 (IL-6), lymphopenia, and increased LDH. Further, meta-analysis of another seven studies on COVID-19 patients revealed that raised CRP, lymphopenia, and increased LDH were significantly associated with severity of the disease [36]. Viral RNA has also been detected in stool samples [37]. Proteomic analysis of plasma samples of multiple hospitalized patient cohorts of COVID-19 showed that markers of neutrophil activation such as resistin, lipocalin-2, hepatocyte growth factor, interleukin-8, and granulocyte colony-stimulating factor increased with severity of the disease and using a machine-learning prediction algorithm, it has been suggested that these markers are strong predictors of critical illness [38].

Obesity, a potential Risk for COVID-19-epidemiological evidence

Obesity has emerged as an important risk factor for increased severity of COVID-19. Ever since the start of the pandemic, considerable epidemiological and clinical data have been generated on the link between obesity and COVID-19. Earlier studies, which were mostly based on hospitalized cases, were composed of preliminary reports from different countries. Subsequent to the spread of the disease globally, data from several hospitals worldwide have been analyzed and published in the form of case studies, retrospective studies, and meta-analysis [39–56], which have been extensively reviewed [57–60].

The data summarized in Table 1 on multiple case studies carried out notably in China, Mexico, UK, Germany, Spain, Italy, Middle East and the USA show that obesity, independently, or along with comorbidities such as T2D is strongly associated with higher disease severity [30, 31, 61, 62]. Subjects with higher BMI (> 30) had a greater risk of developing severe disease as compared with subjects with low BMI. Obesity was significantly correlated with increased hospitalization rates, increased requirement of ICU and IMV and higher mortality in COVID-19 patients [63–74]. The Open Safely study reported a greater risk for COVID-19 related death in obese subjects (with a hazard ratio of 1.4 for a BMI between 35 and 39.9, and 1.92 for a BMI over 40) [75].

During the latter half of 2020 and early 2021, additional data have been generated in new case /cohort studies, retrospective, and meta-analysis examining the role of factors such as age, gender, BMI, percentage of obesity more importantly focusing on adiposity, and body composition on the risk for severity of COVID-19 disease. In most of the earlier studies, the impact of obesity on COVID-19 outcome has been generally examined by considering BMI as an index of adiposity (greater or less than 30 kg/m^2). A UK-based Biobank study showed a linear relation between BMI and risk of testing positive for COVID-19 [76]. However, a hospital-based study in New York showed a J-shaped relation between BMI and the risk of intubation or death [65]. But these studies carried out mostly in hospital settings, did not give much information regarding the association between adiposity/BMI and the natural course of COVID-19 disease. Two studies comprising patients enrolled in the US Veterans Health administration (VHA) also demonstrated a J-shaped relationship between BMI and risk of adverse outcome in COVID-19 [77, 78]. A general population-based cohort study involving follow-up of 2,524,926 participants conducted in Spain showed that, out of 57,443 individuals who tested positive, 10,562 were hospitalized and 2467 died due to COVID-19. BMI was positively associated with COVID-19 infection and hospitalization and showed a J-shaped relationship with the risk of COVID-related death indicating that both under nutrition and over nutrition (BMI ≤ 18.5 and high BMI) can contribute to COVID-19 -related severe disease [79].

While BMI is widely employed to define overweight and obesity, body composition particularly visceral adiposity (VAT), unlike subcutaneous adiposity, is considered to be a greater risk for obesity-related diseases [80]. Given the role of VAT in increasing risk of pathological conditions in obesity, meta-analysis of epidemiological studies showing computed tomographic analysis of visceral adiposity in COVID-19 patients is particularly relevant. It revealed that COVID-19 patients requiring ICU or IVM-support had increased visceral fat area than those who did not [81, 82]. Watanabe et al. reported that increased subcutaneous fat area was not associated with higher risk for ICU admission [83]. Yang et al. also did not find SFA > 100 mm^2, a risk factor for ICU admission [84]. But higher VFA/SFA ratio was associated with a greater risk for ICU admission [85]. Computed tomographic analysis of different fat depots in 165 COVID-19 overweight patients showed an association of severe COVID-19 disease with visceral fat area (VFA) (p = 0.022) but not with subcutaneous fat (p = 0.64); SFA was not altered in patients with mild or severe COVID-19. Further, the ratio of SFA/VFA was significantly low in patients with severe disease.[86]. Not only VFA, but visceral fat thickness as a measure of visceral adiposity is also associated with severe illness in COVID-19 [87]. It was also reported that epicardial adipose tissue volume, as measured by chest CT, was associated with severity of pneumonia and adverse clinical outcomes [88] as well as a predictor of myocardial injury in COVID-19 [89].

In addition to a relation between radiological assessed visceral adiposity and the development of severe COVID-19, anthropometric indicators of abdominal obesity such as waist circumference and waist to hip ratio have also been correlated along BMI with severe outcome of COVID-19. A higher BMI (> 30), higher waist circumference, waist to hip ratio, and waist to height ratio each are positively correlated with increased incidence of covid mortality [90]. Severe cases also showed higher VAT accumulation [82]. Petersen et al. observed that, apart from BMI, VAT and upper abdominal circumference also significantly increased risk of severe COVID [52]. A general population-based cohort study in the United Kingdom showed that hospitalization of COVID-19 patients increased in a linear upward manner with BMI and waist to hip ratio indicating obesity, and central obesity in particular, are risk factors for adverse outcome in COVID-19 [91].

Age and gender are important factors contributing to central obesity and the risk for obesity-related diseases (WHO Report 2008). Results of epidemiological studies on the relation between gender and age on COVID-19 disease severity

Table 1 Prevalence of obesity and COVID-19 outcome

No	Study type [ref]	Country	No of subjects BMI/obesity	Outcome
1	Meta-analysis[70]		Data from 10 studies. 10,233 COVID cases of which 33.9% were obese with BMI > 25	Patients with pre-existing obesity had 1.88-fold higher risk of ICU admission, IMV requirement, and oxygen saturation less than 90%
2	Meta-analysis[73]	10 countries in Asia, Europe& America	Data from 75 studies. 399,461 COVID patients. BMI 24.9 – 29.4	Obesity increased risk of COVID-19 by 46%. (OR1.46).In obese subjects hospitalization increased by 113% (OR2.13), ICU admission, by 74% (OR1.74), and increased mortality by 48% (OR1.46)
3	Review and meta-analysis[82]	China	Data from 30 studies. 45,650 participants. BMI > 30 (10.9–61.3% obese) VAT amount(by CT)	Increased hospitalization (OR1.76), ICU (OR 1.67), IMV(OR 2.19), Death(OR 1.37). Independent association of hospitalization(OR 2.63) death (1.49) with obesity Higher VAT amount in severe COVID patients (SMD for hospitalization 0.49,, ICU requirement—0.57, and IMV requirement—0.37)
4	Case series study [39]	China	383 COVID patients. 32% overweight(BMI 24–28), 10.7% obese (BMI > 28)	No severe COVID in underweight group. 39% of Obese (OR 3.4) and 29.4% of overweight patients(OR 1.84) progressed to severe cases. Respiratory tract infection symptoms in obese
5	Retrospective study [63]	China	58 COVID patients. BMI < 18.3,normal 21.6-29(overweight) > 25 (obese)	Compared to normal, patients with overweight/ obesity exhibit longer hospitalized duration (17.4±6.1 versus 20.4±4.4 days,) and higher proportion of prolonged hospitalization (26.1% versus 62.1%,)
6	Retrospective cohort study[53]	France	124 COVID patients in ICU;BMI > 30 (47.6%) obese; BMI > 35 (28.2%)severe obese	No of patients needing IMV increased with BMI, greatest in > 35. (85.7%). Independent association of IMV requirement with BMI > 35 and male sex
7	Case series study [61]	France	340 COVID patients. 25% were obese (BMI > 30)	Increased prevalence of obesity in patients with severe COVID (1.35) and Critical COVID (1.89). Odds of obesity higher (1.69) in critical COVID patients compared to critical non-COVID patients
8	Case study [50]	Germany	124 COVID patients. Groups: BMI < 25, 25 < BMI <30, BMI > 35	Strong Correlation between BMI of patients and requirement of IMV
9	Cohort[52]	Germany	30 COVID patients. Mean BMI 26.4. Measures of VAT and abdominal circumference	Visceral Fat area and Abdominal circumference correlated with likelihood of ICU admission (OR 1.37 and 1.13) and IMV requirement (OR 1.32 and 1.25)

Table 1 (continued)

No	Study type [ref]	Country	No of subjects BMI/obesity	Outcome
10	Retrospective observational multicentric study[41]	Greece	90 COVID patients. 34.4% obese. Median BMI of 3 groups 30.8, 29.4, 27.7	T2DM and Obesity increase risk for disease severity and mortality in COVID-19. Age is not a risk factor
11	Retrospective analysis [47]	Italy	92 hospitalized COVID patients. 3 Groups with median BMI 22.3 (34%),27.4 (33.7%) 32.4 (31.5%)	Increased occurrence of respiratory failure and need for ICU and IMV in obese (41.4%) and overweight (54.8%) as compared to normal (18%). Both overweight and obese subjects have higher risk of severe clinical symptoms irrespective of age
12	Retrospective analysis[44]	Italy	140 COVID patients. 49% overweight. (BMI 25–29.9) 29% obese (BMI > 30)	Odds of overweight (3.27) and obesity (3.42) higher in COVID patients with ARDS requiring IMV compared to non-COVID patients requiring IMV.
13	Case study [66]	Kuwait	1158 COVID patients in ICU.5 groups of increasing BMI from 18.5 to ≥40	Independent association between overweight (OR 2.5) Grade 1 obesity (OR 3.5) and morbid obesity(OR 5.2)and risk of ICU admission
14	Case control study[43]	Mexico	12,269 cases (classification of groups not specified)	obesity is the strongest predictor for COVID-19 among Mexicans followed by diabetes and hypertension. Higher odds ratios observed in females(OR 5.5) than males (OR 4.7)
15	Data base from Mexican ministry of health[46]	Mexico	51,633 COVID Subjects. 10,708 obese and 40,925 non-obese. (Classification not specified)	Obesity is a COVID-19-specific risk factor for mortality, ICU admission, tracheal intubation, and hospitalization, and it even increases risk in patients with comorbid diabetes and COVID-19
16	Analysis of data from health survey Mexico[45]	Mexico	10,544 Obesity 20.05%	Combination of hypertension, obesity and diabetes associated with higher risk of hospitalization (OR 1.85)and mortality (OR 2.1). as compared to obesity alone ((1.74)
17	Retrospective analysis from institutional database[98]	Mexico	323,671 COVID subjects (out-patients and in-patients)	Age, male sex, pneumonia, diabetes, hypertension, obesity were independent risk factors for mortality. Population attributable fraction for obesity was 8% in in-patients and 16.8 in out-patients
18	Retrospective analysis[74]	Dubai	417 COVID patients. Average BMI 29 ± 6.2	Patients with BMI > 29 and comorbidities showed significant increase in ICU admission, need for IMU ventilator and increased mortality than those with BMI < 29 and comorbidities

Table 1 (continued)

No	Study type [ref]	Country	No of subjects BMI/obesity	Outcome
19	World meters.info data [54]	Spain	Determinants of COVID-19 mortality in 140 countries. BMI≥30	Countries with a larger proportion of people above 65 years of age, and a larger obesity rate have greater COVID-19 mortality
20	Retrospective Case control study	Spain	172 patients with COVID-19 pneumonia. BMI>30 compared with BMI<25	obesity together with lymphopenia, especially lowered CD8 T lymphocytes, are factors that predict a poor prognosis in COVID-19 patients
21	Population based cohort study[79]	Spain	57,443 COVID patients. BMI 25–30 and BMI>30 compared with BMI<25	BMI positively correlated with being diagnosed and hospitalized with COVID-19. J-shaped association between BMI and risk of mortality Risk pronounced for younger age group (18 –59y).
22	Population based cohort study[96]	Spain	433,995 patients. 23-79y. Groups: BMI>40. BMI<40	Severe obesity is an independent risk factor for COVID-19 hospitalization and for severe COVID-19. This excess risk is more pronounced in younger adults
23	Cohort study in out-patient and in-patient[95]	Spain	US 502,650 subjects. Spain 105,822. UK 2336. BMI 30—60	Obesity more common among COVID-19 than influenza patients, Obese patients present with more severe forms of COVID-19 with higher hospitalization, intensive care, and fatality than non-obese patients.Obese hospitalized COVID-19 patients were more often female and younger than non-obese COVID-19 patients or obese influenza patients
24	Prospective observational cohort study [56]	UK	20,133 COVID patients in 208 hospitals Classified as lean/obese	Obesity was associated with increased disease severity and mortality
25	Population study[64]	UK	387109 subjects. 760 COVID positive. 24% obese (BMI>29)	Higher risk of hospitalization in obese (RR 2.05)
26	Case study series[ICNARC report 2020]	UK	3383 COVID patients. 72% overweight or obese	Obesity increased admission to ICU by 38%
27	Retrospective study[75]	UK Open SAFELY, NHS	10,926 COVID patients. 3 groups BMI 30–35, 35–40, >40	COVID-related deaths associated with Severe obesity (BMI>40) (HR 1.92), related to male gender, age, diabetes, and severe asthma
28	Retrospective study[76]	UK Biobank	2494 subjects,882 (35.4%) were positive; 4 groups. 18.5≤BMI≤25 25≤BMI≤30 30≤BMI≤35 BMI≥35	BMI and waist circumference associated with testing positive for COVID-19. The adjusted odds ratio for overweight (1.31), obese (1.55) and severely obese subjects (1.57) compared to normal weight

