Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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1. Introduction

The pandemic resulting from the acute respiratory SARS-CoV-2 infection and the associated COVID-19 syndrome is reaching its third year and has impacted all regions of the globe. At the time of writing approximately 317,500,000 people have been infected with the virus and over 5,500,000 deaths have been attributed to its complications. Importantly, approximately 50% of deaths related to COVID-19 have been in people with co-existing vascular and metabolic disorders [1]. Despite the ready availability of vaccines in some countries and improved therapeutic approaches, daily global infections remain at approximately 3,000,000 with some 8,000 deaths per day. These numbers will likely only decrease relatively slowly as effective global vaccination is undertaken which itself is impacted by vaccine availability and hesitancy to be vaccinated. Further 'spikes' in infection and transmission may be expected as virus mutation occurs, as shown with the rapid spread of the more recent delta and omicron variants (B.1.617.2 and B.1.1.529 SARS-CoV-2, respectively) and due to 'break through' infections resulting from the less than 100% efficacy of vaccination and impaired immune responses. Based on this, it remains vitally important to continue to identify, and understand the susceptibility of, at risk populations.

In addition to advancing age, a number of comorbidities have been associated with poorer COVID-19 outcomes as reflected by prolonged and more intense hospitalization, requirement for mechanical ventilation and death [2–4]. Significantly contributing to poorer outcomes is the coexistence of SARS-CoV-2 infection with obesity, cardiometabolic dysfunction and type 2 diabetes [2,4–7]. The existence of multiple comorbidities in individuals has, however, proved a challenge to definitively establish the level of risk provided by each coexisting disorder.

Recently a substantially more nuanced approach has been taken to understanding the relationships and interactions between obesity, dysmetabolism and poor outcomes following SARS-CoV-2 infection. More specifically, the importance of adipose distribution has been stressed with visceral adiposity being shown to be more predictive of poorer outcome than is the level of subcutaneous fat [8–10]. This relates to the fact that excess energy stored outside the subcutaneous fat normal storage space leads to metabolic abnormalities and micro-inflammation which in turn lead to complications [11,12]. Similarly, accumulation of cardiac and perivascular adipose tissue has been suggested to impact severity of COVID-19 outcomes [13,14]. Related to these observations, questions have been raised as to how levels of obesity should be clinically assessed [15]; is the readily available measurement of BMI sufficient or should more attention be paid to adipose distribution as assessed by CT scans, waist circumference and clinically waist to hip ratio. Further limitations in BMI measurements relate to genetic differences in various ethnic populations, particularly in Asian communities where BMI is typically less than that of Western societies yet dystopic fat accumulation including excess visceral fat accumulation is often evident. Similar to all dysmetabolic conditions, the utility of BMI is limited in individuals with high muscle to fat ratios [16]. Along these lines an additional consideration that is relevant to the heterogeneity of obesity and COVID-19 outcomes is whether there are differences in metabolically healthy (in whom fat may be more than normal but still not exceeding the normal storage space of the organism in subcutaneous adipose tissue) and metabolically unhealthy obese patients (with the latter having dystopic fat accumulation)?

In a recent article published in Metabolism Clinical and Experimental, Kim et al. [17] in a retrospective analysis examined the relationship between metabolic health and COVID-19 outcomes. Subject data were obtained from the Korean National Health Insurance Service COVID-19 data base with a diagnosis of COVID-19 being confirmed by a SARS-CoV-2 PCR test. 4069 COVID-19 patients, with available metabolic characterization, were subdivided into four groups; 1. metabolically healthy normal weight; 2. metabolically healthy overweight; 3. metabolically unhealthy normal weight; and 4. metabolically unhealthy obese. Stratification into these groups was based on BMI (obese > 25 kg/m^2) and a metabolic health assessment (metabolically unhealthy being defined as showing three of: elevated fasting blood glucose or taking glucose lowering agents; blood pressure > 130/85 mm Hg or taking antihypertensive medications; elevated serum triglycerides or taking lipid lowering agents; low plasma HDL levels; waist circumference >90 cm for men and >85 cm for women). The primary outcome measure was a composite of admission to the ICU, mechanical ventilation extracorporeal membrane oxygenation and death occurring during a 4-month follow-up period from diagnosis. Based on uncorrected calculated Hazard Ratios (HR) metabolically non-obese unhealthy subjects and obese subjects (both metabolically healthy and unhealthy) showed higher risk for severe COVID-19 outcomes. After adjusting HR for confounding factors (including age, sex, smoking, alcohol consumption and physical

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activity) only metabolically unhealthy patients maintained a significantly higher risk for severe outcomes (composite measure and mortality). Based on this analysis the authors concluded that metabolic health is a stronger predictor for severe COVID-19 outcomes than obesity per se.

An interesting observation made by Kim et al. was that the risk of severe COVID-19 outcomes increased in an approximately linear manner with the number of indicators of metabolically impaired health even after correction for BMI [17]. Collectively the results suggest that metabolic dysfunction presents as a risk for severe COVID-19 outcomes independently of obesity. Nevertheless, metabolically unhealthy obese (MUO) patients showed the highest risk for mortality. As patients in the various outcome categories were relatively small and the results reflect a single ethnic population, the general applicability of the findings requires wider study. Further the available data did not include specific information relating to body composition, adipose tissue distribution or diet/diet quality. Such information, along with more detailed information relating to physical activity, may give further insight into the heterogeneity of obesity and the classifications of metabolically healthy and unhealthy phenotypes.

