

## Review Article



# Obesity, Diabetes Mellitus, and Metabolic Syndrome: Review in the Era of COVID-19

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### Conflict of Interest

The authors declare that they have no competing interests.

## ABSTRACT

Coronavirus disease 2019 (COVID-19), a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is now at pandemic levels leading to considerable morbidity and mortality throughout the globe. Patients with obesity, diabetes, and metabolic syndrome (MetS) are mainly susceptible and more probably to get severe side effects when affected by this virus. The pathophysiologic mechanisms for these notions have not been completely known. The pro-inflammatory milieu observed in patients with metabolic disruption could lead to COVID-19-mediated host immune dysregulation, such as immune dysfunction, severe inflammation, microvascular dysfunction, and thrombosis. The present review expresses the current knowledge regarding the influence of obesity, diabetes mellitus, and MetS on COVID-19 infection and severity, and their pathophysiological mechanisms.

**Keywords:** COVID-19; Obesity; Diabetes mellitus; Metabolic syndrome; SARS-CoV-2

## BACKGROUND

The coronavirus disease 2019 (COVID-19), an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first detected at the end of 2019 in Wuhan, China, extended pandemic state in February 2020, and now is observed in all countries around the globe. Yet, no definite therapeutic agents have been recognized, and its infectious feature, hospitalization rates, intensive care admissions, and death are very high [1]. Our comprehension of the pathophysiology of its manifestations has ameliorated, however, the reason why the progression is more severe in some patients is yet not elucidated. Specifically, evidence has verified that obesity, diabetes mellitus, and metabolic syndrome (MetS), are important risk factors for SARS-CoV-2 infection and severity with abundant side effects [2-4].

MetS is consisting of many cardiometabolic risk factors, including insulin resistance, dyslipidemia, hypertension (HTN), and abdominal obesity, which results to endothelial and myocardial harms and cardiovascular events [5]. In addition, MetS is considered as an important risk factor which leads to worse outcomes in people affected by COVID-19 [4,6].

### Author Contributions

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In addition, type 2 diabetes mellitus (T2DM) is also associated with severe COVID-19 and its severe side effects. It was reported that patients with diabetes mellitus and MetS who were hospitalized for COVID-19 had a higher risk of adverse outcomes [7]. In a meta-analysis conducted on 44,672 patients with COVID-19 in China, patients with SARS-CoV-2 and T2DM had 4.4 times higher risk of death compared to patients without T2DM (unadjusted RR, 4.43, 95% confidence interval [CI], 3.49–5.61) [8]. In influenza-like diseases, hyperglycemia leads to elevate plasma glucose level in airway secretions. Moreover, high viral replication in vivo and repression of the antiviral immune response is reported [9]. Elevated vasculature penetrability and successive alveolar epithelium collapse have major influences on pulmonary work [10] and may justify the higher rates of mortality reported in the patients [11].

Additionally, some suppositions have been suggested for elucidating the worse outcomes in obese patients infected with COVID-19 [12]. A large meta-analysis (75 studies with 399,461 patients from Europe, Asia, North America, and South America), revealed that individuals with obesity have higher risk of infection with COVID-19 (odds ratio [OR], 1.46, 95% CI, 1.30–1.65) and also had a higher risk of severe difficulties in the COVID-19 course (hospitalization, OR, 2.13, 95% CI, 1.74–2.60; intensive care unit admission, OR, 1.74, 95% CI, 1.46–2.08; and death in hospital, OR, 1.48, 95% CI, 1.22–1.80) [13]. Obesity is a condition with systemic metabolism alterations, including insulin resistance, elevated serum glucose levels, a high ration of leptin to adiponectin, and inflammatory status [14].

In this review, we will investigate the current knowledge on the influence of obesity, diabetes mellitus, and MetS on infection with COVID-19 and its severity, as well as their pathophysiological mechanisms. Comprehension of the mechanisms associated with the higher risk both of being infected by COVID-19 and of evolution a more severe SARS-CoV-2 disease could be valuable for promoting therapeutic interventions.