Table 1 (continued)

No	Study type [ref]	Country	No of subjects BMI/obesity	Outcome
29	Community based cohort[91]	UK	334,329 patients 640 hospitalized 4 groups 18.5≤BMI≤25 25≤BMI≤30 30≤BMI≤35 BMI≥35	Increase in risk of admission due to COVID-19 with increasing BMI (OR for Overweight 1.18, Obese I 1.2, Obese II 1.95) and waist circumference
30	Cohort[69]	UK	3802 subjects. 587 COVID+ 30.6% obese	Higher odds of a positive test among people who are obese (142 [20.9%] of 680 people with obesity vs 171 [13·2%] of 1296 normal-weight people; adjusted OR 1·41
31	Retrospective study[90]	UK biobank	502,493 subjects. 40-69y, 54% women. BMI>30	A higher BMI, waist circumference, waist-to-hip ratio and waist-to-height ratio were each associated with a greater risk of death from COVID-19,. Risk higher in women The women-to-men ratio of hazard ratios was 1.20
32	Retrospective study[68]	USA	265 patients in ICU. 25% BMI<26. 25% had BMI 29.3, 25% had BMI>34.7	Significant inverse correlation between age and BMI; younger individuals admitted to hospital were more likely to be obese
33	Case series[103]	USA	50 COVID-19 patients, (children) 22% obese	Obesity associated with disease severity. And most significant risk factor associated with IMV requirement in children 2 y and above
34	Cohort[62]	USA	103 hospitalized COVID-19 patients. 47.5% obese. 2 groups BMI>35, BMI<30	severe obesity (BMI≥35) was associated with ICU admission (OR: 5.39,) history of heart disease and obesity (BMI≥30 kg/m²) were independently associated with the use of IMV
35	Retro case study[97]	USA	3406 patients. 17% were <50y. 2 groups, BMI 30–39.9, BMI≥40	Hospitalized patients younger than 50y with BMI>40 were at higher risk of mortality than the older age group(OR:5.1) BMI≥40 was also independently associated with mortality to a lesser extent(OR:1.6)
36	Retrospective observation cohort study[67]	USA	393 COVID-19 patients. 34.6% obese. BMI≥30	33.1% patients developed respiratory failure leading to IMV requirement. and was linked to obesity, male sex, elevated liver-function values and inflammatory markers (ferritin, d-dimer, C-reactive protein, and procalcitonin)

Table 1 (continued)

No	Study type [ref]	Country	No of subjects BMI/obesity	Outcome
37	Cohort[102]	COVID-NET USA	180 COVID hospitalized patients. Obesity 48.3%	Hospitalization rates increased with age, with a rate of 0.3 in persons aged 0–4 years, 0.1 in 5–17y, 2.5 in 18–49 years, 7.4 in 50–64 years, and 13.8 in ≥65 years. Highest Prevalence of obesity in 18–49 and 50–64 age group
38	Case series[31]	USA	463 patients(77% hospitalized). 57.6% obese, 17.8% severely obese	Male sex ([OR:2.0), severe obesity (OR:2.0) and chronic kidney disease (OR:2.0) were independently associated with ICU admission
39	Cohort[30]	USA	1150 hospitalized patients(46% obese). 3 groups BMI > 30, > 35, > 40	Obese mortality (39%). IMV requirement 79%. severe obesity (BMI≥40) could not be identified as an independent risk factor for mortality. Older age, cardiopulmonary comorbidities, and higher concentrations of D-dimer and IL-6 were independent risk factors for in-hospital mortality
40	Restrospective cohort study[65]	USA	2466 hospitalized patients. BMI < 18.5 (68) 18.5 < BMI <24.9(542) 25 < BMI <29.9 (717) 30 < BMI <34.9 (444) 35 < BMI <39.9 (199) BMI > 40(142 patients)	Increased risk for intubation or death, in underweight (H.R 1.2), class 2 obesity (HR 1.3) and class 3 obesity (HR 1.6) Risk varied by age – more in patients younger than 65y. (P value for interaction, 0.042),
41	Retrospective study[51]	USA	200 COVID patients. BMI <25 (31.6%), BMI 25 – 34 (17.2%). BMI > 35 (34.8%).	BMI > 35 were independently associated with increased requirement of oxygenation (OR 3.09), intubation (OR 3.87) and mortality (OR 3.78) along with male gender, and increased age
42	Retrospective analysis[42]	USA	770 hospitalized COVID patients 3 groups. BMI < 18.5 (28). BMI 18.5–30(465), BMI > 30 (277)	Obesity(> 30) independently associated with significantly higher rate of ICU admission (RR 1.76), intubation (1.72) or death (1.15)
43	Retrospective analysis[49]	USA	3615 COVID patients. 2 groups: BMI 30–34, BMI > 35	Increased risk of admission to acute (OR 2.0) and critical care (OR 1.8) in patients aged < 60 years with a 30 < BMI <34) compared to patients with BMI < 30 Increased risk of admission to acute (OR 2.2) and critical care (OR 3.6) in patients aged < 60 years with a 30 < BMI <34) compared to patients with BMI < 30
44	Retrospective observational[48]	USA	442 hospitalized COVID patients, BMI ≥ 30	Greater risk of need of higher levels of care in obese (OR 1.95)

Table 1 (continued)

No	Study type [ref]	Country	No of subjects BMI/obesity	Outcome
45	Retrospective cohort[71]	USA	684 hospitalized COVID-19 patients. BMI <18.5 (27%) 18.5 <BMI <24.9 (30%) 25 <BMI <29.9 (43%)	Increased risk of intubation and mortality in overweight (OR 2.0 and 1.4) and obese (OR 1.3 and 2.4) compared to normal
46	Case series study[72]	USA	5279 COVID-19 patients 4 groups with increasing BMI from 18.5 to >40	Obesity (BMI >40) significant risk for critical illness (HR 1.71)
47	Meta-analysis [81]	4 studies—Italy, US, China, Germany	COVID patients requiring ICU, IMV. Visceral Fat Area quantified by CT	Higher VFA in COVID-19 patients requiring ICU admission (SMD 0.46), and IMV (SMD 0.38)
48	Retrospective single centre [83]	Italy	150 patients. Visceral Fat Area quantified by CT	VFA higher in patients requiring ICU admission. Independently associated with need for ICU. (OR 2.5)
49	Retrospective single centre [84]	China	143 patients. VFA and SFA quantified by CT and their ratio (VSR). Intramuscular fat by mean attenuation of skeletal muscle	High VSR (OR 2.47) and high IMF (OR 11.9) independently associated with increased risk for critical illness. Risk more pronounced in patients <60 y
50	Retrospective single centre [85]	USA	51(41 hospitalized, 10 out-patients). VFA &SFA(by CT)	Higher VAT levels associated with greater risk for hospitalization
51	Retrospective single centre	France	165 cases. VF and SF quantified (CT)	Higher VF, low SF/ VF ratio, but not SF, associated with requirement of Intensive care or death
52	Single centre cohort[87]	Italy	144 COVID-positive, 136 COVID-negative. VF and SF thickness (CT) and their ratio	Increase in VAT thickness (OR 1.16) and VSR (a OR for 20% rise: 1.25) independent risk for ICU requirement
53	Retrospective cohort[92]	USA	6916 COVID patients. 6 groups of increasing BMI from 18.5 to >40	J-shaped association between BMI and risk for death. Risk more pronounced among Age <60 and males
54	Multi-centric [94]	USA	7606 COVID patients. 88 centers	Increased risk for mechanical ventilation and death in class I obese, (1.28) class II obese (1.57) and class III obese (1.8) Association of BMI and adverse outcome more pronounced for age <50y

*VAT associated with obesity,VF-visceral fat.SF-subcutaneous fat

did not appear to be consistent. While some reports indicate that case fatalities are higher in obese males and increased with age, other reports suggest that obese women are more prone than men [65, 92–94]. Recalde et al. reported that the risk of death after hospitalization associated with BMI was higher among females than men [95]. A population-based cohort study in 4,33,995 subjects, (age group 18–79 y) in Spain revealed a similar increase in risk of hospitalization and serious disease due to severe obesity(> 40 BMI) in young adults (< 50y) and aged subjects (65-79y) [96]. Recalde et al. also reported that the incidence of adverse outcome of COVID-19 in obese individuals was higher among the 18–59-year age group compared to older age groups [95]. Further, the risk of hospitalization and disease severity was higher in < 60 age group as compared to > 60y [48, 49, 97, 98] with higher risk in males. On the other hand, in a retrospective study in 200 COVID patients, male gender and increased age were independently associated with disease severity [51]. An analysis of patient data from the QResearch database of general practices in England revealed a positive association between increasing BMI and ICU requirement among COVID-19 patients over the entire BMI range and an increase in risk of hospital admission and death among subjects with a BMI > 23 kg/m^2. The increase in risk of hospitalization and ICU requirement with a rise in BMI was greater among subjects without T2D than those with T2D. It was also seen that this increase in risk was higher in subjects with hypertension compared to normotensive subjects and also in subjects with CVD compared to those without CVD [99].

Ethnicity is also considered a determinant for obesity and obesity-related disease. In addition to a higher prevalence of obesity in South Asian, Black, and Arab populations, the obesity-associated cardiometabolic risk at a given BMI in these ethnic communities is also higher than that in the White population. It has been consistently shown that subjects of certain ethnicities are at a higher risk of both contracting COVID-19 as well as an adverse outcome of the disease. Even after considering for ethnicity, it was shown that obesity was associated with adverse outcome as suggested by an increase in hospital admission, ICU/IMV requirement, and mortality. Although this was seen across Chinese, South Asian, and Arab ethnicities, this association was most prominent in populations with Black ethnicity [99–101].

The association of obesity and COVID-19 was also seen in children in two case studies in the US. In COVID-19-affected children (2–18 years) with 22–37% obesity, disease severity, hospitalization, and incidence of pneumonia were higher in obese children [102, 103].

Why is obesity a risk for COVID-19 ?—pathways and molecular mechanisms

A number of studies reveal that obesity, more importantly central obesity reflecting expansion of visceral adipose tissue, is critical in leading to adverse outcome in COVID-19 infection. Expansion of VAT causes metabolic dysfunction, endoplasmic reticulum stress, infiltration of immune cells, polarization of macrophages to a pro-inflammatory phenotype, adipocyte cell death, and inflammation. This is also associated with altered expression of adipokines and cytokines causing systemic effects and dysfunction of endocrine and metabolic organs. Such a challenged state of adipose tissue particularly associated with multiple organs such as lungs, vasculature, heart, and kidney may predispose obese subjects to adverse outcomes of COVID-19 infection. It is becoming evident that underlying mechanisms contributing to adverse outcomes for COVID-19 in obesity may include a) pathways of viral entry and spread, b) dysregulated RAS pathway, c) endoplasmic reticulum stress and dysregulated UPR pathway, d) endocrine dysfunction, particularly altered adipokine responses, and e) metabolic reprogramming and altered immune metabolism.

Virus entry and extended shedding in obesity

There is increasing evidence to indicate that ACE2 is the principal host cell receptor that determines the tissue tropism of SARS-CoV2 [15, 16, 104–108]. ACE2 is a single-chain trans-membrane multifunctional protein with an extracellular domain that recognizes the receptor-binding domain (RBD) of the S1 subunit of spike protein [109]. This is followed by S2 subunit-mediated fusion of the virus particle to the host cell membrane and internalization of the virus. The level of ACE2, its relative affinity to viral protein ligands, as well as its organization in the lipid raft structures on the plasma membrane appear to be critical in determining binding, fusion, and internalization of the virus [110]. Another host cell surface factor critical in viral entry is TMPRSS2, a cell surface serine protease that cleaves the viral spike protein into S1 and S2 subunits and primes viral fusion with the host cell membrane.