An additional paper also recently published in Metabolism, Clinical and Experimental by Kouvari and colleagues [18] emphasizes the heterogeneity that exists within subjects classified as metabolically healthy obese (MHO) and calls for the inclusion of an additional criterion to define subjects as metabolically unhealthy i.e. dystopic excessive fat deposition in the liver, non-alcoholic fatty liver disease (NAFLD). Specifically, using data from the ATTICA prospective cohort study, these authors divided MHO patients (stringently defined as showing no evidence for alteration in accepted markers for metabolic syndrome) into those exhibiting evidence (assessed by non-invasive indices) of NAFLD. Over a 10-year period those subjects with NAFLD at baseline showed a greater rate of progression to the MUO state and were at higher risk for cardiovascular events and/or death. Interestingly, several studies have presented evidence for an association between NAFLD and severity of COVID-19 outcomes, independent of obesity [19–22]. Thus, hepatic accumulation of fat, similarly to visceral and perivascular fat, conceivably contributes to an inflammatory environment prior to marked changes in BMI and perhaps predisposes to more severe COVID-19 outcomes. Relevant to this, markers of systemic inflammation (proinflammatory monocyte counts) have been reported to be higher in both MUO and MHO subjects compared to controls [23]. Regardless of the exact relationships, the prospective studies of Kouvari and similar findings of Hwang et al. [24] suggest that the MHO state is not necessarily stable or benign and may transition to the MUO state, particularly when NAFLD co-exists. As the SARS-CoV-2 pandemic continues this suggests that attention should be given to markers of NAFLD (in addition to those for metabolic syndrome that are usually used to classify obesity as MUO) to identify a subgroup of patients who may show progression to MUO and susceptibility to poor COVID-19 outcomes. Similarly, an increased understanding of genetic factors contributing to the heterogeneity obesity and propensity for transition from healthy to unhealthy states is required. Collectively, such knowledge may inform individualized treatment strategies for obese patients that are important in preventing poor outcomes following SARS-CoV-2 infection.

In the following paragraphs we briefly review possible mechanisms which may underlie the interaction between the metabolically unhealthy state, SARS-CoV-2 infection, and COVID-19 severity – including the roles of coexisting inflammation, immunomodulation, thrombosis and altered renin-angiotensin-aldosterone (system) RAAS signaling. Further we highlight strategies to protect this at-risk population including through weight loss interventions both pharmacological and lifestyle. In addition to preventive measures the impact of obesity and metabolic dysfunction on post SARS-CoV-2 infection or 'long COVID-19 syndrome' is discussed.

2. Mechanisms linking metabolic dysfunction and obesity to severity of COVID-19 outcomes

The overall immune dysfunction that is observed in obese individuals, is associated with accumulation of resident immune cells, including macrophages, neutrophils, eosinophils, T and B cells, as well as dendritic cells, across different tissues leading to enhanced cytokine and chemokine production and ultimately heightened basal inflammation. The extent of systemic inflammation can be further aggravated in some obese individuals by impaired levels of adipokines, lipokines, hepatokines, myokines and branched-chain amino acids. The sum of these obesity-triggered disruptions in physiological immune function lead to a persistent low-grade inflammation coupled with a compromised immune response that likely render obese individuals prone to reduced SARS-CoV-2 clearance in the early stage of infection and a high viral load, as well as a hyper-inflammatory response. Obesity is well-known to disrupt the integrity of multiple tissues, leading to inflammation mainly in the adipose, respiratory tract, lymphoid, and gut tissues [25]. Key mechanisms linking metabolic dysfunction and obesity to severity of COVID-19 outcomes are detailed below and shown schematically in Fig. 1.

2.1. Adipose tissue

In adipose tissue (AT), multiple mechanisms are believed to contribute to the heightened inflammatory state and suppressed immune response that is observed in obesity. In brief, overnutrition-driven hyperinsulinemia, induces adipocyte hypertrophy and hyperplasia, followed by hypoxia, adipocyte death, lipotoxicity and altered extracellular matrix [26], while the excessive production of adipokines and inflammatory mediators promote the recruitment of a range of different immune cells to AT. At the molecular level, this has a multitude of implications. Among them, the AT dendritic cells present with increased toll-like receptor (TLR) expression that leads to M1 macrophage activation, while the secretion of AT inflammatory cytokines (such as TNF, IL-6, angiotensin II and plasminogen activator 1) promote the activation of M1 macrophages systemically [27,28]. Meanwhile, the heightened secretion of adipocytokines (and especially leptin and resistin) further augments the production of TNF, IL6 and IL12, directly impacting the nuclear factor kappa B and JNK pathways and activating the unfolded protein response. Notably, high plasma levels of leptin, TNFα and CXCL-10 have been suggested to be a predictor of COVID-19 severity in obese individuals [29], while IL-6 is a key mediator of the cytokine storm (CS) and disease progression to acute respiratory distress syndrome (ARDS) observed in COVID-19 [30]. Importantly, the IL6 blocker tocilizumab was the second drug ever recommended by the World Health Organization (WHO) for people with severe COVID-19. In addition, in obesity, the observed NLRP3 inflammasome activation in AT mediates reactive oxygen species (ROS) activation, release of interleukins 1β and 18, free oxygen radical production and promotion of a systemic proinflammatory state that can also promote the presentation of CS [30–32]. Two additional, yet poorly understood mechanisms of immunomodulation by AT are believed to involve epigenetic histone modification and miRNA related mechanisms [33,34]. However, the role of AT in obesity-triggered inflammation is likely to be even more complex, since different AT depots throughout the human body present with notable differences in their physiology, susceptibility to inflammation and the heterogeneity of the inflammatory cell population. A prime example is the strong association of visceral, but not subcutaneous, fat with an exaggerated inflammatory state in obese individuals, which could at least in part explain poor clinical outcome of COVID-19 patients with increased visceral as opposed to subcutaneous adiposity [10,35].

