

**REVIEW ARTICLE**

# Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19)

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**Abstract**

The outbreak of the coronavirus disease 2019 (Covid-19) has become an evolving worldwide health crisis. With the rising prevalence of obesity and diabetes has come an increasing awareness of their impacts on infectious diseases, including increased risk for various infections, post-infection complications and mortality from critical infections. Although epidemiological and clinical characteristics of Covid-19 have been constantly reported, no article has systematically illustrated the role of obesity and diabetes in Covid-19, or how Covid-19 affects obesity and diabetes, or special treatment in these at-risk populations. Here, we present a synthesis of the recent advances in our understanding of the relationships between obesity, diabetes and Covid-19 along with the underlying mechanisms, and provide special treatment guidance for these at-risk populations.

**KEYWORDS**

Covid-19, diabetes mellitus, obesity, severe coronavirus disease 2019

## 1 | INTRODUCTION

The outbreak of the coronavirus disease 2019 (Covid-19) has become a public health emergency of international concern,<sup>1</sup> which caused by a novel enveloped RNA beta-coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>2</sup> The manifestations of Covid-19 pneumonia run the spectrum from asymptomatic disease to severe acute respiratory infection.<sup>3-6</sup> The recognized human-to-human transmission of Covid-19 significantly increases the risk of much wider spread of the disease.<sup>7-9</sup> As of June 3, 2020, 6 287 771 confirmed Covid-19 cases and 379 941 deaths were reported globally, with most of the cases being reported from United States, Europe and Eastern Mediterranean.<sup>10</sup> At present, the number of Covid-19 cases is still increasing around the world, and there are increasing global concerns about this outbreak.<sup>11</sup>

Obesity and diabetes are increasingly worldwide health concerns, and have been regarded as critical risk factors for various infections, post-infection complications and mortality from severe infections.<sup>12</sup> Both of obesity and diabetes have been shown deleterious effects on host immunity, which primarily increased the risk for infectious susceptibility and severity.<sup>12,13</sup> Having diabetes generally worsens

infection prognosis, with these patients showing increased morbidity and mortality from sepsis compared to the general population.<sup>14</sup> Obesity has been shown to affect lung function in multiple ways, related to mechanical and inflammatory aspect, making the obese more likely to suffer with respiratory symptoms and progress to respiratory failure.<sup>15</sup>

In the Covid-19 epidemics, researchers found the comorbidities were present in nearly half of inpatients with Covid-19, with hypertension being the most common comorbidity, followed by diabetes and coronary heart diseases (CVDs).<sup>4-6,16,17</sup> Moreover, the percentages of diabetes and CVDs are much higher among the fatality cases than among the confirmed Covid-19 cases.<sup>3,18</sup> At present, although clinical characteristics of Covid-19 have been constantly reported, no article has systematically illustrated the role of obesity and diabetes in Covid-19, or how Covid-19 affects obesity and diabetes, or special treatment in these at-risk populations. The aim of this article is to provide a review of the relationships between obesity, diabetes and the Covid-19, concerning the epidemiology, pathogenicity and treatment attention. In doing so, we aim to enhance public awareness of the association between obesity, diabetes and Covid-19 pathogenesis, and provide treatment guidance for these special populations.

## 2 | DIABETES AND COVID-19

### 2.1 | Impact of diabetes on Covid-19

It's known that individuals with diabetes are at higher risk of various acute and chronic infections compared with non-diabetic individuals. During the SARS pandemics, the rate of admission to intensive care unit (ICU), need for mechanical ventilation, and mortality of diabetic patients was 3.1-fold greater than that of non-diabetic patients.<sup>19</sup> It was reported that diabetes triples the risk of hospitalization after influenza A (H1N1) and quadruples the risk of ICU admission.<sup>20</sup> Under middle east respiratory syndrome coronavirus (MERS-Cov) infection, diabetes was also considered as an important risk factor for developing into severe cases.<sup>21</sup> With the outbreak of the Covid-19, a high proportion of patients with diabetes were also observed. Yang et al<sup>18</sup> showed that among the non-survivors from a group of critically ill patients, diabetes (22%) was a predominant underlying comorbidity. In the largest series reported by the Chinese center for disease control and prevention comprising of 72 314 Covid-19 cases, diabetic patients had higher mortality (7.3% in diabetes vs 2.3% overall).<sup>22</sup> Recent data from Italy showed that more than two-thirds of those who died by Covid-19 had diabetes.<sup>23</sup> Some clinical researches<sup>24-27</sup> studying the biochemical features of Covid-19 patients with diabetes have been conducted, which showed that Covid-19 patients with diabetes were more likely to develop severe or critical condition with higher incidence rates of death compared with those without diabetes, and both diabetes history and hyperglycemia are independent predictors for the fatality of Covid-19. Interestingly, Guo et al<sup>24</sup> suggested that the severity of Covid-19 in diabetes could be hidden by an initial milder presentation of SARS-CoV-2 infection, with the absence of classical worrisome signs and clinical symptoms, which may result in a life-threatening delay in providing the needed care. Several factors may be responsible for the increased severity of Covid-19 in diabetes (Table 1).