## PATHOPHYSIOLOGY OF COVID-19

### Pathology and laboratory disturbances in SARS-CoV-2

Most patients with Covid-19 show mild symptoms and do not need to be hospitalized. Lymphopenia, neutrophilia, increased lactate dehydrogenase (LDH), elevated C-reactive protein (CRP), some elevations in liver enzymes (including alanine aminotransferase and aspartate aminotransferase), higher concentrations in ferritin, D-dimer, and pro-calcitonin are sometimes reported in these patients. Insistent lymphopenia and increased CRP, D-dimers, lactate, and pro-calcitonin are well-known predictors of severe COVID-19 disease [15]. Moreover, bilateral multi-lobar ground-glass opacifications are characteristically observed in the periphery of lower lobes of the lung [16]. Histopathologically, hyaline membranes, diffuse alveolar damage, interstitial edema, mononuclear inflammation and respiratory cell activation were observed, as well as capillary congestion, microvascular thromboembolism, thrombi in the small pulmonary arteries, and endothelialitis [17,18]. Interstitial edema, membranes thickening, as well as microvascular and venous thrombi may lead to disturbances in oxygen spreading and mismatching of ventilation/perfusion and subsequently results to considerable and quick aggravating of hypoxemia in these patients.

### Clinical manifestations of SARS-CoV-2

The clinical manifestations of SARS-CoV-2 are different and consist of the asymptomatic carrier state, mild respiratory infection, pneumonia, and acute respiratory distress syndrome

(ARDS), as well as failure in the function of some organs [12]. The common age range for patients with SARS-CoV-2 is 45–60 years and the mean time for incubation is approximately 5 days, but in 98% of the patients who reveal symptoms, this time is 12 days [12]. The prevalence of asymptomatic patients is very different (20%–86%) and is a major factor in the quick spread [12]. This virus is transmittable and extends via contact and airborne spreading [19]. There is considerable spreading even between the patients without symptoms [20]. Along with laboratory-confirmed COVID-19 infection, those with acute respiratory disease exhibit fatigue, fever, and respiratory (including coughing, dyspnea), and gastrointestinal (including nausea, diarrhea, vomiting, and loss of taste) complaints, but no significant chest imaging abnormalities [21,22]. Patients with pneumonia show respiratory difficulties and abnormalities on chest imaging. Pneumonia, in severe form, can manifest as ARDS resulting to severe hypoxia, respiratory problems, multiorgan failure, and death [16,21,22]. Ischemic myocardial infarction, myocarditis, cardiac arrhythmias, and acute neurological stroke can be probably part of SARS-CoV-2 manifestations [23]. According to the clinical perspective, the course and severity of COVID-19 are determined by the virus load, the timing and magnitude of the host response to the virus, the gender and age of the patient, as well as certain other co-morbidities.