In addition to the compromised function of AT in obesity, it also appears to be a favored target tissue of SARS-CoV2. Specifically, SARS-CoV-2 enters target cells via binding of its spike protein to the cellular receptor angiotensin-converting enzyme 2 (ACE2), a member of the RAAS

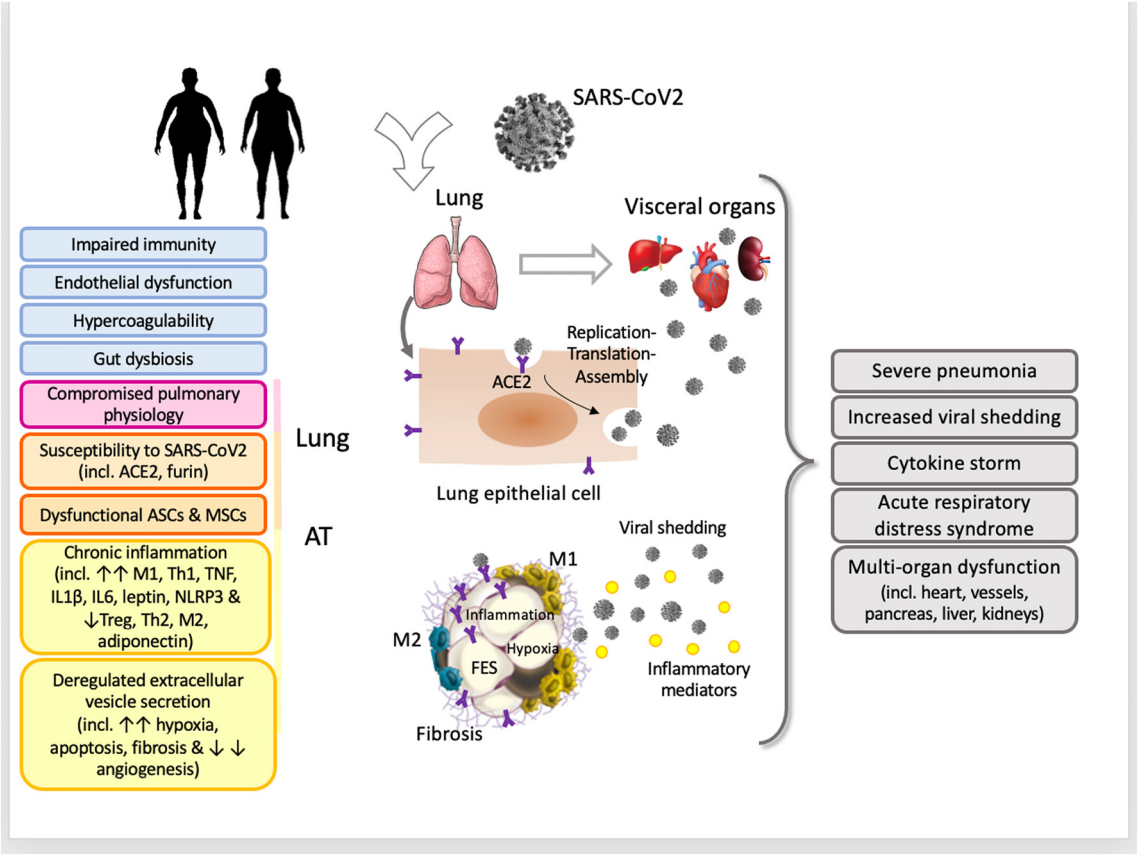

Fig. 1. Key mechanisms linking metabolic dysfunction and obesity to severity of COVID-19 outcomes: SARS-CoV2 enters the human body through the respiratory tract and penetrates the lung epithelial cells via specific binding of its spike (S) protein to ACE2, with the assistance of other intracellular proteins including furin. Once inside the cells the viral RNA is replicated and through a series of molecular processes its proteins are translated, and new viral particles assembled and secreted via exocytosis. Through this process the virus spreads to other tissues expressing ACE2, with AT being a prime target, since ACE2 is abundantly expressed in the lung and AT, and further overexpressed in obesity. Within AT, SARS-CoV elicits an inflammatory response that could contribute to the observed cytokine storm and acute respiratory distress syndrome. The AT of visceral organs has been proposed to serve as a SARS-CoV2 reservoir, leading to increased viral shedding. The apoptotic and necrotic death of SARS-CoV2 inside the adipocytes fuels the inflammatory response, contributing the development of fat embolism syndrome. In the background of obesity both the lung and AT are compromised due to impaired pulmonary function and loss of functional lung MSCs, as well as persistent low-grade inflammation and ASCs dysfunction in AT. Furthermore, the impaired immunity, endothelial dysfunction, hypercoagulability and gut dysbiosis, render obese individuals considerably more vulnerable to SARS-CoV2 infection [4].
Abbreviations: ACE2, angiotensin-converting enzyme 2; ASCs, adipose stem cells; AT, adipose tissue; FES, fat embolism syndrome; IL, interleukin; M1, M1 macrophages, M2, M2 macrophages, MSCs, mesenchymal stem cells; NLRP3, NACHT, LRR and PYD domains-containing protein 3; Th1, T helper type 1 cells; Th2, T helper type 2 cells; TNF, tumor necrosis factor; Treg, regulatory T cells.