The initial viral load appears to be one of the determinants of severity of SARS-CoV2 infection and is higher in patients with severe disease than patients with milder forms [111–115]. Analysis of viral RNA in plasma, the respiratory tract, and urine of patients with a wide range of disease severity, including those recovered from COVID-19, showed that disease severity increased with increase in viral load and was predictive of mortality. Further, plasma viral load was also associated with indicators of disease severity such as lower absolute lymphocyte counts, and elevated

inflammatory markers CRP and IL-6 [116] which are elevated in obese patients. However, in a hospital-based study, viral load was not seen to be associated with either length of oxygen support or overall survival [117] although clearance rates reported in symptomatic patients were longer than those in asymptomatic subjects [118]. Like influenza A virus infection, SARS-CoV2 also targets lungs and adipose tissue. Longer duration of shedding of influenza A virus has been found in symptomatic obese patients [119], and the viral RNA content in expired aerosol was shown to correlate with BMI of influenza patients [120]. Similarly, COVID-19 patients with obesity could have a higher viral load and longer persistence.

The integral viral load is determined by, among other factors, the relative level of the host cell receptor ACE2. Both ACE2 and TMPRSS2 are expressed in epithelial cells in different human tissues including kidney, liver, heart, lungs, adipose tissue, and GI tissue [121–123]. ACE2 overexpressing Hela cells showed greater SARS-CoV2 infection and replication [124]. ACE2 was upregulated both by a diet rich in sucrose or fructose as well as in experimental models of obesity induced by a high-fat diet [125–127]. More importantly, the ACE2 expression is increased in lung tissue in experimentally induced obese mice [128]. ACE2 expression was higher in bronchial epithelium of overweight/obese COPD patients compared to patients with BMI < 25 kg/m^2 [129]. Elevated expression of both ACE2 and TMPRSS2 has also been shown in obese human subjects [130]. Further, a possible regulation of ACE2 expression by excessive calorie intake was indicated by its decreased expression in subcutaneous adipose tissue of obese subjects who had lost weight following a low-calorie diet [128, 131]. In patients with diabetes [132], kidney disease [133] and non-alcoholic fatty liver [134], who are at greater risk of SARS-CoV2 infection, ACE2 expression is upregulated. It has been suggested that lipid deposits in large airways in lungs make these sites that potential viral reservoirs and its presence in the proximity of alveolar epithelial cells expressing high amounts of ACE2 make obese patients more susceptible to SARS-CoV2 infection [135]. Elevated expression of ACE2 in lower respiratory tract in diet-induced obese male mice, unlike female mice, suggested that a sex-dependent modulation of expression of ACE2 which is significant as incidence of serious SARS-CoV2 infection is higher in males [136]. Although ACE2 is critical in SARS-COV2 infection, other cell surface molecules such as neuropilin [137, 138] and CD147[139] also may function as co-receptors.

Obesity involves hypertrophic and hyperplastic expansion of adipose tissue with enhanced storage of lipids. As pre-adipocytes differentiate into mature adipocytes, significant increase in the expression of ACE2 gene occurs. Apart from mature adipocytes, other resident cells of adipose tissue also express ACE2 [140–142] and are known to be targets

for multiple viruses [119, 143, 144] including SARS-Cov [145]. Upregulation of ACE2 is apparently mediated through activation of the transcription factor PPARγ as indicated by stimulation of ACE2 expression by PPAR ligands such as thiazolidinedione [126]. Further, while both subcutaneous and visceral adipose tissue express ACE2, its expression was higher in visceral adipose tissue [86]. An association between the activity of transcription factors that regulate expression of genes involved in lipid metabolism such as SREBP1 and PPARγ and ACE2 gene expression in both in vitro as well as in animal models of obesity, suggested a relation between factors regulating lipid metabolism and adiposity, and ACE2 expression [128]. Chronic inflammation is a feature of obesity, and recent reports show that pro-inflammatory cytokines upregulate the expression of ACE2 [146, 147]. Adipose tissue, which is distributed extensively in the body, both under the skin and around different organs—intra-thoracic fat in lungs, epicardial fat in heart, perirenal fat in kidney, and mesenteric fat in intestine—expresses relatively higher levels of ACE2 than lungs [122, 123]. ACE2 expression in adipose tissue makes it a target for SARS-CoV2 infection, and its elevated expression is associated with adverse outcomes of COVID-19 [123]. Elevated expression of ACE2 in adipose tissue in obese/overweight conditions [148] may also lead to greater viral entry and replication, and it may act as a reservoir enhancing viral shedding and spread [144]. Adipose tissue has been reported to be a reservoir for persistence of other viruses [149]; the importance of lipid droplets in virus production [150] is also pertinent in this regard. However, it is still debated whether it is a relative increase in expression of ACE2 gene or ACE2 protein, or an increase in fat mass that results in higher levels of ACE2 in obesity. Although in vitro studies indicated that SARS-CoV2 infects adipocytes and that the virus can persist for longer period of time [130], SARS-CoV2 virus has not been detected in vivo in the adipocyte. But it has been suggested that SARS-CoV2 virus can alter the fate of adipocyte-like cells in lungs [122] and immunohistochemistry for SARS –CoV2 N-protein in autopsy samples showed sporadic positivity in cells in mesocolic and omental fat [151].

Viral replication and mTOR pathway

Another factor determining the integral viral load is the extent of replication and assembly of the virus inside the host cell. The virus uses the machinery of the host cell to replicate its gRNA, transcribe and translate the genes, transport the proteins, assemble and secrete the viral particles[12]. Nearly two third of the viral genome comprising 5' capped ORF1a and ORF1ab is translated to generate two polyproteins. These are proteolytically cleaved generating 16 different NSPs, including RNA-dependent RNA polymerase (RdRp), which drives transcription of subgenomic

RNA and viral genome replication. Virus-induced double membrane vesicles, packed with replication –transcription complex with NSPs and genomic RNA, fuse with ER. Both the genomic and subgenomic viral mRNA acquire 5'cap structure in a process which is mediated by its NSPs particularly NSP14 [12, 152]. Replication and subgenomic RNA synthesis is followed by translation of N –protein mRNA in cytosolic ribosomes whereas mRNAs of S-, E-, and M-proteins are inserted into ER and translated by the ribosomes present in ER. Protein synthesis by 5'cap-dependent translation of viral mRNA occurs by employing host cell machinery involving eukaryotic elongation factors (elFs) [153]. 7-Methyl-GTP cap structure present at the 5' termini mediates formation of translation-initiation complex which positions the ribosomes near the 5'terminus of the mRNA. It is facilitated by eukaryotic initiation factor 4G (elF4G) acting as a scaffold protein for formation of a protein complex elF4F comprising of initiation factor 4A, an RNA helicase (elF4A) and elF4E,the cap-binding protein[154]. Initiation factor elF 4E is the rate limiting factor and its binding to elF4G is regulated by elF4E–binding protein (4E-BP) causing suppression of translation [155]. Phosphorylation of 4E-BP in response to mitogenic stimuli, dissociates 4E-BP leading to formation of active elF4F complex and initiation of translation. Importance of this pathway in corona virus replication was evident from suppression of human corona virus 229E replication by inhibiting the activity of elF4F complex by blocking elF4E binding to elF4G [156].

The mammalian(mechanistic) target of rapamycin mTOR)-pathway, that modulates activity of elFs, appears to be critical in viral replication and it has been postulated that hyper-activation of this pathway in obesity may contribute to adverse SARS-CoV2 infection[157]. mTOR is a nutrient and energy sensing kinase and it regulates cellular processes like cell survival, proliferation, growth and metabolism in response to nutrient availability and cellular energy levels, by integrating distinct signaling pathways [158, 159]. It is a serine/threonine kinase present as mTOR complex1 (mTORC1) and mTOR complex 2 (mTORC2). mTOR can transmit signals to regulate the expression of major adipogenic transcription factors like PPAR-γ and C/EBP-α family of transcription factors, and thereby stimulate adipogenesis [160]. mTORC1 is a downstream target of PI3K/Akt signaling pathway and is important for regulation of a number of cellular processes including, ribosomal and mitochondrial biogenesis, transcription, and translation [159, 161, 162]. It is activated by increase in ATP, nutrients, growth factors and hormones while absence of growth factors and nutrient deficit cause its inhibition. Activation of mTORC1 leads to phosphorylation and activation of two key effectors-p70 S6 Kinase 1(S6K1) and elF4E binding protein. mTORC1 directly phosphorylates S6K1 on Thr389 leading to its further phosphorylation and activation by phosphoinositide dependent kinase-1 (PDK1). S6K1 phosphorylates and activates elF4B, a positive effector of 5'cap-binding elF4F complex enhancing the translation efficiency. mTORC1 phosphorylates elf4E-BP at multiple sites causing its dissociation from elF4E which can then bind to elF4G and allow translation to occur.

However, dysregulation of mTOR signaling seems to contribute to the disease process in obesity, aging, cancer, and T2D [163–167]. mTORC1 is highly active in multiple tissues during obese and high-fat-fed conditions[168–170]. Consistent with this, the activity of S6K1, downstream effector of mTOR, is elevated in human visceral adipose tissue in obesity [171]; S6K1 knockout mice are resistant to obesity [169]. Over-phosphorylation of 4E-BP has also been shown in obesity [172]. Inflammatory mediators such as TNFα, which are upregulated in obesity, activate mTORC1 by activating IκB kinase-β (IKKβ), [173]. Further, insulin resistance in obesity is closely linked to mTOR stimuli [174].

It therefore appears that overactivated mTOR pathway in the obese condition sets a favorable milieu for the SARS-CoV2 viral replication. Transcriptome and proteome study of SARS-CoV2-infected cells showed that inhibition of AkT, upstream of mTOR reduced virus production [175]. Viral infection-associated dysregulation in renin-angiotensin pathway can further activate mTOR/S6K pathway contributing further to pulmonary vasculopathy[176]. SARS-CoV2 infection was shown to increase activity of mTORC1 in kidney epithelial cell line and lung-air interface mucociliary cultures and inhibition of mTORC1 by FDA approved drugs appeared to reduce viral replication. Activation of mTORC1 has also been shown in lung tissue from COVID-19 patients [177]. However, the enzyme catalyzing the formation of 5'-Cap structure is yet to be characterized in SARS-CoV2.

Obesity, endoplasmic reticulum stress, and COVID-19

An important factor that can contribute to SARS-CoV2 replication and disease in obesity is ER stress. Dysregulation of protein folding homeostasis that occurs in response to environmental and cell-intrinsic challenges results in build-up of unfolded proteins in ER lumen causing ER stress. This activates the Unfolded Protein Response (UPR) signaling mediated by three ER resident trans-membrane sensors: PKR-like ER protein kinase (PERK), inositol-requiring protein-1(IRE1) and activating transcription factor-6 (ATF6). These are regulated by an ER-chaperone, glucose-regulatory protein (GRP78), which dissociates from these receptors during ER stress leading to their activation. UPR is an adaptive mechanism which initially aims at rebalancing protein folding homeostasis by shutdown of the cellular protein synthesis, enhances ER-chaperone expression and

mediates misfolded protein degradation through ER-associated degradation (ERAD) pathway. But, if the cells fail to recover when the load of misfolded proteins exceeds, such as during viral infection, UPR triggers apoptotic signaling by activating (a) C/EBP homologous protein (CHOP) (b) c-Jun N-terminal kinase(JNK) pathway and (c) ER-associated caspases, eventually resulting in activation of caspase-3. ER stress-related inflammation and apoptosis in various cells are associated with the pathogenesis/progression of several diseases [178–181].

Infection by several viruses including SARS-CoV caused ER stress [182–184]. Corona virus appears to induce ER stress in host cell by (a) excessive synthesis of viral proteins, their post translational modification (PTM) and folding, (b) restructuring of the ER membrane while forming double membrane vesicles for replication, and (c) the exhaustion of the ER membrane due to continued formation of the virion [182]. Though one of the mechanisms to overcome ER stress is shutdown of global protein synthesis [183], the viruses have evolved mechanisms to counteract this and ensure viral protein translation. For instance, viral NSP1, apart from its role in suppressing host cell immune response by IFN inhibition, inhibits host cell translation by blocking mRNA binding to 40S subunit of ribosomes, and promotes mRNA degradation [185, 186] but the presence of 5'leader sequence in viral mRNA prevents its degradation, allowing viral protein translation [187, 188]. This appears to be a general phenomenon in coronaviruses. SARS-CoV2 NSP 16 disrupts host mRNA splicing by binding to mRNA recognition domains of snRNAs and NSP 8 and NSP 9 disrupt protein trafficking by binding to signal recognition particle in HEK293T cells infected with SARS-CoV2. Further, NSP1 is also known to bind in the mRNA entry channel of ribosome causing translational inhibition of host cell proteins [189]. Recent proteome data in SARS-CoV2-infected cells also showed suppression of host cell protein production and dysregulation of ER proteostasis pathways, and increase in serum levels of GRP78 and CHOP in COVID-19 patients indicating ER stress and suppression of IFN production[108, 189–191].