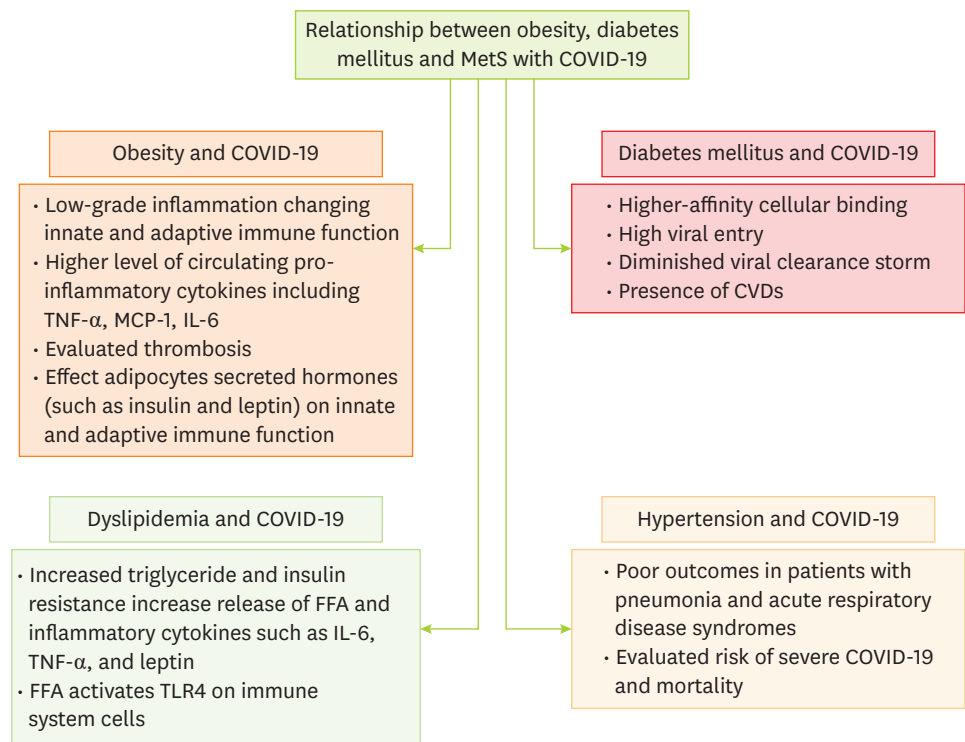
## RELATIONSHIPS BETWEEN OBESITY, DIABETES MELLITUS, AND MetS COMPONENTS WITH COVID-19, AND RELATED MECHANISMS

Obesity, T2DM, and MetS independently elevate the risk and severity of difficulties and death resulted from SARS-CoV-2. The mechanisms that contribute to this elevated risk are not fully known. According to present evidence and the data from previous studies in animals and clinical symptoms in SARS and Middle East respiratory syndrome (MERS), it was suggested possible mechanisms that highpoint the elevated risk (**Figure 1**).

### Obesity and COVID-19

Obese people have an elevated incidence of diseases such as renal insufficiency, cardiovascular diseases (CVDs), T2DM, some cancers, and endothelial dysfunction. These diseases are important factors contributed to COVID-19 severity and its mortality. However, much evidence suggests that excess weight is a very important factor for poor outcomes in patients affected by COVID-19. It was reported that obesity was a significant risk factor for worse outcomes in those with other chronic problems including dyslipidemia, HTN, T2DM, cardiomyopathy, chronic pulmonary diseases, and cancer. Hence, there is rational to suppose that many other factors make obese individual susceptible to severe disease and poor consequences due to COVID-19 infection [24].

Whilst anthropometric data for evaluating the influence of obesity in patients affected by COVID-19 are few, previous evidence indicates that elevated body mass index (BMI) leads to poor prognosis. An analysis on the data of 383 patients with COVID-19 in Shenzhen, showed that compared with normal-weight patients, overweight and obese patients had 2.4-fold higher and 86% greater odds, respectively, for progression to severe pneumonia [25]. Another investigation in France concluded that BMI > 35 kg/m<sup>2</sup> elevated the risk of ventilation (OR, 7.4, 95% CI, 1.6–33.1) [26]. In addition, a research among 4,103 patients with COVID-19 in New York City reported that BMI > 40 kg/m<sup>2</sup> was an important factor contributed to



**Figure 1.** Related mechanisms between obesity, diabetes mellitus, and MetS with COVID-19. MetS, metabolic syndrome; COVID-19, coronavirus disease 2019; TNF, tumor necrosis factor; MCP, monocyte chemoattractant protein; IL, interleukin; CVD, cardiovascular disease; FFA, free fatty acid; TLR, Toll-like receptor.

hospitalization (OR, 6.2, 95% CI, 4.2–9.3) [27]. Another research in the UK, obesity was an important risk factor for mortality with a powerful BMI gradient (hazard ratio [HR], 1.27 for BMI 30–34.9 kg/m<sup>2</sup>; 1.56 for BMI 35–39.9 kg/m<sup>2</sup>; and 2.27 for BMI > 40 kg/m<sup>2</sup>) [28]. Based on the results from these studies, it can be assumed that obesity is a major factor related to disease severity and mortality due to SARS-CoV-2.