and is proteolytically cleaved by the transmembrane protease serine 2 (TMPRSS2). Among other proteases that can mediate the proteolytic activation of the spike protein, furin is of particular interest as it is also involved in viral exit from the host cells enabling viral particles to attack neighboring cells or be released into the circulation [35]. During SARS-CoV-2 infection, ACE2-expressing tissues become direct targets, among which are the multiple AT depots in the human body. RAAS intrinsic to WAT modulates inflammation, oxidative stress, and immune status of both visceral and ectopic fat depots. Of importance in COVID-19 severity, ACE2 and furin are highly expressed in the AT of normal weight individuals, and further overexpressed in obesity [35]. Within AT, SARS-CoV-2 has been shown to target specifically mature adipocytes and AT macrophages, eliciting an inflammatory response that includes secretion of known inflammatory mediators of severe COVID-19 [36]. An extensively pursued hypothesis is that this inflammatory response is due to increased angiotensin-II production following the SARS-CoV-2 induced impairment of ACE2 enzymatic activity in visceral fat. It has therefore been proposed that RAAS imbalance could trigger the cytokine storm observed in severe COVID-19 [37]. Due to these attributes AT is considered a reservoir for SARS-CoV2, enabling increased viral shedding, immune activation, and cytokine amplification [37]. Importantly, given its anatomical distribution AT, and especially visceral AT, would be able to drive severe COVID-19 through augmented inflammation at an organ level in the heart, vasculature, pancreas, liver, and kidneys [37].

2.2. Respiratory system

Pulmonary status can also be impaired in obese individuals. In terms of pulmonary physiology, a decrease in total respiratory system compliance is observed, which is due to the accumulation of fat in the areas of the ribs and diaphragm, leading to decreased chest wall compliance, as well as the increased airways resistance, respiratory muscle inefficiency, and ventilation-perfusion inequality [38]. As a consequence, there is decreased ventilatory reserve along with a propensity to respiratory failure, under challenging circumstances such as SARS-CoV-2 infection.

At the molecular level, partly through the heightened release of pro-inflammatory mediators (especially leptin) and the reduced release of anti-inflammatory adiponectin by AT, obese individuals are susceptible to pulmonary infections. Upon viral infections, an enhanced pulmonary inflammation is anticipated followed by an increased risk of exacerbated airway obstruction [39]. In SARS-CoV-2 infected patients, pneumonia is a frequently encountered symptom, while 42% of those with pneumonia and 61–81% of those requiring intensive care will present with ARDS [40]. The compromised pulmonary function in combination with the abundant expression of ACE2 and furin in the lung, and the

overexpression of ACE2 in obesity, could be contributing factors in COVID-19 severity [41,42]. Interestingly, in a diet-induced obesity mouse model, only male (and not female) mice presented with a significant increase in lung ACE2 expression, which is reminiscent of the major sex-differences in patients with COVID-19 requiring hospitalization or intensive care (increased in men by up to 50% and 300–400%, respectively) [43,44].

An additional concern in obese patients, is the loss of functional lung mesenchymal stem cells (MSCs), which has been shown to contribute to pulmonary fibrosis development [45,46]. Pulmonary fibrosis or fibrous stripes is a severe complication in COVID-19, reportedly observed in approximately 17% of hospitalized patients.

2.3. Other considerations

In lymphoid tissues the ectopic lipid accumulation alters both structure and function, leading to impaired development of leucocytes, altered leucocyte subpopulation distribution, impaired lymphocyte activity and a compromised innate lymphoid cell response, which render obese individuals conducive to severe COVID-19 outcomes [47].

A higher risk of hypercoagulability, and thereby arterial and venous thromboses has been described in COVID-19 patients [48,49]. Notably, lungs from patients who died from COVID-19 ARDS demonstrate pulmonary thrombosis and vascular angiogenesis that are unique compared with ARDS without COVID-19. Obese patients with COVID-19 may have nearly three times the risk of developing pulmonary embolism. Although the mechanisms linking pulmonary embolism and obesity in COVID-19 require further exploration, the endothelial dysfunction, increased ACE2 expression in bronchial epithelial cells (which correlates with interferon responses), and exaggerated inflammatory responses are likely to be contributing factors. Interestingly, patients taking statins to lower cholesterol before presenting with COVID-19 were less likely to have pulmonary embolism.

Although there is still a great deal to learn about the full spectrum of mechanisms through which obesity promotes severe COVID-19, some of the additional leads relate to common features of obesity, namely dyslipidemia (involving decreased HDL and increased total cholesterol, triglycerides, and LDL) and gut microbiome dysbiosis. Since cholesterol plays a critical role in viral entry and replication, in obesity an unfavorable response to SARS-CoV-2 infection is anticipated. Multiple observational analyses have examined relationships between circulating lipids, statin use, and outcomes, so far however, with somewhat conflicting conclusions [5,50]. Meanwhile, the underlying gut dysbiosis in obesity can be aggravated during SARS-CoV-2 infection, either by cytokines from the infected respiratory tract or from direct infection of the gut, or both [51]. Enhanced gut dysbiosis leads to augmented intestinal permeability, ultimately exacerbating the systemic inflammatory response [51]. Indeed, an association between the gut microbiome, the levels of cytokines and inflammatory markers, and COVID-19 severity has been described [52]. Furthermore, the gut microbiota dysbiosis after disease resolution could contribute to persistent symptoms potentially contributing to the long term COVID-19 syndrome [52].