Several types of viruses like Zika virus[192], Coxsacki virus [193], Dengue virus [194], Japanese encephalitis virus [195] take advantage of the chaperone property of GRP78 to bind to viral proteins for their entry and replication within the host cells. Though GRP78 is primarily an ER protein aiding protein folding and vesicular transport to Golgi, it has also been shown on the cell surface, probably due to its mis-sorting or due to saturation of its binding to the KDEL receptor for its reverse transport to ER [196]. It may act as a co-receptor for the viral entry. Structural analysis and molecular docking suggested binding of S-protein of SARS-CoV2 to GRP78 [197]. The nascent S-protein, M-protein, and E-protein of SARS-CoV and SARS-CoV2, undergo post translational modification,particularly glycosylation

and folding in the ER. Accumulation of these nascent viral proteins causes ER stress. In vitro and in vivo studies have suggested that different types of cells including endothelial cells, alveolar epithelial cells, cardiomyocytes are under ER stress in subjects with comorbid conditions such as diabetes and obesity. Circulating GRP78 levels, due to shedding from cell surface increased in subjects with diabetes and obesity and correlated with CRP levels [198]. Both metabolic stress and chronic inflammation occurring in obesity appear to influence the level and distribution of GRP78. Treatment with pharmacological chaperones that alleviate ER stress suppressed NF-kB activity and inflammation in obese mice suggesting that ER stress contributes to the chronic inflammation occurring in obesity [199]. It, therefore, appears that ER stress associated with metabolic stress and inflammation in obesity, by virtue of increase in GRP 78, might contribute to increased viral entry. However, direct evidence supporting a role for GRP78 in SARS-CoV2 infection is lacking, although serum levels of GRP78 were found to be higher in patients with COVID-19 compared to those with pneumonia, and healthy controls [191]. Signaling pathways of UPR and inflammation are linked by mechanisms like the generation of ROS, calcium efflux from ER, activation of NF-κB by PERK, NF-κB and MAPK activation by IRE1, and induction of the acute-phase response. Further, Ang-II that accumulates (as discussed later) during SARS-CoV2 infection, acts on ER through AT1R to increase ER stress and downstream inflammatory signaling through NF-κB; it also induces TGFβ-mediated apoptosis and fibrosis [200]. The systemic inflammation of adipocytes in obesity is primarily mediated through ER dysfunction. UPR signaling is also implicated in vascular inflammation and possibly endothelial cell dysfunction [201, 202] and such ER stress-mediated pre-activation make obese subjects vulnerable to severe COVID-19. Further, loss of ACE2-mediated protection of ER stress through suppression of apoptosis on viral infection exacerbates ER stress [203, 204].

Dysregulation of Renin-angiotensin system and COVID-19-related respiratory dysfunction

As indicated before, the most common complication of COVID-19 is altered respiratory function associated with infection of the lung progressing to SARS. Obesity may increase the risk of developing respiratory dysfunction by different mechanisms including pulmonary restriction and imbalance between ventilation and perfusion. Accumulated fat within the thorax and abdominal cavity may mechanically affect both chest wall and lung compliance. Restriction of diaphragmatic mobility and chest wall movement reduces functional residual capacity [205, 206]. One of the major molecular pathways that regulate pulmonary function is the renin-angiotensin system (RAS) which is critical

for maintenance of blood pressure, electrolyte and fluid balance and affects the functions of several organs including heart, lungs, kidney, liver, blood vessels and adipose tissue [207, 208]. The classical RAS pathway consists of the enzyme renin which proteolytically cleaves angiotensinogen to Ang1; it is then converted to Ang-II by angiotensin-converting enzyme (ACE1) [209]. Ang-II, through its cell surface receptor (AT1R) regulates vasoconstriction, inflammation and oxidative stress. It is further cleaved by ACE2 to Ang(1–7), which binds to Mas receptor and exerts vasodilation, vasoprotection, anti-proliferative and anti-inflammatory effects. Balance between ACE/Ang-II/AT1 receptor and ACE2/Ang(1–7)/Mas receptor axis contributes to cellular homeostasis and vascular function. ACE2 also serves to regulate the kallikrein/kinin system that generates, by sequential proteolysis, ligands for bradykinin-II and bradykinin-I receptors which play a role in blood pressure regulation, inflammation and coagulation. Further, by inactivating BI receptor ligands, ACE2 protects against pulmonary edema, whereas decrease in ACE2 increases pulmonary vascular permeability, edema, hypertension, inflammation, ARDS and cardiac failure [210–214].

As ACE2 is a multifunctional molecule actively involved in pathways critical to cellular homeostasis, hijacking this host molecule by SARS-CoV2 can adversely affect host cell function. Evidence in support of hyper-activated RAS pathway as one of the potential mechanisms contributing to adverse outcome of COVID-19 in obese subjects is accumulating. RAS pathway is active in lungs, vascular tissue, heart, adipose tissue, liver and kidney [215, 216] and the presence of significant amount of ACE2 in lungs, vasculature and adipose tissue of obese subjects allows entry of SARS-CoV2 virus [217, 218]. Significantly elevated levels of angiotensinogen in obese subjects feed more amounts of Ang-II into the RASpathway [219–221] and it will accumulate if sufficient ACE2 is not available as happens in SARS-CoV and SARS-CoV2 infection [206 214]. Serum levels of Ang-II are raised in COVID-19 patients [222] and relate positively with viral load and lung injury [111, 223, 224], indicating dysfunction/reduced action of ACE2. Accumulation of Ang-II causes pulmonary dysfunction as suggested by earlier studies in experimentally induced acute lung injury where Ang-II has been shown to cause pulmonary edema and inflammation [225] Further, it has pro-coagulant effects as infusion of Ang-II caused platelet activation [226]. Binding of SARS-CoV2 to cell surface ACE2 through the viral spike protein, followed by cell entry is associated with decrease in ACE2 [104, 227, 228]. This may be due to cleavage of its ectodomain by ADAM17, the cell surface metalloprotease that also activates TNFα by its proteolytic cleavage [229]. Presence of cleavage sites in the ectodomain and endodomain suggests a possible cleavage of ACE2 by TMPRSS2 as well [230]. Plasma ACE2, a result

of proteolytic shedding of cellular ACE2, was higher in COVID-19 patients than in healthy controls [231]. Further, in SARS-CoV2-infected cells in culture, there was a significant reduction in the expression of both TMPRSS2 and ACE2 [232] and the levels of total ACE2 [190]. Though it is not clear how cell surface ACE2 is downregulated in SARS-CoV2 infection, cleavage of ACE2 by proteases as indicated by elevated levels of plasma form of ACE2 and a shutdown of host gene expression, by downregulation of translation and degradation of host mRNAs [233] are two possible mechanisms. Further, a feed-forward effect of AT1R activation by accumulating ANG-II could transcriptionally downregulate ACE2 expression [234]. SARS-CoV1 infection has also been associated with a decrease in ACE2 [227, 233, 235]. Modulation of RASpathway, particularly ACE2 expression by metabolic regulators including hormones such as insulin [236] and glucagon-like peptide-1 receptor agonist [237] suggest a role for host's metabolic state in regulating viral entry and response to infection.

The dysregulation of the RAS pathway and its implications in the development of severe disease in obese subjects infected with SARS-CoV2 is illustrated in Fig. 1. A decrease in ACE2 can affect the equilibrium between pro-inflammatory Ang-II and anti-inflammatory Ang(1–7). Accumulation of Ang-II triggers receptor-mediated JAK-STAT pathway while decrease in Ang(1–7) shuts down Mas receptor signaling causing upregulation of pro-inflammatory factors and downregulation of anti-inflammatory factors. Decrease in ACE2 and consequent accumulation of ANG-II on SARS-COV2 infection in obese subjects can have effects beyond RAS pathway contributing further to pulmonary vasculopathy. For instance, accumulation of ANG-II can heighten activation of mTOR/S6K pathway and further impact insulin responsiveness and cause endothelial dysfunction [160, 238, 239]. Activation of mTORC1, as discussed before, can increase SARS-CoV2 replication. Ang-II, acting through G-protein coupled ATR1 increases ROS production by stimulating Nox family NADPH-oxidase and cause lung endothelial dysfunction. It also disturbs mitochondrial function and modifies cell metabolism [200]. Further, ER stress-induced inflammation and apoptosis of alveolar epithelial cells is regulated by Ang-II/Ang(1–7) system [203]. Decrease in ACE2/Ang(1–7) on SARS–Cov2 infection of the lung epithelium can lead to loss of the protective effect of Ang(1–7) against ER stress-induced inflammation and apoptosis as shown earlier in experimentally induced ER stress in lung epithelium and microvascular endothelial cell [204].

Metabolic reprogramming in host cell on SARS-CoV2 infection

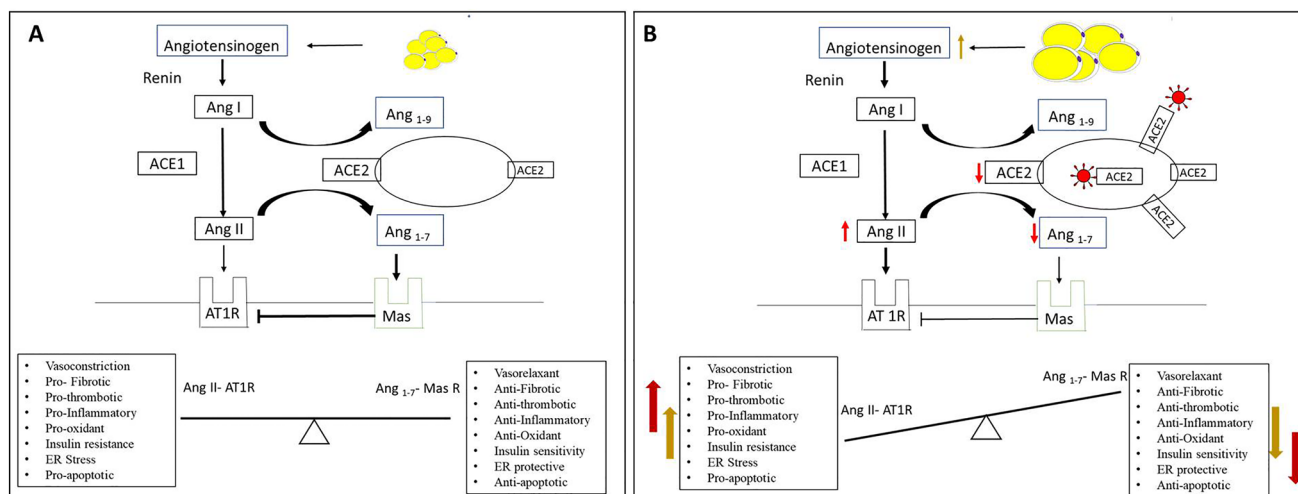Viruses appear to have developed suitable strategies to reprogramme host cell metabolism to their advantage for

Fig. 1 Dysregulation of RAAS pathway in Covid-19 subjects with obesity. A. Angiotensinogen is converted by Renin to Ang I which is converted by ACE 1 to Ang-II that acts through AT1R to exert vasoconstrictive and inflammatory effects. Ang-II is alternately cleaved to Ang 1–7 which can act through the Mas-R and exert a vasoprotective, anti-inflammatory and anti-thrombotic effect. Balance between the Ang-II-AT1R and Ang 1–7 – Mas-R axes maintains normal cellular homeostasis. B. Increased ATN in obesity increases amount of Ang-II in the RAAS. ACE2-mediated entry of SARS-CoV2 leads to decreased ACE2 availability and imbalance between Ang-II-AT1R and Ang 1–7 – Mas-R axes resulting in increased Ang-II and a shift toward Ang–II-AT1R-mediated effects, leading to increased inflammation, thrombosis and cellular dysfunction. Thick arrows-increased, Thin arrows-decreased. Red-Effect of SARS-CoV2 (☀). Gold-Effect of Obesity

replication and survival; specific host cell metabolic pathways of carbohydrate, lipids, amino acids and nucleotides are differentially affected by viral infection. Viral infections such as influenza virus have been reported to induce a shift into glycolytic metabolism of glucose and inhibition of glycolysis reduced severity of infection suggesting that virus-induced shift into glycolytic phenotype was critical for its survival [240–242]. Reprogramming of host cell metabolism as an adaptive mechanism to potentiate host immunity is also likely. SARS-CoV2 infection also appears to cause diverse effects in host cell metabolism, though detailed information is not available yet. In vitro studies in monocytes supplemented with glucose or monocytes isolated from obese/diabetic patients showed that increase in glucose resulted in increase in viral load indicating that glucose load favored SARS-COV2 infection. SARS-CoV2 infection leads to stimulation of glycolysis along with an increase in the glycolytic capacity in monocytes, and inhibition of glycolysis resulted in reduced viral replication and cytokine production suggesting that glycolysis is required to sustain COV2 infection in monocytes [243]. Alteration in whole body metabolism was indicated by plasma metabolomics and lipidomic analysis of COVID-19 patients of varying disease severity; decrease in TCA cycle intermediates such as malic acid indicated altered energy metabolism. There was a gradual decrease in carbamoyl phosphate, an intermediate of the urea cycle, with increase in fatality, indicating hepatic dysfunction. Both GMP and carbamoyl phosphate were significantly lower in fatal cases than mild ones [244]. Metabolomic analysis of plasma samples of COVID-19 patients revealed alteration in pathways of metabolism of amino acids, lipids, and energy metabolism. A meta-analysis of six such studies revealed a decrease in TCA cycle and propionate pathway as well as perturbation of porphyrin metabolism pathway [245].