#### 2.1.1 | Aggravated inflammatory storm in diabetes

Individuals with diabetes are generally affected by a low-grade chronic inflammation, which might facilitate the cytokine storms, contributing to the severe outcomes of Covid-19 and the eventual death.<sup>28,29</sup> Guo et al<sup>24</sup> published the first study of biochemical features of Covid-19 patients with diabetes, which indicated that the absolute count of lymphocytes in diabetic patients is significant lower than those without diabetes, while the count of neutrophils is remarkably higher. Similarly, subsequent retrospective studies<sup>25-27</sup> comparing the clinical features between Covid-19 patients with and without diabetes also showed a higher neutrophil-to-lymphocyte ratio (NLR), high-sensitivity C reaction protein, and procalcitonin. The levels of some inflammation-related biomarkers were also increased in diabetic patients, while interleukin (IL)-6 among the different markers (fibrinogen, C-reactive protein and D-dimer) were found to be more elevated.<sup>25,30</sup> The higher NLR and lymphocyte-to-C-reactive protein

ratio, as well as the elevated inflammation-related biomarkers, were identified as independent risk factors for severe outcomes in Covid-19 patients.<sup>30,31</sup> Additionally, recent preliminary observations have shown that tocilizumab, a monoclonal antibody against the IL-6 receptor, may help the treatment of Covid-19. It is actually being used off-label in some Italian centers and is currently being tested in a randomized controlled trial.<sup>32</sup> Besides, a significant increase in serum ferritin also indicates the activation of the monocyte-macrophage system, which is a crucial part of inflammatory storm.<sup>26</sup> Therefore, these results indicate that patients with diabetes are susceptible to form an inflammatory storm, which eventually lead to rapid deterioration of Covid-19.

#### 2.1.2 | Immunodeficiency in diabetes

Besides the higher NLR, recent studies showed the number of total T cells, and CD4+ and CD8+ T cell subsets were significantly reduced and functionally exhausted in Covid-19 patients, especially among severe cases,<sup>33,34</sup> suggesting a role for dysregulated immune responses in Covid-19 pathogenesis. Actually, in diabetic individuals, persistent hyperglycemia could lead to a series of abnormal metabolic changes,<sup>14,35</sup> which together increase the production of superoxide and activation of inflammatory pathways, promoting the dysfunction of immune system.<sup>36</sup>

Non-specific and fast-acting innate immune defences, which provide initial host response to the SARS-CoV-2 invasion, are impaired in multiple ways in diabetes. In particular, neutrophils exhibit defects in almost all functions, including migration to inflammatory sites, release of lytic proteases, phagocytosis, production of reactive oxygen species (ROS) and apoptosis.<sup>37</sup> A study evaluating cytokines from neutrophils in subjects with type 2 diabetes (T2D) found excessive release of tumour necrosis factor (TNF)- $\alpha$ , (IL)-1 $\beta$ , and IL-8 in both the basal and stimulated state, which increased the susceptibility to invasive pathogens.<sup>38</sup> In diabetic individuals, there is an increased ratio of M1 pro-inflammatory macrophages releasing inflammatory mediators,<sup>39</sup> contributing to the increased local and systemic inflammation. The phenotypes and activity of natural killer (NK) cells are also altered in diabetes,<sup>40</sup> with significant decreases in NK receptors recognizing virus and activating receptors on NK and CD8+ T lymphocytes. Hyperglycemia and hyperinsulinemia could also induce a pro-inflammatory cytokine profile in dendritic cells (DCs), together with the stimulation of AGE (advanced glycosylation end products) products and leading to their maturation.<sup>41</sup> However, the role of the maturation and activation of DCs in immune responses is still not well understood.