Different theories have been mentioned to contribute to the adverse prognosis in patients with both obesity and COVID-19. Individuals with surplus weight have low grade inflammation changing both innate and adaptive immune function. Patients with obesity have higher level of inflammation cytokines including interleukin (IL)-6, tumor necrosis factor (TNF)- $\alpha$ , and monocyte chemoattractant protein-1 which mostly secreted from visceral and subcutaneous adipose tissue resulting to disturbances in pro-inflammatory response [29]. Moreover, in obese patients some changes in the metabolic profile of T cells may damage the adaptive immune function [30]. Sometimes, obese patients show damaged respiratory function described by diminished lung volumes, reduced diaphragmatic strength, elevated resistance in airway, and damaged gas exchange [31]. Adipose tissue acts as a pool for influenza A and the time length of viral shedding is increased in patients with obesity [32].

Additionally, since thrombosis is elevated in obesity and pro-thrombotic events are more common in severe COVID-19, it is reasonable to suggest that this may be a factor in higher morbidity. Also, numerous vascular beds show microvascular endothelial dysfunction [33], which is probably exacerbated by COVID-19 infection.

In addition to insulin, another hormone that is secreted from adipocytes, named as leptin, has substantial impacts on immune function. Leptin is an important regulator for metabolic homeostasis and it basically puts on its influences through Leptin receptors, that are highly revealed in arcuate pro-opiomelanocortin neurons in the hypothalamus, which is the base for regulation of energy expenditure and appetite. Leptin receptors are stated in cells of the immune system and some reports have documented the role of leptin in modulating different aspects of development and activity of immune cell [34,35]. Leptin regulates innate and adaptive immune function through the modification of metabolism, proliferation, and activity of immune cells. Circulating concentrations of leptin are profoundly elevated in individuals with surplus weight but the response of target tissues to leptin is harmed because of leptin resistance [36,37]. Hence, leptin resistance may importantly influence the appropriate development and function of immune cells in individuals with obesity, impair the defense in host, and elevate the likelihoods of serious disease and worse outcomes in patients affected by SARS-CoV-2.

It is suggested that high expression of angiotensinogen converting enzyme 2 (ACE2) would enhance the virus entrance into the cells and so, lead to serious disease and poor clinical consequences. Growing documents report that the expression of ACE2 is elevated in those with overweight and obesity. In addition, it has been reported enhanced the expression of ACE2 in the bronchial epithelium of patients with both chronic obstructive pulmonary disease and overweight or obesity in compared to those without excess weight [38]. The researchers proposed that high expression of ACE2 may be linked with elevated the severity of disease in patients with both COVID-19 and excess weight. Adipose tissue works as a pool for other pathogens in humans [39]. Noticeably, lipid droplets in adipose tissue exert an important effect in producing of the hepatitis C virus [24]. Hence, there is rational to suggest that adipose tissue might work as a pool for SARS-CoV-2 and lipid droplets might accelerate virus production and escalate.

Much evidence has demonstrated that excess weight is linked with hypercoagulable condition and so, individuals with obesity have high concentrations of prothrombin agents and low concentrations of anti-thrombin molecules [40,41]. Because of patients with serious COVID-19 disease are often related to coagulopathy/thrombosis and excess weight could make it more unpleasant. A cohort in 49 patients hospitalized for SARS-CoV-2 infection, it was demonstrated that low concentration of antithrombin was significantly related to elevated mortality [42]. The researchers of this study reported that BMI indicated a considerable difference between the patients with low and high concentrations of antithrombin. More works are required to prove this finding.