COVID-19 and glucose metabolism

Obesity and diabetes mellitus are characterized by insulin resistance and defective glycemic control, which are associated with worse prognosis in COVID-19 patients [246]. Earlier data showed that influenza virus infection caused skeletal muscle insulin resistance in otherwise healthy subjects without hyperglycemia [247], while patients with obesity and diabetes had a higher risk of loss of glycemic control [248]. SARS-CoV2 also appears to affect glucose metabolism. Non-diabetic COVID-19 patients developed hyperglycemia, and patients with severe COVID-19 tended to have higher plasma glucose levels [249]. Further, based on an observational retrospective cohort study in Spain it was concluded that admission-hyperglycemia is a predictor of mortality in patients hospitalized with COVID-19 irrespective of diabetic status [250]. In support of the clinical data indicating impaired glucose homeostasis, in vivo and ex vivo experimental data showed that SARS-CoV2 infects cells of both exocrine and endocrine pancreas through ACE2; it caused reduction in number of β-cells and impaired glucose-stimulated insulin secretion confirming β-cell tropism [251]. As elaborated in earlier studies on pulmonary

vascular dysfunction in metabolic syndrome [252], obesity and SARS-CoV2 infection-associated hyperglycemia may increase pulmonary vascular permeability and inflammation further worsening inflammation in SARS-CoV2 infection. Reduction in levels of TCA cycle intermediates and several acyl carnitines such as palmitoyl carnitine, stearoyl carnitine [253] probably indicated a reduced mitochondrial activity in COVID-19 patients. Transcriptome analysis of different cell types infected with SARS-CoV2 virus in vitro and nasopharyngeal swabs showed downregulation of genes involved in TCA cycle and mitochondrial oxidative phosphorylation [254]. Reduction in the activity of pathways of oxidative energy metabolism might be a metabolic adaptation to lower oxygen levels consequent on reduced lung function in severe disease conditions. Further, in bronchial epithelial cells and PBMCs, expression of genes coding for glycolytic enzymes was upregulated in SARS-CoV2 infection. Significantly, upregulation of lactate metabolizing enzymes resembling 'Warburg effect' in cancer cells, was also reported. Upregulation of expression of genes in the conversion of serine (SDS and SDSL) and alanine (GPT2) to pyruvate was also observed. Dysregulation of glucose metabolism and increased severity of disease associated with hyperglycemia suggest that loss of hyperglycemic control may be a risk factor; observational studies have linked hypoglycemic drugs such as metformin to reduced mortality [255–257].

Downregulation of the genes involved in pentose phosphate pathway, folate metabolism and de novo synthesis of glutathione indicated dysregulation of oxidant metabolism [254]. Further, a significant increase in plasma biliverdin, the oxidized form of bilirubin was reported in COVID-19 patients indicating enhanced oxidant stress [253]. Infection triggers mitochondrial ROS production resulting in stabilization of hypoxia-inducible factor-1α (HIF-1α) and remodeling of glucose metabolism to glycolysis in monocytes; it also resulted in blunted T-cell response and reduced lung epithelial cell survival [243]. Inducing a pro-oxidant state in the host cell facilitates viral proliferation and pathogenesis [258].

COVID-19 and lipid metabolism

Plasma lipidome analysis showed alteration in several lipids in COVID-19 patients. Decrease in levels of glycerophospholipids including phosphatidic acid, phosphatidyl inositols and phosphatidyl choline with increase in the levels of corresponding lysophospholipids probably due to increased phospholipase action, was reported [259]. Alteration in phospholipidome in COVID-19 might affect HDL formation as indicated by decrease in circulating HDL with increase in disease severity [253]. Dysregulation of this pathway is also reported in obesity, independent of viral infection [260]. Another key metabolite that showed decrease at the

time of admission and increased as the patient recovered is sphingosine-1-phosphate (SIP) [253, 261], a product of sphingosine kinase, formed in macrophages and involved in resolution of inflammation. SIP is an important lipid mediator modulating a number of cellular processes that act as a ligand for G-protein coupled receptor-mediated signaling pathways. Serum level of SIP negatively correlated with CRP, LDH, ferritin, D-dimer, which are important indices of COVID-19 severity [261]. Decrease in SIP in Covid patients was also associated with its transport proteins, serum albumin and apolipoprotein M, as well as erythrocyte counts. A decrease in serum SIP may reflect a decrease in its levels in vascular endothelial cells and erythrocytes, but it is not known how this key signaling molecule is affected in other cell types. Unlike SIP, certain other sphingolipids such as sphingomyelin and ganglioside (GM3) increased in severe disease [253]. It is pertinent that these complex lipids that have a role in assembly of lipid rafts critical to viral entry, are increased in plasma in obesity and diabetes independent of viral infection [262].

Transcriptome analysis of different human cell lines and bronchial epithelial cells infected with SARS-CoV2 as well as nasopharyngeal swabs from patients, revealed several differentially expressed genes related to lipid metabolism, particularly lipid storage, HDL formation and fatty acid oxidation. While transcripts of genes concerned with fatty acid degradation and elongation and fatty acid synthesis were downregulated, genes involved in hydrolysis of triacyl-glycerol were upregulated probably leading to increase in free fatty acids. Apart from downregulation of SREBP1, a negative regulator of lipogenesis, there was increase in transcripts of leptin signaling in infected cells [128]. Further, transcripts of genes with a role in sphingolipid and glycerophospholipid metabolism, and phospholipases that hydrolyze membrane phospholipids were upregulated in cells infected with SARS-CoV2 [254]. However, transcripts of genes involved in synthesis of cholesterol were downregulated. Changes in metabolism of several such lipids associated with plasma membrane and lipid raft structures appear to be critical for viral entry, replication and morphogenesis.

Interestingly, many of these changes in reporter metabolites of differentially expressed transcripts, plasma lipidome, altered mitochondrial oxidation capacity indicated by changes in intermediates of fatty acid oxidation and TCA cycle, and aberrations in HDL metabolism, reveal that several of the metabolic pathways dysregulated in COVID-19 were in line with metabolic pathway alterations seen in obesity. Such a metabolic phenotype representing parallels between changes in metabolism in COVID-19 and metabolic disorders such as obesity and diabetes may make obese patients vulnerable to adverse outcome of SARS-CoV2 infection [263].

MiRNAs, obesity, and host cell response in COVID-19

Transcriptome analysis, discussed before, showed differential expression of a number of genes that regulate host cell metabolism and immune response in COVID-19. However, not much information on the mechanisms underlying altered expression of genes contributing to dysregulation of different cellular processes is available. One of the possible factors contributing to regulation of gene expression is the effect of miRNAs, small non-coding RNAs consisting of 20–22 nucleotide length, which bind to 3'UTR of target mRNA and repress translation or promote its degradation [264–266]. A single miRNA may regulate multiple genes while more than one miRNA may co-operatively regulate a single gene [267, 268]. miRNA expression is related with regulation of cellular metabolism, immune response, endocrine function, cell proliferation, and survival and stress response, and its dysregulation is implicated in pathological states such as obesity and diabetes [269–271]. It is equally important that miRNA packaged within exosomes secreted by cells can exert autocrine, paracrine, and endocrine effects facilitating cross-talk between different organs [272–274]. A number of miRNAs related to metabolism of glucose and lipids, particularly the regulation of adipogenesis, pancreatic β-cell content, and insulin function in physiological and diseased states have been documented. Several miRNAs that target genes and pathways involved in adipogenesis including a number of miRNAs that inhibit adipogenesis have been identified (reviewed in [270]). The microRNAs-miR-33a, miR-378, miR-370, miR-27, miR-143, miR-122, miR-335, and miR-125a-5p have been shown to modulate genes involved in triacyl-glycerol, fatty acid, and cholesterol metabolism [275]. Mir-let-7, a well-conserved family consists of eleven members of miRNAs modulate genes which have critical role in glucose homeostasis and insulin sensitivity. miR-33, by targeting IRS-2 and AMPK, modulate glucose metabolism as well. miR-103/107 and miR-29 also regulate insulin response and glucose metabolism [276].

Several of these miRNAs involved in regulating metabolism and immune response are altered in obesity and are associated with obesity-related diseases [271]. A relation between the expression of these miRNAs in adipose tissue, liver, and pancreas in obesity, and development of metabolic disease has been suggested [277, 278]. MiR-27a and miR-130a modulate adipogenesis by targeting PPARγ; this is consistent with decreased expression of miR-130 in abdominal adipose tissue of obese females. Clonal expansion of adipocytes is accompanied by overexpression of miR-17-92 cluster. Expression of miR-17-5p and miR-132 was reported to differ significantly between obese and normal omental adipose tissue and their expression correlated with BMI [279]. Similarly, miR-1 was upregulated in obese white adipose tissue. Association between obesity and alteration in miRNA

expression was also indicated by changes in miRNA expression during weight loss intervention [280]. Several members of miR-let-7 family, which target insulin receptor and IRS-2 and regulate glucose homeostasis and insulin response [281] and negatively regulate adipogenesis [282], are upregulated in obesity-associated metabolic diseases [270]. MiR-26a, whose expression is decreased in overweight subject, also modulates insulin signaling and glucose and lipid metabolism [283]. Sirtuin 1 (SIRT1), which is an important protein deacetylase with a major role in metabolic homeostasis, is negatively regulated by miR-146b; its overexpression induces adipocyte differentiation through downregulation of SIRT1 [284]. Obesity-induced inflammation in adipose tissue is aggravated by a pro-inflammatory effect caused by NF-κB and miR-155 in adipocytes [285, 286].

Alterations in miRNA in tissues, particularly adipose tissue and liver, and in several metabolic disorders are reflected in the circulating miRNAs which are present, apparently in a nuclease-resistant microenvironment, mostly in exosomes or partly as argonaute protein complex bound to plasma protein such as HDL [287, 288]. For instance, association between changes in the levels of miR-23a, miR-27a, miR-130, miR-195, miR197, miR-320a, and miR-509-5p and metabolic syndrome has been reported [276, 289]. MiR-126, a probable biomarker of endothelial dysfunction, is reduced in T2D [290, 291]. Levels of circulating miR-17-5p and miR-132 decreased in obese subjects [279] whose omental fat also showed reduced expression of these miRNAs. Further, elevated levels of circulating miR-140-5p, miR-142-3p and miR-222 and decrease in miR-532-5p, miR-125b, miR-130b, miR-221, miR-15a, miR-423-5p and miR-502c-3p were reported in morbidly obese subjects. Reversal of the expression pattern of circulating miRs as a result of surgery-induced weight loss was indicated by decrease in the levels of miR-140-5p, miR-122, miR193a-5p, and miR-16-1 and an increase of miR-221and miR-199a-3p, further suggesting an association between the changes in these circulating miRNAs and adipose tissue-related pathophysiology in obesity [292]. The adipose tissue-derived exosomes containing the miRNAs present in circulation can be taken up into different types of cells of other tissues and modulate the function of the recipient cell by modulating key target genes by exosomal miRNA [293]. Both cell-based and animal studies have shown that miRNA-containing exosomes from adipose tissue macrophages are taken up by insulin target cells and modulate glucose homeostasis and insulin response [294]. Deep sequencing of exo miRNA demonstrated the presence of about 500 miRNAs and identified 20 differentially expressed miRNAs in adipose tissue macrophages from obese animals [294]. MiR-155, which was overexpressed in obese condition, was shown to decrease PPARγ expression and impair insulin signaling [294]. Adipose tissue-derived exosomes, containing miRNAs, have

emerged as an important signaling system mediating systemic cross-talk contributing to obesity-related inflammation and metabolic dysfunction.