While the preceding discussion centers on mechanisms by which obesity contributes to severity of COVID-19 outcomes, an important question relates to how the metabolically unhealthy phenotype similarly leads to poor outcomes or alternatively whether there is a relative protection in the MHO phenotype. Thus, as mentioned earlier it is likely that the metabolically unhealthy phenotype is associated with more prominent low-grade inflammation, impaired immune responses, tendency toward hypercoagulability and greater pulmonary dysfunction. Consistent with this, inflammatory cytokines such as IL-6 and TNF are increased in insulin-resistant subjects independent of obesity. Further, the gut microbiota is reported to differ between metabolically healthy and unhealthy phenotypes [53,54].

3. Prevention strategies for limiting the impact of metabolic dysfunction and obesity to severity of COVID-19 outcomes

Global efforts to mitigate the spread of COVID-19 and to prevent severe disease in those infected have been met with tremendous scientific developments, spearheaded by the production of several vaccines with high efficacy and safety [55] (Fig. 2). Prevention strategies for outpatients with COVID-19 at risk of severe disease include neutralizing monoclonal antibodies targeting SARS-CoV-2 [56] and two novel oral antiviral agents —Paxlovid and molnupiravir—that are currently under review for emergency use authorization (EUA) by the Food and Drug Administration (FDA) [57]. While a significant proportion of morbidity and mortality has been avoided because of these advancements, COVID-19 continues to be a serious threat, particularly for individuals with risk factors for severe disease. Recently, attention has been raised regarding waning vaccine-induced immunity [58,59], prompting the recommendation that all adults receive a booster vaccination six months after completion of the initial Pfizer or Moderna series or two months after completion of the Johnson&Johnson vaccination. This recommendation is particularly relevant for individuals with obesity and metabolic dysfunction, as these populations may already be at higher risk of vaccine breakthrough infections [60]. With the recent rise of the Omicron variant, and concerns regarding potential immune escape [61], strategies to mitigate poor outcomes in persons with obesity and metabolic dysfunction are even more salient.

While a renewed focus on the obesity epidemic and strategies for treatment is urgent, there is evidence that the COVID-19 pandemic has made the treatment of obesity even more challenging. One study examining the effects of stay-at-home orders during the pandemic in a sample of adults from an obesity medicine and bariatric surgery clinic found that 69.6% of adults reported more difficulty in losing weight, and 47.9% reported decreased levels of physical activity [62]. While some reports have noted improvement in diet quality in some geographic regions and populations during the pandemic [63,64], many have noted a decline, including increased consumption of sweets and processed foods, and decreased intake of fruits and vegetables [65,66]. Moreover, disparities in access to healthy, affordable foods are likely to have been exacerbated during the pandemic [67]. In the US, the effects of the pandemic on diet quality, exercise, and psychosocial health have contributed to a concomitant worsening of the obesity epidemic. The Centers for Disease Control and Prevention (CDC) recently analyzed data from a longitudinal cohort of more than 400,000 children and adolescents and found that the rate of BMI increase during the pandemic approximately doubled compared with the pre-pandemic period (Longitudinal Trends in Body Mass Index Before and During the COVID-19 Pandemic Among Persons Aged 2–19 Years — United States, 2018–2020 | MMWR (cdc.gov)). Another analysis from the CDC found that the number of states with an adult obesity prevalence ≥35% increased to 16 in 2020, up from 12 states one year earlier (Obesity, Race/Ethnicity, and COVID-19 | Overweight & Obesity | CDC).

In this context, the importance of addressing the root causes and underlying drivers of obesity and cardiometabolic risk factors that predispose to severe outcomes is apparent. The mainstay of obesity treatment is comprehensive lifestyle modification, including dietary restriction and increased physical activity [68] (Fig. 2). For individuals that do not reach treatment goals and have a BMI ≥30 kg/m^2 or BMI >27 kg/m^2 with one or more weight-related comorbidities pharmacotherapy should be considered as an adjunct to lifestyle modification [69] (Fig. 2). Several medications are FDA-approved for obesity, including phentermine/topiramate, orlistat, naltrexone/buproprion, liraglutide, and the recently approved semaglutide [70] but are severely underutilized, to a certain extent due to cost. One recent study suggested that use in eligible patients may be as low as 1.3% and that a minority of physicians prescribe these weight loss medications [71]. Although randomized clinical trial (RCTs) have not directly proven benefits among patients with COVID-19 one would have reasonably expected such benefits. Below we will briefly review current recommendations for the treatment of obesity in the context of recent data relating to COVID-19.