### Diabetes mellitus and COVID-19

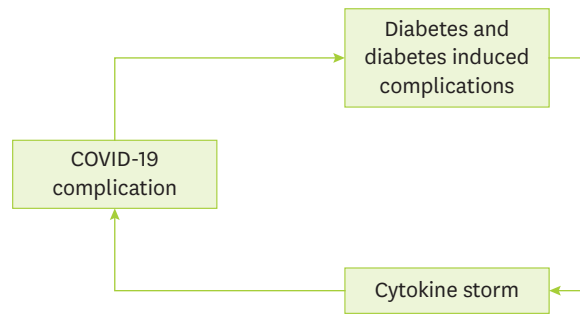
Numerous mechanisms were proposed to justify the elevated vulnerability of diabetic to severe SARS-CoV-2 disease, such as higher-affinity cellular binding, high virus entrance, diminished viral removing, decreased the function of T cell, high vulnerability to hyperinflammation and cytokine storm, and the occurrence of CVDs [3]. Phagocytosis by monocytes, neutrophils, and macrophages was low in diabetic patients who also suffer from disruptions in neutrophil chemotaxis, anti-bacterial activity, and innate immune function [43]. Surprisingly, short-term hyperglycemia reduces innate immune function [44]. Next to their malfunction in innate immune response, diabetic patients also have a disturbed adaptive immune function [45].



For explanation the elevated severity of difficulties in patients with both diabetes and COVID-19, several mechanisms were mentioned. As reported in animal models with diabetes mellitus, enhanced cellular binding and infection with COVID-19 is anticipated because of high ACE2 expression in the lung, heart, kidney, as well as pancreas [46,47]. Insulin injection diminishes ACE2 expression in the lungs of diabetic mice [47]. Liraglutide, an agonist of glucagon-like peptide-1 (GLP-1), restores low mRNA expression in the lungs of diabetic rats [48]. Rosiglitazone is a thiazolidinedione that increases ACE2 expression in the vascular system of hypertensive rats [49]. Additionally, atorvastatin and fluvastatin elevates cardiac ACE2 expression in rats [50,51]. The concentrations of furin, as a cellular protease that resulted to accelerating viral entrance by cutting the S1 and S2 domains of the spike protein, are high in diabetic individuals [52]. Diabetes mellitus impedes phagocytosis, neutrophil chemotaxis, and intracellular killing of microbes. Late activation of Th1 cell-mediated immune function and a delay in hyper-inflammatory response is repeatedly occurred in diabetic patients [45]. In a study, Kulcsar et al. [53] demonstrated that when diabetic male mice were infected with MERS-CoV, the disease appeared more critical over time and was characterized by changes in CD4<sup>+</sup> T cell counts and disruptions in cytokine response. These results are parallel with the alterations in immune and cytokine in COVID-19 described by lower counts of CD4<sup>+</sup> and CD8<sup>+</sup> T cells, higher ratio of pro-inflammatory Th17 CD4<sup>+</sup> T cells, and enhanced cytokine concentrations [12]. Thus, diabetic patients may likely have made blunt anti-viral interferon responses, and delay in Th1 activation may lead to the heightened inflammatory response. Moreover, neutrophil extracellular traps in T2DM patients were higher compared with individuals without T2DM [54,55]. These reports propose that immune and microvascular dysfunction in type 2 diabetes patients may lead to the worse consequences in SARS-CoV-2.

Another probable mechanism explained the elevated hazard of serious COVID-19 disease in patients with diabetes might be due to the hyperinflammation state, termed as “cytokine storm.” Diabetic patients suffer from cytokine storm, subsequently seems to be associated with more severe COVID-19 pneumonia and to posterior death [56]. Diabetic patients have a damaged adaptive immune function described by an initial delay of Th1 cell-mediated immunity and late hyperinflammatory state [45]. Without an immunostimulant, diabetes is related to an enhanced inflammatory cytokine response indicated as high secretion of IL-1, IL-6, IL-8 and TNF- $\alpha$  [43]. High cytokine concentrations might be due to advanced glycation end products (AGEs) [57], which contain the residues of glucose and lysine/arginine [43]. It was mentioned that high emergence of AGEs observed in poorly managed diabetic patients. Some documents have confirmed an elevate in cytokines after AGE binding to non-diabetic cells, in the absence of direct stimulation [58-60]. So, high AGE production in diabetic patients could be indicative of enhancing cytokine production [43]. In summary, the availability of high glucose leads to an elevation in cytokine production; yet, following the stimulation, cytokine production declines in compared to a status without glucose. Low IL production following stimulation might also result from intrinsic cellular deficiency in diabetic patients [43,61]. Continuous inflammatory state in diabetes mellitus is more increased with COVID-19, leading to a violent inflammatory state (**Figure 2**).