Host miRNA and SARS-CoV2 replication

MiRNAs of host cell or viral origin could influence viral life cycle positively or negatively. They may directly target viral RNA by binding to its coding region to suppress translation or bind to its 5'NTR to stabilize and promote replication of viral RNA [295]. Suppression of translation and replication of influenza virus by binding of host miRNAs such as miR-323, miR-485, miR-491, and miR-654 have been reported [296]. On the other hand, miR-122 promotes HCV replication by binding to viral RNA [297]. Viral miRNA can modulate the expression of host cell factors which may be essential for progression of its life cycle, or serve as receptors for viral entry, or assist the virus in escaping the host immune system by influencing interferon production or signaling. Transmissible gastroenteritis virus evades interferon effect by downregulating miR-30a-5p [298]. Role of exosomal miRNA in mediating cell–cell interaction and influencing host cell defense was evident from the disruption of lung epithelial cell integrity and mitochondrial function by exosomes containing miRNA 23a-27a-24 cluster secreted by alveolar macrophage infected with HIV protein [299]. The importance of host cell miRNA in suppression of SARS-CoV replication and immune evasion has also been demonstrated [300]. In this context, investigations into the possible involvement of miRNAs in SARS-CoV2 disease are also underway. Both ACE2 mRNA and protein expression in cardiomyocytes were downregulated by miR-200c [301]. Expression of TMPRSS2 is modulated by miR-98-5p [302]. Different studies employing computational tools, predicted 128 host miRNAs that recognize miRNA-recognizing elements (MREs) on SARs-CoV2 genome [303]. Of these, three miRNAs (hsa –miR-17-5p, miR-20b-5p, and miR-323a-5p) are known to exhibit antiviral effect experimentally. Most of these host miRNAs target ORF1ab and S genes of the genome. Differential expression analysis of miRNA-sequencing data from lung epithelial cells infected with SARS-CoV2, identified 45 host miRNAs of which 17 were upregulated and 28 downregulated. These included six miRNAs {hsa-let7a-3p, miR-135b-5p,miR-16–2-3p,miR-1275 (downregulated), and miR-155-3p and 139-5p (upregulated)} that were predicted to target SARS-CoV2 [303]. Khan et al., employing computational tools, distinguished host miRNAs-targeting viral genome with presumed antiviral function and viral miRNA targeting host genes to evade host defense mechanisms [304]. Gene ontology and pathway enrichment analysis of the host miRNAs showed that these may target different signaling pathways that may affect SARS-COV2 entry, or host pathways that the virus may hijack for viral replication

or immune surveillance and survival pathways. They further predicted 170 miRNAs encoded by SARS –CoV2, which may target host cell pathways such as TGFβ signaling, TNFα signaling, and mTOR signaling, which might help the virus to evade host's immune surveillance. This was evidenced by identification of 35 target genes, which were downregulated in cells infected with SARS-CoV2, involved in different pathways related to immune signaling and organ-specific functions. Transcriptome analysis of three different human cell lines infected with SARS-CoV2 showed induction of inflammation-linked miRNAs such as miR-155, which is correlated with several viral diseases and involved in pulmonary damage in ARDS [305]. Moreover, in SARS-CoV2-infected transgenic mice expressing human ACE2, anti-miR-155 downregulated expression of miR-155 and reduced levels of pro-inflammatory cytokines, and improved survival of experimental animals [306]. Li et al. analyzed differential expression of miRs in blood of ten COVID-19 patients and four healthy controls and identified top ten upregulated miRNAs of which miR-16–2-3p was the most upregulated, and top ten downregulated miRNAs of which miR-627-5p was the most downregulated [307]. Reduced levels of miR-146a-5p in serum of 29 COVID patients who did not respond to tocilizumab suggested that miR-146a-5p could be a useful predictor of the severity of the disease [308].

Alterations in miRNAs common to obesity and COVID-19

Analysis of the reported data, despite being limited, on changes in miRNAs and the pathways related to their target genes in SARS-CoV2 infection and the miRNAs dysregulated in obesity reveals independent parallel changes in several common miRNAs, as illustrated by a few examples discussed below (Table 2). SARS-COV2 infection models showed lower levels of type I and III interferons with a moderate interferon-stimulated gene response indicating reduced innate antiviral response, despite upregulation of hsa-miR-155a-5p[303, 309], which modulate IFN action[286], in infected cells and in circulation of COVID-19 patients. Likewise, hsa-miR-155a-5p is also upregulated in obese subjects [294, 310]. However, hsa-miR-17-5p, an antiviral miRNA [311], which targets ORF 1ab, decreased in PBMC of COVID-19 patients; hsa-miR-17-5p was also decreased in both circulation and omental adipose tissue in obesity [279]. Further, the hsa-miR-155 binding site on SARS-CoV2 genome probably would permit its binding and stabilization of viral RNA [304]. Hsa-miR-146a has a role in the regulation of inflammation and innate immune response and is perhaps the first miRNA induced in response to viral infection. It is a dominant regulator of TLR signaling, regulates IL-6 gene expression, and may limit the excessive inflammatory

Table 2 miRNAs altered in both obesity and COVID-19

Altered miRNA	Implication in Obesity	Reference	Implication in COVID-19	Reference
Hsa-miR-155	Over expressed in obesity, decrease PPARγ expression, and impair insulin signaling. Adipose tissue exosomes. Delivers to lungs. Insulin resistance	Ying et al. 2017 [294] Ortega et al. 2015 [310]	Upregulated in circulation of COVID-19 patients, nasopharyngeal swabs, and in cells infected with SARS-COV2. anti-miR-155 suppress pro-inflammatory cytokine ARDS damage reduced by elimination of 155. Modulates IFN signaling	Garg et al. 2021. [326] Chow and Salmena,2020 [303 Soni et al. 2021 [306] Wyler et al. 2021 [305] Wang etal 2010[286]
Hsa-mir-146a	Decreased in obesity and T2D. Modulates insulin sensitivity. Negative regulator of inflammation in adipose tissue. Negatively regulates NF-kB by repressing IRAK-1 and TRAFβ signaling	Roos et al. 2020 [313] Sanada etal 2020 [314]	Decreased in serum of COVID-19 patients. Anti-inflammatory. COVID-19 patients with its lower levels responded poorly to anti-inflammatory treatment. Targets SARS-CoV2 genome	Desjarlais et al. 2020 [315] Roganovic et al. 2020 [316] Mirzaei et al. 2020 [309] Sabbatinelli et al. 2020 [308]
Hsa-mir-17-5p	Downregulated. in omental fat and reduced in circulation in obesity	Heneghan et al. 2011 [279]	Decreased in omental fat,PBMC, and circulation in COVID-19 antiviral	Tsubota et al. 2014 [311] Khan et al. 2020 [304]
Hsa-mir200-c-3p	Downregulated in Adipose tissue, Repressed by leptin Decrease can increase ace2 expression	Iacomino &S iani 2017 [270] Chang et al. 2015] 319]	Decreased in infection. Modulation of target ACE2 in respiratory cells	Liu et al. 2017 [320]
Hsa-mir-98-5p	Decreased levels in T2D and obesity	Kokkinopoulo et al. 2019 [420]	Modulation of TMPRSS2 expression	Mirzaei et al. 2020 [309]
Hsa-Let-7a/ Let-7f	Downregulated in obesity. Influence glucose metabolism and insulin sensitivity	Deiuliis 2016 [276]	Decreased Let-7a-3p and Let-7f-3p in SARS-CoV2-infected cells. Predicted to target viral genome	Chow and Salmena 2020[, 303]
Hsa-mir-125	Upregulated in WAT in obesity. Over expressed in obese T2D patients Anti-inflammatory, Reduces TLR/NF-kB activities. Target TGFβ signal pathway genes. Regulates insulin sensitivity	Brovkina et al. 2019 [323] Xu et al. 2018 [322]	Upregulated miR-125-5p in cells infected with SARS-CoV2	Chow and Salmena 2020 [303] Desjarlais etal 2020 [315]
Hsa-mir-21	Upregulated in T2D patients with obesity. Targets TGFβ receptor	Guglielmi et al. 2017 [328] Seeger et al. 2014 [327]	Downregulated miR-21-5p in cells infected with SARS-CoV2 and in circulation of COVID-19 patients. Lower levels associated with severe disease	Chow and Salmena2020 [303] Sabbatinelli et al. 2020 [308] Garg et al. 2021[326]
Hsa-mir-126	Downregulated in obesity. Its protective effect on endothelial cells lost on suppression	Gomez et al. 2017[324] Hijmans et al. 2017 [325]	Downregulated miR-126-5p in SARS-CoV2-infected cells and in circulation of COVID-19 patients	Chow and salmena2020, [303] Sabbatinelli et al. 2020 [308]
Hsa-mir107/103	Upregulated in obesity. A toll-like receptor regulated mir dysregulated in obesity. Mir103/107 upregulation causes insulin resistance, altered glucose homeostasis	Iacomino & Siani 2017 [270] Foley and ONeill 2012 [321]	Upregulated miR107 in covid	Chow and Salmena2020 [303]
Hsa-mir-450	Upregulated in obesity. Pro-adipogenic	Kurylowiez et al., 2018 [421]	Downregulated miR-450-5p in SARS Co2 infected cells	Chow and Salmena,2020 [303]

response to virus. It is downregulated in obesity and relates inversely with increase in IL-6 production by macrophages in obesity [312–314]. miR-146a also decreased in SARS-CoV2-infected cells and serum of COVID-19 patients; patients with lower levels of miR-146a responded poorly to anti-inflammatory treatment [315, 316]. Lower levels of miR-146a may make obese patients more susceptible to adverse outcome on COVID infection. SARS-CoV2-induced host miRNAs may downregulate signaling of different TLRs involved in host antiviral response and dysregulate other signaling pathways leading to host immune suppression. A similar suppressive state in morbidly obese subjects may make them more vulnerable. Several central components within the NF-κB pathway are targeted by miR-146/miR-155-axis, miR-17–92 cluster, and miR-181, thus, regulating inflammation [317, 318]. Dysregulation of several of these miRNAs, as indicated above, can, thus, deregulate NF-κB pathway of inflammation.

Hsa-miR-200c-3p, which targets ACE2, is downregulated in obesity [270, 319]. Hsa-miR-200c-3p is also suppressed in respiratory cells infected with avian influenza virus [320]. Hsa-miR-98-5p, which targets TMPRSS2, is downregulated in obesity [309]. Dysregulation of metabolic pathways, particularly metabolism of carbohydrates and lipids and energy metabolism, occurs in obesity. Parallel changes in these pathways independent of obesity also occur in COVID-19. Several miRNAs-targeting genes related to these pathways are induced on infection and pathway enrichment analysis of these target genes showed enrichment of several pathways related to metabolic regulation such as cellular ketone metabolism, insulin and glucagon signaling, fatty acid metabolism, and PPAR signaling critical in carbohydrate and lipid metabolism [304]. It is also predicted that SARS-CoV2 encoded miRNAs can target, among others, insulin signaling and HIF1 signaling, both critical pathways in disease process and cell survival. Upregulation of miR-103/107 pair in obesity causes insulin resistance and dysregulation of glucose homeostasis in metabolic tissues [270, 321]. MiR-107 is upregulated in SARS-CoV2-infected cells as well [303]. Hsa-miR-125-5p, which regulates TGFβ signaling, is overexpressed in obesity and T2D. It regulates insulin response [322, 323]. Its expression was higher in SARS-CoV2-infected Calu3 cells [315]. MicroRNAs from the let-7 family (let-7a, let-7-f) modulate glucose metabolism and insulin sensitivity by their effects on PI3K and mTOR in the insulin signaling pathway. Both let-7a-3p and let-7f-3p were downregulated in obesity [276] and SARS-CoV2-infected endothelial cells [303]. Several COVID-19 patients developed endothelial dysfunction and thromboembolic events with signs of intussusceptive angiogenesis. MicroRNA-126 is involved in angiogenesis in both physiological and pathological conditions and targets SPRED1, an inhibitor of VEGF-induced angiogenesis. It protects EC from damage

induced by free fatty acids and relieves from oxidant stress. miR126-5p is downregulated in obesity and under hyperglycemia [324, 325]. It is also decreased in Calu3 cells infected with SARS-CoV2 and serum of COVID-19 patients compared to sex- and age-matched healthy controls [303, 308]. But upregulation of miR126-5p in monocytes correlates with HIV disease progression probably indicating virus-dependent nature of response. Mir-21-5p decreased in SARS-CoV2-infected Calu3 cells and serum of COVID-19 patients [303, 308]. There was also an association between lower levels ofmiR21-5p in serum and duration of IMV and requirement of extracorporeal membrane oxygenation [326], but it followed an opposite pattern in obesity showing an increase [327, 328], further indicating that parallel changes observed may be selective in nature.