Obesity and diabetes also weaken the control and clearance of pathogens with the dysfunction of adaptive immune system. Generally, the proper balance between pro-inflammatory (Th17 or Th1) and anti-inflammatory [Th2 or regulatory T cells (Tregs)] subsets of CD4+ effector T cells is vital to maintain host immunity and control inflammatory damage.<sup>42</sup> In T2D, T cells are over-activated and the inflammatory processes are promoted.<sup>43,44</sup> In the adipose tissue of diabetic

**TABLE 1** Reasons of increased severity of covid-19 in diabetes and obesity based on various studies

Impact of diabetes on covid-19	Evidence	References
Aggravated inflammatory storm Higher NLR, hsCRP and procalcitonin Higher interleukin (IL)-6, ferritin, fibrinogen and D-dimer	Postulated	24-32
Immune system dysfunction Impaired innate immune defences Impaired adaptive immune defences	Established	33-55
Lung injury associated with diabetes Physiological and structural abnormalities in lung Pulmonary microangiopathy	Postulated	56-60
Increased infectivity and virulence of virus Abnormal expression of ACE2 Increased plasmin Increased furin	Postulated	61, 62, 66-71, 75, 76
Diabetes-related comorbidities Obesity Cardiovascular disease Renal damage Psychiatric disease	Established	3-6, 16-19
<b>Impact of obesity on covid-19</b>		
Immune system dysfunction Chronic inflammation state Interferes with cellular responses Imbalanced crosstalk between immune and metabolic system	Established	114-144
Complement system overactivation	Postulated	145, 146
Altered lung mechanics and physiology Increased airway resistance Abnormal topographical distribution of ventilation Reduced lung volumes and decreased lung compliance Ventilation-perfusion mismatching Respiratory muscle inefficiency High risk of pulmonary embolism	Postulated	147-150
Increased infectivity and virulence of virus High ACE2 expression Elevated viral titers Prolonged viral shed Delayed clearance Increased viral evolution and diversity	Postulated	66-68, 154-158
Obesity-related comorbidities Diabetes Cardiovascular disease Atherosclerosis Psychiatric disease	Established	3-6, 16-19

Abbreviations: ACE 2, angiotensin-converting enzyme 2; COVID-19: coronavirus disease 2019; NLR, neutrophil-to-lymphocyte ratio; hsCRP, high-sensitivity C reaction protein.

**TABLE 2** Impact of covid-19 on diabetes and obesity based on various studies

Impact of covid-19 on diabetes	Evidence	References	Infectious disease reviewed
Glucose dysregulation	Established	24, 78, 79, 167-169	Influenza, CMV infection, COVID-19
Isolation-related irregular lifestyles			
Enhanced stress state			
Acute responses to pneumonia			
Disease-related gastrointestinal symptoms			
Metabolic disturbance associated with infection			
Cause new-onset diabetes	Postulated	79, 81-86	Chicken pox, SARS
Damage pancreas and liver through ACE2			
Impact of covid-19 on obesity			
Change in body weight	Postulated	120, 121, 163-172	Adenovirus infection
Increase in MCP-1 activated by NF-κB			
Suppression of leptin production			
Downregulation of the adipocyte genes			
Increase in glucose uptake by fat cells			
Modulation of hypothalamic monoamines			
Isolation-related irregular lifestyles			
Enhanced stress state			
Cause metabolic imbalance	Postulated	121, 167-169	Influenza, CMV infection
Virus-induced IFN-γ downregulates insulin receptor			
Increase in glycolytic rate			
Reduction in mitochondrial PDC activity			
Decrease in ATP production			

Abbreviations: ACE 2, angiotensin-converting enzyme 2; ATP, adenosine triphosphate; CMV, cytomegalovirus; COVID-19: coronavirus disease 2019; IFN-γ, interferon-γ; IR, insulin resistance; MCP-1, macrophage chemoattractant protein 1; NF-κB: nuclear transcription factor kappa B; PDC, pyruvate dehydrogenase complex; SARS, severe acute respiratory syndrome;