It was disclosed that diabetic patients with COVID-19, in spite of having lower lymphocyte counts in peripheral blood, but they had considerably greater neutrophil counts in compared to those without diabetes [62]. Among the different inflammatory biomarkers increased in COVID-19 patients with diabetes, IL-6 attracts special notice as it has been related to lung injury and worse prognosis [63,64]. Serum concentrations of IL-6 in diabetic patients without



**Figure 2.** COVID-19, diabetes mellitus, cytokine storm: a vicious cycle. COVID-19, coronavirus disease 2019.

SARS-CoV-2 were markedly greater comparing to those in healthy individuals without diabetes [62]. This might be due to the high cytokine concentration in diabetes mellitus, which is more amplified in COVID-19. These reports conclude that IL-6 could be an appropriate predictor for disease severity and prognosis. In addition, it can be concluded that in patients with diabetes and COVID-19, an inflammatory storm is more intense, resulting in rapid failure.

### HTN and COVID-19

Some previous documents have demonstrated that HTN is a hazard factor for poor consequences in patients who suffer from pneumonia and ARDS [65,66]. It is probable that the co-occurrence of HTN and COVID-19 might elevate the hazard of worse consequences. An investigation in China did not report any relationship between HTN and COVID-19 [67]. But, in a pooled analysis, it was concluded that HTN was related to a 2.5-fold elevated hazard for severe COVID-19 and death [68]. Noticeably, all the previous investigations do not consider probable confounders including age and other CVDs in determining of any causal effect of HTN.

Systemic HTN is related to the activating of the renin-angiotensin-aldosterone system (RAAS). The vascular impacts of angiotensin II (Ang II) are mediated by activating the Ang II type 1 receptor (AT1R) and type 2 (AT2R) receptor. AT1R makes the vasoconstrictive, proliferative, hypertensive, and inflammatory influences of Ang II, while activating the AT2R hinders these impacts. Relative ratios of AT1R and AT2R in the endothelium estimates the final vascular impacts of Ang II [69]. The balance in angiotensin converting enzyme activity (ACE/ACE2 activity) in the lungs estimates the impacts of Ang II [70]. Estradiol diminishes, but testosterone elevates ACE function in the lung [71]. ACE, Ang II, and aldosterone modified innate immune function [12]. Activating the RAAS favors a pro-inflammatory and procoagulant condition that may make vulnerable to COVID-19 and subsequently multiorgan failure. The accurate effect of RAAS in COVID-19 is an interesting topic for research.

As a whole, while the immensity of the risk differs between the studies, it seems that HTN leads to severity and death related to SARS-CoV-2.

### Dyslipidemia and COVID-19

About 30%–60% of T2DM patients have dyslipidemia [72]. Dyslipidemia in patients with T2DM is described by increased triglycerides (TGs) in the majority of patients, a little increased in low-density lipoprotein (LDL), and low high-density lipoprotein [72]. Patients with T2DM have insulin resistance in all insulin-responsive cells, including adipocytes, which elevates fatty acid release and proinflammatory cytokines [73]. Increased free fatty acid (FFA) are removed by the liver and deposited as TGs in fat droplets or are released as very LDL

(VLDL) particles resulting to hypertriglyceridemia. The high blood TGs released from VLDL are placed in cardiac and skeletal muscles, and other insulin-responsive cells and reduce their sensitivity to insulin. High FFA also stimulates atypical protein kinase C that impedes insulin signaling and glucose uptake in skeletal muscle and leads to surplus gluconeogenesis in the liver [74]. Moreover, FFA activates TLR4 that are mostly expressed on immune cells such as dendritic cells, monocytes, and macrophages; activating this receptor results to cytokine secretion and inflammatory response [74]. TG-rich VLDL gradually loses some of their TG and convert to LDL. In T2DM, the LDL molecules are smaller and denser than normal condition and have more atherogenic effects [75]. This somewhat elucidates the elevated early atherosclerosis and CVD incidence in T2DM patients [75].