It is not clear whether the parallel changes reflecting alterations in the expression of several common miRNAs between obesity and COVID-19 cause similar effects, particularly because (a) miRNA expression and action are tissue specific, although exosome-mediated transport and delivery to distal tissues have been demonstrated. MiRNA delivery through macrophage derived exosomes to lung cells have been demonstrated [293, 294]. (b) Each target gene is subject to modulation by different miRNAs, and the same miRNA can regulate multiple target genes and each miRNA exists in multiple isoforms. Much more robust data would be required to understand the implications of these parallel changes in miRNA expression and to consider the possibility of changes in levels of such miRNAs as potential risk predictors.

Adiposopathy and exacerbation of COVID-19 pathology

Adipose tissue, apart from being a metabolic organ, also functions as a key endocrine organ which secretes several hormones and cytokines with significant physiological effects on metabolic organs, vasculature, and immune system [329, 330]. Excess caloric intake and positive energy balance result in expansion of adipose tissue from hyperplasia as well as hypertrophy, accompanied by immune cells infiltration and activation of macrophages which secrete cytokines like TNFα, IL-6, and IL-1β into circulation contributing to an enhanced inflammatory state in obesity [331, 332]. Changes in the profile of the hormones, particularly leptin and adiponectin, secreted by adipose tissue also occur in obesity contributing to altered immune cell metabolism, systemic inflammation, dysregulation of vascular endothelial function, insulin sensitivity, and metabolic organ function. The adiposopathy in obesity that is characterized by an enhanced inflammatory state along with altered adipokine-induced systemic effects, appears to converge with the inflammation and dysregulated cellular and

systemic homeostasis induced by SARS-CoV2 leading to severe COVID-19 disease.

Impact of adipokine imbalance

Circulating leptin level is related to the fat mass as the adipocytes remain the principal source of leptin, though certain cell types in lungs including macrophages, bronchial epithelial cells, and pneumocytes (type II) also secrete this hormone [333]. Leptin acting through its receptor within the hypothalamus provides a satiety signal that suppresses food intake and promote energy expenditure. It also participates in both innate and adaptive immune response and is an important mediator of pulmonary immunity [334]. Leptin modulates immune cell metabolism, and its effect is mediated through cell surface receptor which activates downstream signaling pathways particularly JAK-STAT, PI3K, and MAPK pathways [335–337]. Janus kinase-mediated activation of STAT in response to leptin triggers expression of genes in immune cells where it modulates cell number and function. It induces proliferation and activation of monocytes and the expression of several pro-inflammatory cytokines. An inflammatory-immune phenotype is promoted by leptin in immune cells by activating mTOR-S6K pathway [338]. Leptin mediates upregulation of glucose metabolism to meet energy requirements of the activated T-cells during infection [339]. Requirements of energy and precursor metabolites, for rapid growth of T-cells on activation, are met by employing glycolysis rather than oxidative phosphorylation. Obesity is generally associated with pre-diabetes and insulin resistance which cause impaired glucose uptake and glycolysis by these cells. Hyperleptinemia and leptin resistance in obesity are linked to insulin resistance and impaired insulin receptor signaling through PI3K/AkT/mTOR pathway. This results in failure to supply enough energy to T-Cells to elicit an adequate immune response against viral infection.

It appears that chronic hyperleptinemia impairs pulmonary immunity and defense and may predispose patients to adverse outcome from SARS-CoV2 infection [340]. Increased levels of leptin in bronchoalveolar lavage (BAL) in patients with diabetes and ARDS are associated with increased mortality [341]. Hyperleptinemia-associated leptin resistance adversely affects the immune response. In experimentally induced obese animals infected with influenza virus (H1N1), a rise in mortality and spread of virus, and increased levels of inflammatory cytokines in lungs, were associated with higher plasma leptin levels. Reversal of these effects and increase in survival rate on treatment with anti-leptin antibody suggested that hyperleptinemia was associated with the adverse effects of diet-induced obesity following virus infection [342]. Further, leptin upregulates the expression of the pro-inflammatory cytokine TNFα in

macrophages through phospholipase D1/mTOR/JNK activation [343]. Defective leptin signaling is also implicated in the poor antiviral response to other viral infections such as HIV and Epstein Barr virus [344, 345]. Recently, Wang et al. showed that a subset of monocytes secreting IL-6, TNFα, and IL10 is increased in COVID-19 patients and that this is mediated by leptin, apparently through NF-κB/STAT3 activation. Further, in this cohort group, among several cytokines, leptin was the most significant upregulated component that correlated with monocyte activation and severity of COVID-19 [346]. Higher plasma baseline levels of leptin occurring during expansion of adipose tissue in overweight conditions may cause immune defects and inadequate antiviral response and result in a predisposition to respiratory infection and its increased severity [334, 347].

A weakened innate immune response is a feature of obesity. This was indicated by suppression of IFN-1 responsive gene expression in response to TLR stimulation in PBMCs from obese subjects compared to individuals without obesity [348]. This has been attributed to induction of suppressor of cytokine signaling-3 (SOCS3) which, by inhibiting JAK/ STAT signaling, impairs IFN response [349]. Further, decreased TLR3 activation also leads to decreased IFN-1 production [350]. Increased expression of SOCS3 occurring in viral infection can also result in inhibition of leptin signaling and immune suppression by Treg cells [351]. A reduction in type-1 IFN response has been recognized as a key determinant of severe COVID-19 along with significant downregulation of IFN itself [352, 353]. The impaired IFN response existent in obesity further diminishes the antiviral response of IFN in SARS-CoV2 infection.

Plasma levels of adiponectin are decreased in obesity [354]. This is significant in the context of the reported beneficial effects of adiponectin on vascular endothelium and its anti-inflammatory effect [355–357]. It triggers release of nitric oxide by endothelial cells [358] and improves endothelial redox status by suppressing NADPH-oxidase-derived superoxide formation [359]. In addition, adiponectin downregulates cell adhesion molecules (CAMs) and reduces monocyte adhesion to endothelium [360] while its deficiency enhances leukocyte adhesion [361]. Its insulin-sensitizing, anti-apoptotic, and anti-inflammatory effect is, in part, mediated through activation of AMPK, which is a key enzyme in energy homeostasis [362]. Adiponectin deficiency in mice tends to induce pulmonary inflammation and predispose to developing acute lung injury (ALI) [363, 364]. Its expression is decreased by inflammatory cytokines TNFα and IL-6, which are induced as fat accumulates in adipose tissue [365]. Decrease in adiponectin occurring in obesity and in insulin-resistant conditions [366] may, thus, exaggerate inflammatory response and dysregulation of vascular endothelial homeostasis [356]. Further, adiponectin levels are lower in males who are at increased risk for

COVID-19 than females [367]; similarly, its levels are low in certain ethnic groups [368, 369], who are at increased risk for COVID-19. It has been postulated that decrease in adiponectin in obesity may contribute to respiratory failure in COVID-19 [10]. In a recent study, decrease in plasma levels of adiponectin was observed in 12 COVID-19 patients with respiratory failure compared to non-COVID patients with respiratory failure [370]. It appears that leptin and adiponectin have opposite effects on vascular endothelium, metabolism, immune response, and inflammation, and an inverse pattern of expression with leptin showing an increase and adiponectin decreasing in obesity [364]; the ratio of these two adipokines in circulation might be important in the pathophysiology of COVID-19.

Vascular endothelium and thrombotic risk

It is also evident that dysfunctional adipose tissue contributes to thrombotic risk, which can contribute to adverse outcome in COVID-19 patients with obesity. Apart from pneumonia-related respiratory dysfunction affecting lungs, a clinical feature of COVID-19 in several cases is pulmonary thromboembolism and thrombotic microangiopathy involving endothelial system. Laboratory investigations and imaging studies suggested hyper-inflammation and thrombotic phenomena as important characteristics of severe cases of COVID-19 and SARS-CoV2 may predispose patients to thrombotic disease[371]. Diffuse vascular endothelial inflammation, associated with apoptosis, which is reported to make vascular endothelial cells pro-coagulant [372], suggested that vascular endothelium is a target for SARS-CoV2 [373] and could cause impaired microcirculation. Risk for thrombosis is high in obesity and is associated with a shift to pro-thrombotic state with dysfunctional endothelium [374], activated platelets, and decreased fibrinolytic activity [375–377]. Decrease in fibrinolysis appears to be due to obesity-associated insulin resistance; by modulating the transcription factor Egr-1, insulin is suggested to regulate levels of tissue factor and plasminogen activation inhibitor (PAI-1) [378]. Increased fat mass-associated elevation of circulating PAI-1 can inhibit plasmin-mediated fibrinolysis. Overall coagulation potential and decreased fibrinolysis (as reflected in overall homeostatic potential) have been demonstrated to increase with increase in BMI [379]. Platelet activation in obesity was indicated by higher excretion of 11-dehydroTBX2, a metabolite of thromboxane and a marker of platelet activation, by obese subjects and its reduction to normal levels on weight loss [380]. Further, insulin-induced anti-aggregation of platelets in non-obese subjects was neutralized in obese insulin-resistant subjects indicating that the abnormal metabolic state accompanying insulin resistance, and obesity alters platelet activity [381]. Elevated levels of von Willebrand Factor, TF, factor VII, Factor VIII, and

fibrinogen in circulation indicated a hypercoagulable state in obesity [377, 382]. Moreover, C-reactive protein, of which plasma levels are increased in obesity [383] and severe COVID-19 [384], also exerts a pro-thrombotic effect [385]. It induces TF and PAI-1 and enhances monocyte-endothelial cell interaction by inducing expression of endothelial cell adhesion molecules [386].

Dysregulation of several molecular pathways in obesity can impact endothelial function. For instance, alteration in eNOS activity, increase in pro-inflammatory cytokines and circulating free fatty acids (FFA), and decrease in protective adipokines in obesity contribute to endothelial dysregulation. FFAs induce endothelial dysfunction by several mechanisms including disruption of calcium signaling-mediated NO production, oxidant stress and inflammatory signaling, RAS activation-dependent elevation of endothelin leading to vasoconstriction, and activation of apoptotic pathways [387, 388]. A relation between FFA-induced endothelial dysfunction and RAS was indicated by prevention of FFA effect by inhibition of RAS [389]. FFAs appear to exert this effect by activation of leukocytes through Ang-II production in mononuclear and polynuclear cells and consequent enhanced adhesion of leukocytes to endothelium [390]. Increase in endothelial permeability in obesity permits passage of the virus across the endothelium to infect pericytes or pneumocytes expressing the ACE2 receptor. Plasma levels of VEGF that increase endothelial permeability are increased in obese subjects [391]. Further, increase in FFA can increase endothelial permeability through Nlrp3 inflammasome activation coupled with a decrease in tight junction proteins ZO-1/ZO-2[392, 393]. Plasma metabolomic analysis showed significant increase in FFA correlating with markers of inflammation such as IL-6 and CRP and severity of COVID-19 [394]. FFA-induced immune and endothelial dysfunction, and hyper-inflammation may also make obese subjects vulnerable to adverse outcome in COVID-19.

Recent reports have implicated auto-antibodies in pathogenesis of complications of COVID-19. This was indicated by detection of increased levels of antibodies against interferon-1 (both IFNω and IFNα) in patients admitted with serious COVID-19 [395]. It also appears that the auto-antibodies can contribute to an increased pro-thrombotic state. This was suggested by a higher titer of anti-phospholipid antibodies (aPLs) in serum of patients with severe COVID-19 and an increased ability for IgG antibodies purified from these serum samples to induce venous thromboembolism in an experimental mouse model [396]. The levels of these aPLs were associated with higher platelet count, severe respiratory disease, and low glomerular filtration rate. The antibodies detected were against Cardiolipin, β2 Glycoprotein I, and phosphatidyl serine/prothrombin. A recent meta-analysis also indicated a rise in aPL prevalence in critically ill COVID-19 patients compared to non-critically ill patients

but could not demonstrate any association between the presence of aPLs and requirement of IMV, mortality, D-dimer levels, or development of venous thromboembolism [397]. Obesity has been shown to be associated with increased production of auto-antibodies against intracellular proteins in different organs. Moreover, it has also been demonstrated that obese adipose tissue contributes to secretion of these auto-antibodies [398]. Parallels between the coagulopathy seen in conditions like Anti-phospholipid antibody syndrome and that seen in serious COVID-19, and the increase in circulating auto-antibodies seen in obesity suggest that an altered auto-immune response could be another possible link between obesity and adverse outcome in COVID-19.

Neutrophil activation

The role of peripheral blood leukocytes, particularly neutrophils, in the development of obesity and related diseases is becoming increasingly evident [399–401]. Increase in neutrophil level and its activation indicated by increased expression of elastase and myeloperoxidase, were reported in obese male subjects[402]. High plasma levels of adiponectin were associated with reduced production of the chemokine CXCL8 by neutrophils and the neutrophil activation in obese subjects appeared to be a consequence of decrease in adiponectin [403]. An increase in neutrophils in BAL [404], elevated levels of unique markers of neutrophil activation, and their correlation with disease severity [38] indicated that neutrophil activation is critical for pathogenesis of COVID-19 complications.