subjects, anti-inflammatory macrophages are transformed into pro-inflammatory macrophages, while Tregs transformed into helper Th1 and Th17 CD4+ T cells.<sup>45,46</sup> In particular, the pro-inflammatory Th1, which triggers cell-mediated immunity and phagocyte-dependent inflammation, was upregulated.<sup>47</sup> Th17, another pro-inflammatory CD4+ T cell subtype secreting IL-17 and stimulating TNF-α production, was increased.<sup>48</sup> Treg cells, which suppress Th1, Th2 and Th17 response to improve insulin resistance (IR) and inhibit the inflammatory response, were reduced in diabetes.<sup>49</sup> Additionally, insulin signalling in T cells could cause increased glucose uptake, amino acid transport, lipid metabolism and protein synthesis, which promotes T cell activation and responsiveness.<sup>50</sup> Thus, in addition to the amounts disproportion, the presence of IR or deficiency could suppress the insulin signalling, leading to abnormal T cell response to pathogens. In addition to CD4+ T cells, CD8+ T cells are also essential for the adaptive immune response against infections, by secreting cytokines such as IFN-γ and TNF-α, as well as expressing pro-inflammatory cytokines such as IL-17.<sup>51</sup> It has been showed that diet-induced obese subjects have higher percentages of CD8+ T cells,<sup>52</sup> however, the proportion of CD8+ T cells would decrease after 120 minutes of glucose loading.<sup>53</sup> Besides, pathogenic CD8+ T cell subsets which control hepatic IR and gluconeogenesis were found to accumulate in the liver,<sup>54</sup>

suggesting that the increased CD8+ T cells and subsequent IFN-γ production promote IR and inflammation state.<sup>55</sup> Therefore, the imbalance of CD4+/CD8+ T cells and CD4+ T cells subsets, together with the impaired T-cell response in diabetes make the adaptive immune abnormal.

### 2.1.3 | Lung injury in diabetes

Abundant evidence shows that diabetes is associated with physiological and structural abnormalities in lung tissues and attenuation in lung function,<sup>56,57</sup> reminding that diabetes could worsen the lung injury besides the immunodeficiency. Diabetic individuals tend to exhibit lower forced vital capacity (FVC) and forced expiratory volume in 1 second, and lower diffusion capacity vs non-diabetic individuals.<sup>58</sup> Specially, oxidative stress result from sustained hyperglycemia has been postulated to be a major contributor in diabetic lung injury,<sup>59</sup> which damaged the respiratory system due to the pulmonary interstitial injury mainly caused by microangiopathy.<sup>60</sup> To date, the definitive direction or the exact pathophysiological mechanism to explain the interactions between diabetes and lung function has not been well understood.

### 2.1.4 | Increased infectivity and virulence of SARS-CoV-2 in diabetes

Increasing evidence suggests that Covid-19 uses human angiotensin-converting enzyme 2 (ACE2) as a receptor for cellular entry, which potentially facilitates the person-to-person transmission.<sup>61</sup> Moreover, the SARS-CoV-2 binds ACE2 with approximately 10- to 20-fold higher affinity than ACE2 binding to SARS-CoV,<sup>62</sup> making ACE2 a special target for SARS-CoV-2 invasion. ACE2, which is a central member of the renin angiotensin system (RAS) family that degrades Ang II into Ang 1 to 7, has been implicated in hypertension, diabetes and CVDs.<sup>63</sup> ACE2 expression has been found in multiple organs including kidneys, hearts, testis, lungs, pancreas, bladder, stomach, ileum and liver,<sup>64,65</sup> which may account for the multiple organ failure seen in some Covid-19 patients. Interestingly, experts found that diabetes significantly up-regulated the expression of ACE2 in the circulation, which may be ascribed to a compensatory mechanism of RAS, and insulin administration significantly decreased the ACE2 expression.<sup>66-68</sup> The levels of urinary ACE2 and enzymatic activity were also found increase in both type 1<sup>69</sup> and type 2<sup>70</sup> diabetic patients, and the urinary ACE2/creatinine ratios positively correlated with blood glucose levels.<sup>71</sup> Seen in this light, the diabetes-induced over-expression of ACE2, as a functional receptor for SARS-CoV-2 invasion, might increase the susceptibility to Covid-19. However, there is also experimental evidence for downregulation of ACE2 in kidney tissue in diabetes,<sup>72</sup> suggesting that the expressions of ACE2 in diabetes vary depending on the studied tissues. With the evidence that increased ACE2 and consequently angiotensin 1 to 7 have vasodilatory and antifibrotic effects which showed protective effects against lung injury,<sup>73</sup> some researchers thus considered that the reduced ACE2 may predispose to more severe lung injury.<sup>74</sup> Besides ACE2, diabetes is also associated with increased plasminogen levels which has been postulated to increase the virulence and infectivity of SARS-CoV-2 by cleaving its spike proteins.<sup>75</sup> Increased virulence and infectivity of SARS-CoV-2 in diabetes may also due to an increase in furin, which is a type-1 membrane bound protease involved in the entry of coronaviruses into the cell.<sup>76</sup> Recently, Fadini et al<sup>77</sup> have conducted a meta-analysis regarding the impact of diabetes among subjects with Covid-19, which showed no increased susceptibility, but only higher increase to worsen progression of Covid-19 in patients with diabetes compared with those without diabetes. To date, there is no conclusive evidence supporting that diabetes increases the susceptibility to Covid-19 infection, therefore, additional studies are needed to investigate this possibility.