The dyslipidemia in T2DM patients leads to the insulin resistant condition in a self-reinforcing cycle. The inflammatory condition related to insulin resistance and dyslipidemia increase the inflammatory response by COVID-19 infection.

## MANAGEMENT OF MetS IN COVID-19

MetS is associated with poor outcomes in COVID-19. Evidence of more than 72,000 patients in China reported that the overall case fatality rate due to SARS-CoV-2 was 2.3%, but the case fatality rate was greater with CVD (10.5%), HTN (6%), and diabetes (7.3%) [76]. Long-term consequences of metabolism dysregulation have been recognized in patients 12 years following infection with the 2003–2004 SARS-CoV-1 [77]. T2DM patients without other co-morbidities who contract COVID-19 are at a greater hazard for severe pneumonia, uncontrolled inflammatory response, and hypercoagulability [62]. Furthermore, it was disclosed that insulin needs are disproportionately high in severe COVID-19 patients, indicative of high insulin resistance, in compared to non-COVID-19 serious diseases [78-80]. Even though strong evidence is not available on diabetes mellitus management in COVID-19, tailored therapeutic strategies based on the confirmed guidelines and individualizing treatment according to the type of diabetes mellitus, presence of other risk factors and co-morbidities, and the setting of medical care (outpatient vs. inpatient) can be pursued to manage hyperglycemia in patients with diabetes mellitus and COVID-19 [78,81].

The first aim of outpatient management in individuals with both diabetes and COVID-19 is to make sure optimal glycemic control and prevention of hospitalization. COVID-19 has disturbed usual outpatient diabetes mellitus care, and due to the socioeconomic sufferings, that come parallel to the pandemic, optimal dietary patterns and physical activity will probably be compromised and will continue to take an impact for months after the pandemic solves [82]. The decision to continue or stop oral antidiabetic drugs needs contemplative discernment by comparing the patient's general state and the risk for evolution to severe respiratory disease [83]. Metformin makes the hazard of acute kidney harm and lactic acidosis. Yet, metformin has indicated anti-inflammatory impacts in pre-clinical evidence, and in T2DM patients [84]. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors could also have to propensity to elevate the risk for dehydration and euglycemic diabetic ketoacidosis. Those patients undergoing metformin or SGLT-2 inhibitors must be repeatedly monitored and must be advised to intake sufficient fluid. Patients previously not undergoing SGLT-2 inhibitors should not be initiated on these agents through their COVID-19 illness [78]. Previously, it was indicated that GLP-1 agonists declined the levels of inflammation biomarkers between individuals with both obesity and T2DM [84]. GLP-1 agonists could



be kept on if they are tolerated by the patients. Due to the risk of nausea and dehydration, patients who do not tolerate these medications should be repeatedly monitored [78].

It should be advised on providing sufficient fluids and regular meals intake [78]. Dipeptidyl peptidase-4 inhibitors can be kept on if the patient has been tolerating the drug properly [78]. Sulfonylureas can be kept on through COVID-19 disease, but the patients require to be warned about the hazard of hypoglycemia in case of decreased appetite and decreased oral intake. Patients who were administered insulin at home should be advised to maintain on insulin therapy, and determine the dose according to the blood glucose concentrations [78]. Periodic self-monitoring of blood glucose (with 4 hours intervals) should be recommended [78,82]. T1DM patients should be checked for urinary ketones if they notice disturbances in glycemic control through the disease [85].