One of the mechanisms by which neutrophils exert their effect is through formation of Neutrophilic Extracellular Traps (NETs) in a process called NETosis [405]. This involves release of de-condensed nuclear chromatin, associated with histones and neutrophilic antimicrobial granular proteins, in the form of a reticular scaffold which traps invading pathogens within the DNA fibers. This limits spread of infective agent and recruits antimicrobial factors to the infection site. However, NET action is non-specific and can result in injury to surrounding tissue and worsen the inflammatory response.

The inflammatory state in obesity is also characterized by increase in NETosis [405]. A higher amount of NET formation was observed in plasma of a group of subjects with morbid obesity compared to controls [406]. In experimental mouse models of obesity, there was increased NET formation in the adipose tissue [407].

Viral infections such as influenza A [408], Respiratory Syncytial virus [409], and Chikungunya [410] induce NETosis. Mice on a high-fat diet, infected with influenza, showed higher NETosis than mock-infected controls [411]. In patients hospitalized with COVID-19, there was an increase in markers of NETosis, such as MPO-DNA, in patients requiring mechanical ventilation. Further, sera from COVID-19 patients triggered more NET formation in neutrophils, in vitro, than that from controls [412]. Increase in aPLs in COVID-19 patients was associated with neutrophil hyperactivity and release of NETs, and purified IgG fractions from serum of these patients promoted NETosis in neutrophils isolated from healthy subjects [396]. NETs have been reported to increase in BAL fluid of patients with ARDS [413] as well as those with respiratory failure following acute exacerbation of COPD [414]. Histochemical analysis of autopsy samples of lungs of COVID-19 patients showed the presence of neutrophilic plugs [151]. NETosis has also been implicated in various conditions characterized by arterial and venous thrombosis [415–417]. It, therefore, appears that increased NETosis due to acute inflammation in COVID-19 might further aggravate the pre-existing NETosis in the chronically inflamed obese state, thus, priming it for a more severe outcome.

It appears that dysregulation of the metabolic and endocrine functions of adipose tissue, compounded by inflammation, leads to local and systemic effects that affect functioning of multiple organs, making obese patients vulnerable to a more adverse outcome in SARS-CoV2 infection (Fig. 2). Increase of adipose tissue mass and elevated levels of ACE2 can make it a reservoir for the virus. Besides affecting virus shedding, the pre-existing pro-inflammatory state is aggravated by enhanced acute production of inflammatory cytokines. Higher levels of angiotensinogen and downregulation of ACE2 following infection result in loss of protective effect of ACE2. The resulting dysregulation of the RAAS pathway and ANG-II accumulation further worsen the inflammatory state. Obesity-associated insulin resistance and hyperglycemia are aggravated by SARS-CoV2-induced hyperglycemia consequent to virus-targeting pancreas, leading to further metabolic dysfunction. Dysregulation of endocrine function, particularly a rise in pro-inflammatory leptin and reduction in protective adiponectin, causes systemic effects that affect vascular endothelial function, induce oxidant imbalance, dysregulate immune metabolism, and impair immune response, making obese subjects more prone to severe COVID-19. Alterations in the components of the complement pathway which are mostly of adipose tissue origin and, associated with both adiposity and insulin resistance, can make obese subjects susceptible to microthrombosis in COVID-19. Obesity-associated metabolic and endocrine imbalance can also contribute to dysregulated platelet function and altered fibrinolytic system leading to increased risk for thrombotic events in COVID-19 patients. Several of these changes in adipose tissue function that occur in obesity and have implications for adverse outcome for COVID patients with obesity, could be reversed on calorie restriction-induced weight loss or by surgical intervention
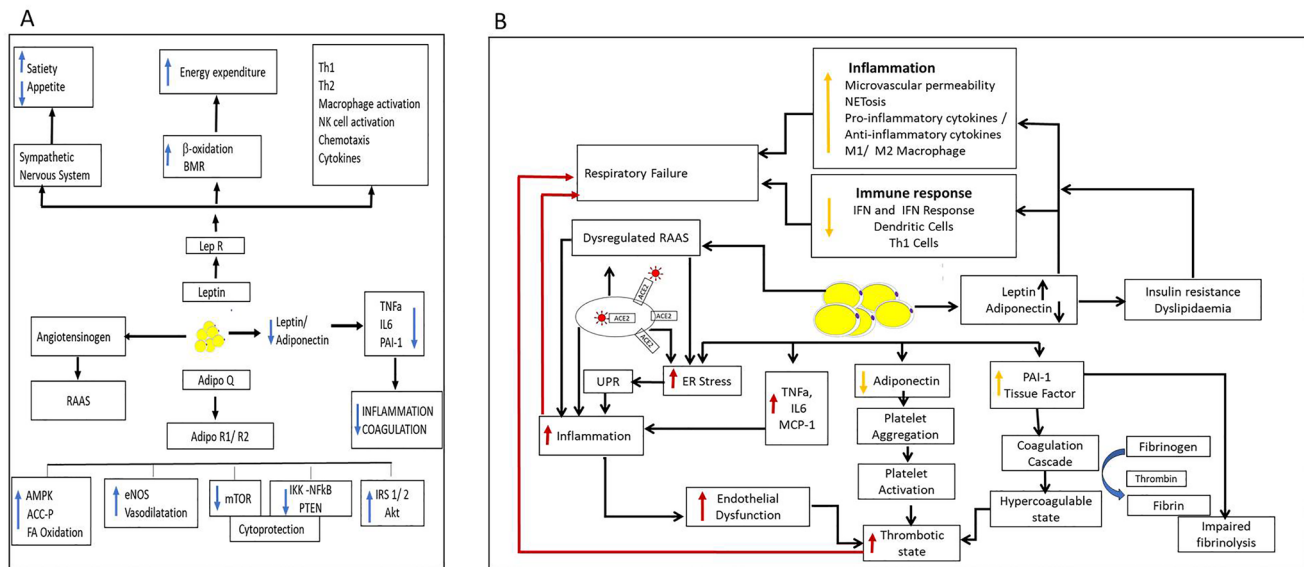
Fig. 2 Challenged adipose tissue and exacerbation of COVID-19. A. Leptin, through its receptor-associated JAK/ STAT-dependent and independent pathways in central and peripheral tissues, regulates energy homeostasis, glucose and lipid metabolism, and immune function. It stimulates polarization of CD4 T-cells to a pro-inflammatory Th1 rather than anti-inflammatory Th2 type, activation of monocytes and macrophages, NK cell activation, the production of pro-inflammatory cytokines, and neutrophil chemotaxis. Adiponectin acts through its two receptors, mediated via AMPK or PPARα, to promote fatty acid oxidation and inhibit lipogenesis, suppress mTOR and IKK-NF-kB-PTEN signaling, and improve insulin signaling. Adipose tissue produces pro-inflammatory cytokines of which levels depend on the relative levels of pro-inflammatory leptin and anti-inflammatory adiponectin. Adipose tissue also contributes to the RAAS pathway. B. Obesity is characterized by metabolic dysfunction, increase in inflammation, ER stress, immune impairment, RAAS dysregulation, and an increased thrombogenic state. Altered adipokine and cytokine production can result in systemic effects adversely affecting organ function. Increased leptin action causes increased immune cell-mediated inflammation with increased vascular permeability, neutrophil activation with neutrophilic extracellular traps, increased pro-inflam-matory, and decreased anti-inflammatory cytokines and increased polarization of macrophages to a pro-inflammatory M1 type from an anti-inflammatory M2 type. It also results in depressed innate and adaptive immune response with reduced interferon response and decreased dendritic cell activity. Dysregulated adipokine production and Insulin resistance affect immune cell metabolism and diminishes immune response. Increase in pro-inflammatory cytokines, decrease in adiponectin, and increased ER stress lead to endothelial dysfunction. Decreased adiponectin also leads to platelet activation. Increased tissue factor and PAI-1 from adipose tissue lead to activation of coagulation cascade and decreased fibrinolysis, respectively. Anti-fibrinolytic effect, hypercoagulable state, and activated platelet with endothelial dysfunction lead to a highly thrombotic state. This challenged system is further compromised by SARS-CoV2 entry that exacerbates inflammation and ER stress. It dysregulates RAAS, leading to loss of protective effect of ACE2 and accumulation of Ang-II, causing further ER stress and inflammation leading to more endothelial dysfunction. Impaired immune response, increased inflammation, and activated thrombotic state can increase severity of COVID-19 in obesity. Red effect of SARS-CoV2 (☀). Gold effect of Obesity

suggesting the possibility of adopting weight reduction strategies to reduce risk for severe COVID-19 disease.

Conclusion

A series of epidemiological studies revealed obesity, particularly central obesity, to be an independent risk factor contributing to higher morbidity and mortality among SARS-CoV2-infected patients. Data from clinical samples of infected patients and studies of cells infected with SARS-CoV2 virus suggest that the underlying mechanisms contributing to adverse outcomes of COVID-19 in subjects with obesity include (a) molecular mechanisms enhancing viral entry and spread and (b) dysregulation of host cell homeostasis adversely affecting functions of key organs which remain critically challenged in obese subjects.

Increased expression of host cell proteins, particularly ACE2, and overactivated mTOR can lead to increased viral entry and spread. Aggravated ER stress, dysregulated RAS pathway, and reprogrammed host cell metabolism may contribute to an adverse outcome.

Disproportionate expansion of adipose tissue, more importantly that of VAT, results in dysfunctional, metabolically challenged and pro-inflammatory adipose tissue leading to distorted cross-talk and loss of homeostasis. The resulting imbalance between pro- and anti-inflammatory cytokines and adipokines causes local and systemic inflammation and an altered immune response due to dysregulated immune cell metabolism. Altered redox balance, decrease in protective adipokines such as adiponectin, and increase

in free fatty acids induce vascular endothelial damage. This adiposopathy increases the risk for adverse outcome of COVID-19 in patients with obesity. Adipose tissue as a reservoir would increase the latency of the virus which might become susceptible to mutation. Appropriate in vivo model-based studies would be required to obtain further insights.

Host-cell response involves differential expression of several genes including those relating to various metabolic and signaling pathways, and a number of miRNAs that target genes regulating cellular processes that contribute to progression and severity of the disease. However, not much information on the targeting of SARS-CoV2 genes by host miRNAs, or sequestering of host miRNAs by viral mRNAs causing loss of regulation of host genes is available. Whether cell/tissue tropism of SARS-CoV2 depends on miRNAs, apart from ACE2, as has been suggested for liver tropism of HCV by miR-122 [418] is also relevant.

Several molecular and signaling pathways dysregulated in SARS-CoV2 infection align with parallel changes in these molecular pathways in obesity, to exacerbate the pathological process and cause severe disease outcome. Some of these molecular pathways are so critical that targeting them could have immense therapeutic potential. Since mTOR pathway is critical in viral replication and elevated in obesity, it is a potential therapeutic target. FDA approved mTOR inhibitors which showed suppression of viral replication in cell-based studies could be clinically tested for their therapeutic potential. ANG-II/RAS pathway is another important therapeutically potent molecular system that contributes significantly to severe disease in COVID-19 patients with obesity. Based on experimental studies on angiotensin receptor blockers (ARB) and ACE inhibitors, concern has been expressed regarding a possible compensatory upregulation of ACE2 that could increase viral load and lung injury. Further, it is also debated whether use of such inhibitors should be continued in CVD patients infected with SARS-CoV2 [419]. As elevated levels of serum ANG-II are correlated with viral load, assessment of serum ANG-II may be done before considering the use of ARB or ACE inhibitors. Yet another molecular pathway involved in acute inflammation and associated complication is the interleukin and JAK/STAT pathway. IL-6 is one of the key upregulated interleukins in SARS-CoV2 infection aligning with its elevated levels in pre-existing chronic inflammation in obesity. Antibodies against IL-6 receptor (Sarilumab and Tocilizumab) and IL-6 (Siltuximab) are two types of IL-6 inhibitors approved by FDA and the NIH panel on COVID-19 treatment guidelines has recommended Tocilizumab along with corticosteroids in certain hospitalized cases with severe disease.

Several of the derangements in metabolism, inflammation and immune cell metabolism and associated molecular pathways, with implications for severe COVID-19, in obesity could be reversed by weight reduction either by diet and life style-based caloric restriction or surgical intervention. Such obesity reduction approaches could be effective in reducing risk for adverse outcome in COVID-19 infections and could even reduce risk for post COVID-19 diseases.

Availability of data and material Not applicable.

Declarations

Conflict of interest The authors declare that there are no conflicts of interest.

Ethical approval Not applicable.

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