### 2.1.5 | Diabetes-related comorbidities

In addition to the detrimental effects, chronic comorbidities associated with diabetes like obesity, hypertension, coronary artery disease and chronic kidney disease, could further worsen the prognosis of Covid-19.<sup>3-6,16-19</sup>

### 2.2 | Impact of covid-19 on diabetes

Viral infection might in turn induce glucose dysregulation in pre-existing diabetes, or even cause new-onset diabetes in those without a history of diabetes (Table 2), which worked as an amplification loop and formed a vicious circle.

Recent clinical researches showed that the insulin dose increased and blood glucose became difficult to control after diabetic patients were infected with SARS-CoV-2.<sup>24,78,79</sup> Particularly, Guo et al<sup>24</sup> observed that 37.5% of the diabetic patients took oral drugs before and started insulin therapy after admission, and 29.2% of the patients took insulin before and increased the dose of insulin after admission. Zhou et al<sup>78</sup> retrospectively analysed 881 capillary blood glucose (BG) tests in patients with both diabetes and Covid-19, and found that 56.6% of the tests showed abnormal BG levels, 69.0% of the patients had non-ideal BG levels and 10.3% of the patients suffered at least one episode of hypoglycemia. In general, during the illness and social isolation, an increasing number of diabetic patients are cancelling their routine visits to diabetes clinics. This development along with the enhanced stress associated with disease and isolation, reduced physical activity, irregular diets and the disease-associated gastrointestinal symptoms, provides a fertile ground for worsening glycemic control. Under the stress state of infection and mood instability, elevated secretion of hyperglycemic hormones such as catecholamines or glucocorticoids might further increase the BG instability. Additionally, despite that the corticosteroid use is not among the first line therapy in Covid-19 treatment,<sup>80</sup> we still should admit that the use of glucocorticoids will induce sharp rises in BG.

On the side, some viruses have been shown diabetogenic.<sup>81</sup> Jali et al<sup>82</sup> reported two subjects presenting with acute insulin-dependent diabetes for a brief and transient period after being infected with chicken pox. SARS was also found to cause secondary hyperglycaemia in patients who had no history of diabetes and had not used any glucocorticoids during the course of the disease.<sup>83</sup> Interestingly, experts found the immunostaining of ACE2 is strong in islets,<sup>83</sup> and indicated that SARS-CoV might enter islets using ACE2 as its receptor and cause acute diabetes by damaging islets. Similarly, secondary hyperglycaemia was also found in patients without a history of diabetes infected with SARS-CoV-2.<sup>79</sup> Pancreatic injury, determined by assessment of plasma levels of amylase and lipase, was observed in 17.3% patients with Covid-19 in China, and 66.7% patients also exhibited moderate increases in BG.<sup>84,85</sup> The emerging putative association of pancreatic injury and SARS-CoV-2 is consistent with expression of ACE2 in the exocrine and endocrine pancreas.<sup>86</sup> Thus, we assume that SARS-CoV-2 may bind to ACE2 in vital organs including liver and pancreas, with a potential role in the development of IR and impaired insulin secretion, causing acute diabetes or worsen diabetes prognosis. However, to date, no studies have determined whether Covid-19 induces new-onset diabetes or which signalling pathways it adopts, thus additional studies are needed to investigate this possibility.

## 2.3 | Diabetes therapy under covid-19

Under the Covid-19 epidemic, all of the life styles, treatment strategies, and therapeutic effects of diabetic patients could be severely impaired, increasing the difficulty of the BG management. An individualized strategy for BG management should be developed according to the clinical typing of Covid-19, condition of diabetes and its complications. All of the psychological care, healthy lifestyle, intensive BG monitoring, and reasonable medicine treatment are necessary for diabetes care in patients with Covid-19.<sup>87</sup> Specially, in regard to the choices of drug uses in diabetic patients, there are a few points to note.