In patients with both diabetes and COVID-19, inpatient management of hyperglycemia is crucial, and some documents have reported worse consequences in hospitalized patients with diabetes mellitus and SARS-CoV-2 [76,86]. Additionally, favorable glycemic control through hospitalization is related to ameliorated consequences [80]. In a retrospective investigation in China, COVID-19 patients with well-controlled blood glucose ( $\leq 10$  mmol/L or  $\leq 180$  mg/dL) had lower concentrations of CRP, IL-6, and LDH. They had greater lymphocyte counts and lower neutrophil counts in compared to patients with defectively-controlled blood glucose concentrations ( $\geq 10$  mmol/L or  $\geq 180$  mg/dL) [87]. The HR for all-cause mortality was considerably lower in the well-controlled glycemia group in compared to the defectively-controlled group (0.13, 95% CI, 0.04–0.44;  $p < 0.001$ ) even after considering age, gender, severity of COVID-19, co-morbidities and related side effects [87]. Additionally, those with the well-controlled glycemia displayed lower occurrence of ARDS, septic shock, acute cardiac dysfunction, disseminated intravascular coagulation, and acute kidney disease. These results underline the significance of favorable glycemic control in patients hospitalized for COVID-19 disease. Oral antidiabetic drugs should not be continued, and insulin should be administered to attain favorable glycemic control in an inpatient setting [79,83,85]. Severe diabetes mellitus patients affected by SARS-CoV-2 admitted to monitored units may indicate high degrees of insulin resistance and are ideally controlled by insulin injection [78,88]. Hypoglycemia monitoring is of importance, particularly in patients with ARDS who may require ventilation, and may disturb feeding [82]. For patients with both obesity and T2DM underlying fatty liver disease, the risk of cytokine storm is higher, and frequent monitoring of hepatic transaminases, prothrombin time, ferritin, fibrinogen, erythrocyte sedimentation rate, IL-6, CRP, and D-dimer is necessary for this patient group [78,89]. Treatment of diabetic ketoacidosis must be immediately started with closely monitoring of blood glucose and anion gap. Intravenous hydration, correction of electrolyte disturbances (hypomagnesemia, hypokalemia, hypophosphatemia), and insulin injection must be undertaken according to the guidelines [90]. Due to the great prevalence of thromboembolic difficulties related to COVID-19, pharmacologic prophylaxis must be advised in all patients without the contraindications [91].

A study in New York reported no considerable elevate in risk of COVID-19 in individuals undergoing 5 important classes of anti-hypertensives (calcium channel blockers, thiazides, ACE inhibitors (ACEIs), angiotensin receptor blockers [ARBs], and beta-blockers) [92]. Some associations of cardiology and heart failure advised the continuation of ACEIs/ARBs in patients affected by COVID-19 [93]. Moreover, statins upregulated ACE2 levels in rats [94]. While, due to the cardiovascular advantageous, in vitro evidence of suppression of IL-6-induced CRP expression by statins, and the epidemiologic evidence on lower odds of

mortality from COVID-19 between those receive statin, treatment with statins can be kept on through COVID-19 disease [78,95].

## CONCLUSION

While it is accepted that the presence of comorbidities including obesity, diabetes mellitus and MetS is related to more severe course of SARS-CoV-2, obesity is a major risk factor for its severity and more generally for disturbed metabolic health and is also associated with an elevated risk for pneumonia. Evaluation of anthropometric indices and metabolic biomarkers is critical to better estimate the risk of difficulties in patients affected by COVID-19. This paper presented various mechanisms that may elucidate the pathophysiology of COVID-19 such as virus entrance, viral toxicity, thromboinflammation, endothelial dysfunction, dysregulation in the immune function, and the RAAS. Finally, we discussed the potential strategies for the management of metabolic disturbances. In spite of sex differences not being discussed in this review, it should be noted that in order to properly protect all individuals, more research is needed to understand how biological sex and MetS influence COVID-19 vulnerability, disease severity, and vaccine effectiveness. The developing of a vaccine for immunization is still the best long-term solution for the prevention of later outbreaks of COVID-19. Furthermore, people with any age who have pre-existing problems, including heart disease, diabetes, surplus weight, among others, also require to redouble their care to prevent COVID-19.

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