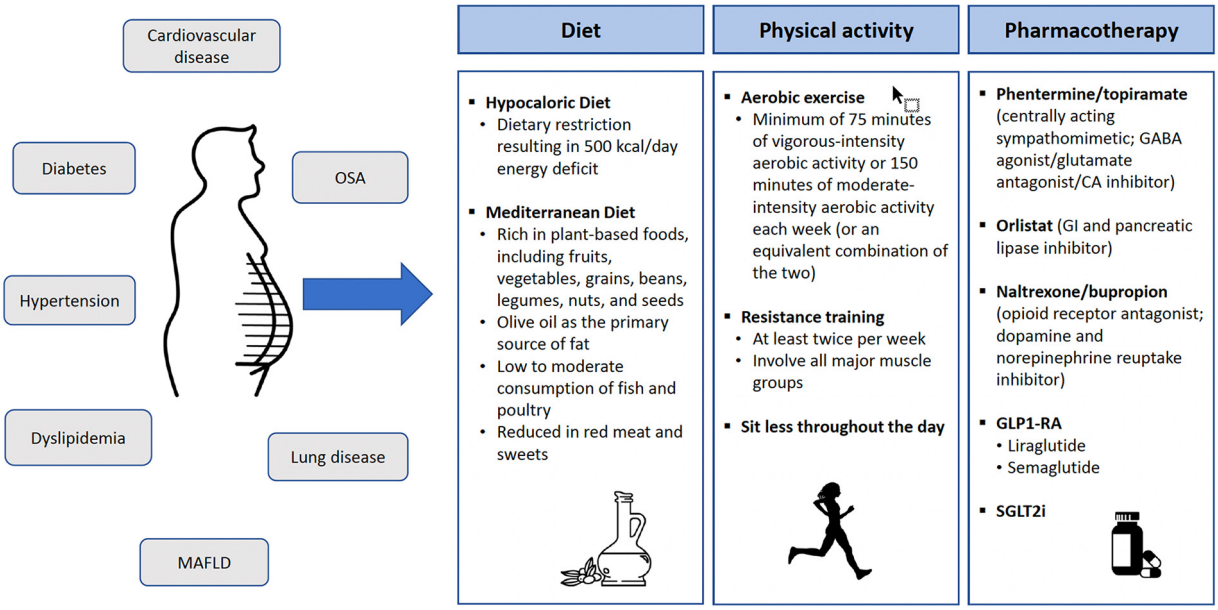

Fig. 2. Overview of lifestyle and pharmacological treatment for obesity.
Obesity is associated with several weight-related comorbidities, including cardiovascular disease, hypertension, dyslipidemia, metabolic associated fatty liver disease, lung disease, and obstructive sleep apnea. The cornerstone of treatment for obesity is lifestyle modification, namely the prescription of a hypocaloric diet and increased physical activity. The Mediterranean diet may have additional health benefits that are relevant to COVID-19, including antioxidant and anti-inflammatory properties. For patients with a BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 in the presence of obesity-related comorbidities who do not reach weight loss goals, pharmacotherapy should be considered as an adjunct to lifestyle modification. In the US, the FDA-approved medications for obesity include phentermine/topiramate, orlistat, naltrexone/bupropion, liraglutide, and semaglutide. Sodium-glucose cotransporter-2 inhibitors are not FDA-approved for weight loss but are also used in the clinic for this purpose.
Abbreviations: CA, carbonic anhydrase; GABA, gamma aminobutyric acid; GI, gastrointestinal; GLP1-RA, glucagon-like peptide 1 receptor agonist; MAFLD, metabolic associated fatty liver disease; OSA, obstructive sleep apnea; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

3.1. Dietary interventions

The Mediterranean diet (MD) been proposed as a potential dietary approach to address both short- and long-term risks associated with COVID-19 [72]. The MD is characterized by high intake of plant-based foods, including fruits, vegetables, grains, beans, legumes, nuts, and seeds; olive oil as the primary source of fat; low to moderate consumption of fish and poultry; and low intake of red meat and sweets [73]. Notably, the effects of a poor diet on biomarkers of oxidative stress and inflammation have been observed within 60 min of feeding [74]. In contrast, the MD may exert anti-inflammatory and antioxidant effects through the action of foods rich with bioactive polyphenols that dampen pro-inflammatory cytokine proliferation and inhibit the nuclear factor-κB signaling pathway [72]. Given the exaggerated immune response and pro-thrombotic state associated with severe COVID-19, this dietary pattern may serve to limit further "fuel on the fire" in the short term while conferring long-term beneficial effects on cardiovascular health [75]. While clinical trials testing the beneficial effects of the MD on COVID-19 have not been conducted, a limited amount of observational data suggests that a healthy diet may reduce the risk of severe disease from COVID-19. One large prospective study of more than 500,000 UK and US participants of the smartphone-based COVID-19 Symptom Study found that a high diet quality characterized by healthy plant-based foods was associated with a lower risk of severe COVID-19 (HR 0.59; 95% CI: 0.47–0.74 for the highest vs. lowest diet quartile) [76]. Notably, the MD is characterized by mainly plant-derived nutritional components; however, trials specifically testing the MD as a potential therapeutic strategy against COVID-19 are warranted.

3.2. Physical activity

Studies have shown that high physical activity levels are protective against COVID-19 mortality in persons with both average weight and obesity [77,78]. A recent prospective cohort study of more than 250,000 participants from the UK BioBank cohort investigated the impact of physical activity on COVID-19 mortality in adults with obesity [78]. Physical activity level (ascertained by self-report) was classified as high in individuals achieving ≥3000 MET min/week (metabolic equivalent minutes of physical activity), moderate for ≥600 MET min/week, and low for the remainder of activity levels. Compared with highly active adults with a normal BMI as the reference group, the multivariable-adjusted odds ratio (OR) for COVID-19 mortality was 2.85 (95% CI: 1.74 to 4.57) for lowly active adults with obesity and 1.61 (95% CI: 0.98–2.64) for highly active individuals with obesity. While the risk of mortality among highly active adults with obesity vs. highly active adults with normal BMI did not differ significantly, the authors noted that the magnitude of the OR and the 95% CI approaching 1.0 suggests that high levels of physical activity may not entirely attenuate the increased risk of mortality in adults with obesity [78]. Physical inactivity and visceral obesity are associated with low-grade chronic systemic inflammation, and trials have suggested that exercise and physical activity may improve biomarkers of systemic inflammation [79]. While the mechanistic basis for the observed protective effects of physical activity on COVID-19 in persons with obesity requires further study, physical activity remains an essential aspect of any weight-loss program. Several professional societies and committees recommend that adults perform a minimum of 75 min of vigorous-intensity aerobic activity or 150 min of moderate-intensity aerobic activity each week (or an equivalent combination of the two), in addition to resistance training at least twice per week [80,81]. While maintaining optimal amounts of physical activity in the setting of COVID-19 restrictions poses unique challenges, the WHO and others have provided guidance on strategies to reach the recommended amounts of daily physical activity during the pandemic (Stay physically active during self-quarantine (who.int)).

3.3. Pharmacotherapy

Several studies have investigated the benefits of glucose-lowering medications on risk of COVID-19 infection or severe outcomes but are largely limited to observational data. Among the glucose-lowering

medications studied, sodium-glucose contransporter-2 inhibitors (SGLT2is) and metformin are also often used off-label for their weight loss effects, whereas glucagon-like peptide-1 (GLP-1) receptor agonists (GLP1-RAs) are FDA-approved as described above. In a population-based study of 2.85 million English adults with type 2 diabetes mellitus (T2DM), people prescribed metformin, SGLT2is, and sulfonylureas had a lower risk of COVID-19-related mortality than those not prescribed these medications, whereas the prescription of insulin or DPP4 inhibitors were associated with a higher risk [82]. The use of GLP1-RAs or thiazolidinediones was not significantly associated with risk of COVID-19-related mortality. Another large US population-based study found that compared with DPP4 inhibitor use, both GLP1-RA and SGLT2i use was associated with a lower 60-day COVID-related mortality [83]. Moreover, in a large cohort of Veterans Health Administration patients with T2DM ($n = 64{,}892$) and COVID-19, the use of SGLT2i, GLP1-RA, or metformin was associated with a lower odds or hazard of adverse outcomes [84].

While premorbid use of several glucose-lowering agents appears to have a beneficial effect on COVID-19 outcomes based on the above observational data, a limited number of trials have investigated the initiation of anti-hyperglycemic agents as a treatment for COVID-19. The DARE-19 trial was a double-blind, placebo-controlled, phase 3 trial of hospitalized patients with COVID-19 with at least one cardiometabolic risk factor in which patients were randomly assigned to dapagliflozin (SGLT2i) 10 mg oral daily or placebo for 30 days. While dapagliflozin was well-tolerated, there was no statistically significant difference in the rates of organ dysfunction or death between randomized groups [85]. The TOGETHER trial was a placebo-controlled, randomized trial that examined the use of metformin in patients with COVID-19 and at least one risk factor for severe disease and did not find any benefit in any of the pre-specified outcomes, including risk of hospitalization [86]. While other clinical trials are currently underway, observational data should be interpreted cautiously pending confirmation in well-designed randomized trials [87].

While the possible role of glucose-lowering medications for the prevention or treatment of COVID-19 requires further study, the intersection of the obesity epidemic and the COVID-19 pandemic highlights the urgent need to address the prescription gap for patients meeting criteria for pharmacotherapy for obesity. Semaglutide is a GLP1-RA that was recently approved by the FDA for the treatment of obesity after clinical trials demonstrated a mean weight loss of roughly 15–16% from baseline in the context of lifestyle interventions [88,89]. Liraglutide, a member of the same class of medications that preceded semaglutide as an approved medication for obesity, has also been shown to effectively promote healthy weight loss maintenance in conjunction with exercise [90]. Trials of several gut peptide hormones with dual- and triple-agonist formulations are in the drug development pipeline and have the potential to reach weight loss thresholds that approach that of bariatric surgery [70]. While several factors contribute to the low utilization of weight-loss medications, lack of insurance coverage is a major barrier and efforts to ensure the equitable availability to all that meet criteria are of paramount importance.

3.4. Nutrition and obesity stigma/disparities

In the US and other areas globally, disparities in nutrition and obesity based on race, ethnicity, and socioeconomic status are closely linked with several cardiometabolic conditions that contribute to disparities in COVID-19 outcomes [91]. Moreover, implicit bias against individuals based on body size (i.e., weight stigma) is highly prevalent and may lead to worse outcomes from COVID-19 for persons with obesity through several mechanisms, including unintended weight discrimination by medical providers and reluctance of persons with obesity to seek medical care based on negative prior experiences [92]. To achieve population-level changes in obesity and metabolic dysfunction, coordinated responses that address the root cause of the problem are needed. While governmental authorities have increased educational efforts to raise awareness of the salutary effects of increased physical activity and a healthy dietary pattern, many have argued that the root causes of the problem, including poverty, inequity, and financial incentives of the food and drink industry to promulgate energy-dense, ultra-processed foods have not been adequately addressed by current initiatives [93].

3.5. Alcohol consumption

It is likely that a complex relationship exists between alcohol consumption and COVID-19 outcomes. Importantly, studies have suggested that factors such as social isolation and depression during the pandemic have increased alcohol consumption [94,95]. Conversely alcohol consumption may contribute to depression [96]. Excessive alcohol consumption could contribute to severe outcomes through a variety of mechanisms including weight gain, poor nutrition, impaired immune responses and heightening of the inflammatory environment particularly in organs such as liver, pancreas, and heart [97–99]. Relevant to COVID-19 outcomes a recent meta-analysis concluded that high alcohol consumption significantly increases the risk of ARDS [100]. Further, the results of a Mendalian Randomization study using data from the UK Biobank suggests an interaction between alcohol consumption and severe COVID-19 outcomes (ICU admission and mortality) in obese subjects [101] although this study was limited in terms of racial diversity, robustness of self-reporting of alcohol consumption and detailed assessment of outcomes.

4. Do metabolic dysfunction and obesity predispose to 'long term COVID syndrome'

Early in the pandemic, COVID-19 was initially considered an acute disease without long-term effects. However, many people, including physicians, started to share impressions of lasting effects from the infection in social support groups. It slowly became clear that a number of COVID-19 survivors experience persistent symptoms. Scientific and medical communities identified the constellation of long-term symptoms as long COVID or post-COVID syndrome [102,103]. While the exact definition of long COVID is not well established of yet, the most common description is symptoms lasting for more than three months after first symptom onset.

The most frequent symptoms of long COVID are fatigue and dyspnea [104]. Other symptoms include cognitive disorders, headache, myalgia, chest pain, joint pains, smell and taste dysfunctions, hair loss, upper respiratory symptoms, and gastrointestinal issues. The exact mechanism for the development of long COVID has not yet been identified. It has, however, been proposed that it could result from a combination of sequelae of organ damage, persistent chronic inflammation, and a non-specific effect of prolonged hospitalization. Individuals with long COVID can also present with endocrinopathy including diabetes mellitus [105]. Studies suggest that COVID-19 may induce an autoimmune destruction of islet cells leading to new-onset diabetes mellitus or worsening of hyperglycemia. The pro-inflammatory environment induced by cytokine storm could lead to hyperglycemia, insulin resistance, and beta-cell dysfunction which may persist even in the post-acute phase of COVID-19 [106].

Interestingly, long COVID may affect individuals regardless of age or disease severity. Some studies identified risk factors of long COVID including female sex, more than five early symptoms, and initial acute COVID-19 severity [104]. Metabolic comorbidities including diabetes and obesity have been established to cause more serious COVID-19, but there is no clear link yet between these risk factors and long COVID. A study of more than 4000 adults with long COVID, found that elevated BMI is associated with an increased risk for long COVID [104]. The risk for long COVID is more pronounced in adults with moderate and severe obesity [107,108]. Among different preexisting conditions including diabetes, asthma was the only other condition associated

with long COVID [104]. In comparison, among pediatric population, older age and allergic disease are risk factors for long COVID but has no association with metabolic dysfunction [109]. On the contrary, a recent review regarding the association of long COVID-19 and diabetes emphasized the bidirectional relationship between these two conditions. Diabetes increases severe outcomes of COVID and eventually predisposes to long COVID. On the other hand, COVID-19 can result in new-onset hyperglycemia or worsening glycemic control [110,111]. It has been postulated that diabetes increases the risk for long-term sequelae from COVID because both disease processes share similar pathology including hyperglycemia, inflammation, tissue damage, hypercoagulability, and endothelial dysfunction which could lead eventually to organ dysfunction causing prolonged symptoms [112].

In managing patients with long COVID, studies suggest a multidisciplinary and holistic approach to screen, diagnose, and treat affected patients [113–116]. Prompt identification of patients at risk for long COVID should be performed. Regarding metabolic derangements, useful investigation tools include blood glucose, hemoglobin A1c, C-peptide, and urine/plasma ketones depending on the clinical scenario [115]. Minor symptoms including cough and pain can be treated symptomatically. Since chronic inflammation and oxidative stress are potential mechanisms of long COVID, non-steroidal anti-inflammatory drugs, corticosteroids, antioxidants, and CoQ10 are potential treatment options [116]. In managing metabolic factors, adequate control of diabetes, appropriate use of glucocorticoids, proper nutrition, and exercise could help decrease the risk and also manage long COVID. Lastly, early rehabilitation appears equally important to help improve long-term recovery and functional status of individuals with long COVID [117].

5. Conclusion

Obesity, cardiometabolic dysfunction and type 2 diabetes are now well accepted to be substantial risk factors for poor outcomes (intensive hospital stays, mechanical ventilation and death) following SARS-CoV-2 infection. While emphasis has generally been placed on overt obesity (as assessed by BMI), the metabolically unhealthy phenotype (characterized by dystopic fat deposition outside of the normal storage space in subcutaneous adipose tissue, accompanied by dysregulated adipose tissue distribution intra-abdominally and in organs such as liver causing NAFLD accompanied by abnormal markers of metabolic syndrome) appears to contribute to poor COVID-19 outcomes, irrespective of marked obesity. Although the precise mechanisms linking metabolic dysfunction to a poor clinical course require further clarification it is likely that baseline low grade tissue and systemic inflammation adds to the viral-induced inflammatory response leading to manifestations including cytokine storm, a hypercoagulable state and multi-system dysfunction. Given the ongoing nature of the pandemic and the identification of a long COVID syndrome close attention needs to be paid to patients who are obese or who demonstrate metabolic dysfunction. In addition to promoting vaccination and strategies to mitigate exposure to SARS-CoV-2, close and proactive clinical management is required with respect to proper nutrition, weight management, pharmacotherapy and psychosocial issues which has the potential to greatly diminish morbidity and mortality from SARS-CoV-2.

CRediT authorship contribution statement

All authors contributed to the content, writing, and editing of the manuscript.

Declaration of competing interest

No relevant disclosures exist for this work.

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