First comes the confounding role of ACE inhibitors (ACEis) and angiotensin II type-I receptor blockers (ARBs), which are widely used in diabetic individuals. There is concern that the pharmacologic RAS inhibition will indirectly increase ACE2 expression,<sup>88</sup> thus increasing the susceptibility to viral host cell entry and propagation, regardless of the insufficient evidence supporting the changes in serum or pulmonary ACE2 levels with the ACEis/ARBs use. Conversely, mechanistic evidence from related coronaviruses suggests that SARS-CoV-2 infection may downregulate ACE2, leading to toxic overaccumulation of angiotensin II that induces ARDS and fulminant myocarditis, while RAS inhibition could mitigate this effect.<sup>89,90</sup> Recent retrospective analyses of Covid-19 patients have indicated no increased risk of in-hospital death associated with the use of ACEis/ARBs.<sup>91</sup> Given that investigators have variably hypothesized that both the use or withdrawal of RAS blockade could lead to improved outcomes from Covid-19,<sup>92,93</sup> randomized controlled trial and high-quality observational data associated with RAS blockade in Covid-19 need to be rapidly performed. Anyhow, the European Society of Cardiology, Council on Hypertension, and HFSA/ACC/AHA have recently released policy statements advocating for patients to continue ACEis/ARBs as prescribed and that changes in medications in the setting of Covid-19 should be completed only after careful assessment.<sup>94,95</sup> Second, human dipeptidyl peptidase 4 (DPP4) has been identified as a functional receptor for the spike protein of the MERS-Cov, and antibodies directed against DPP4 inhibited hCoV-EMC infection of primary human bronchial epithelial cells and Huh-7 cells.<sup>96,97</sup> By expressing human DPP4, transgenic mice were made susceptible to MERS-Cov.<sup>98</sup> DPP4 activity also potentially modulates the levels and bioactivity of multiple immunomodulatory chemokines and cytokines.<sup>99</sup> Seen in this light, despite of the lack of evidence specific for Covid-19, DPP4 may represent a potential target for reducing the risk and the progression of the acute respiratory complications that diabetes may add to the Covid-19 infection. Fadini et al<sup>100</sup> have recently conducted a case-control study to analyse the association between DPP4 inhibitor (DPP4i) and Covid-19, which showed no evidence that DPP4i might affect hospitalization for Covid-19. However, with a retrospective case-control study design, and not necessarily representative study population, the result should be considered with caution. Whether DPP4i is a good candidate for BG control in diabetic patients infected with SARS-CoV-2 still needs future randomized clinical trials to explore. Next, metformin,

$\alpha$ -glycosidase inhibitors, and GLP-1 receptor agonists are inappropriate for Covid-19 patients who have obvious gastrointestinal symptoms, considering their gastrointestinal side effects.<sup>101</sup> Given that SGLT2 inhibitors may increase the risk of ketoacidosis under stress state,<sup>102</sup> it's not recommended to use SGLT2 inhibitors in severe or critical Covid-19 cases. Instead, for severe or critically ill patients requiring ICU admission, insulin is the first-line treatment option.

## 3 | OBESITY AND COVID-19

### 3.1 | Impact of obesity on covid-19

Interest in the interactions between obesity and infection has been prompted by the H1N1 pandemic in 2009.<sup>103-106</sup> Published data indicated that obese individuals were more susceptible to respiratory virus infection, to a greater severity of illness and adverse endpoints after infection including higher rates of hospitalization, admission to ICU, and death.<sup>103-107</sup> In this Covid-19 epidemic, a greater rates of obesity and severe obesity among Covid-19 patients, relative to historical non-Covid-19 controls, has also been reported. In the case series including 5700 patients hospitalized with Covid-19 in the New York city, a higher prevalence of obesity (41.7%) compared to diabetes (33.8%) was found,<sup>108</sup> suggesting obesity as an underappreciated risk factor for Covid-19. The risk associated with obesity might be particularly relevant in the USA because the prevalence of obesity is approximately 40%, vs a prevalence of 6.2% in China, 20% in Italy, and 24% in Spain.<sup>109</sup> Report from the USA also showed that, among Covid-19 patients younger than 60 years, those with a BMI 30 kg/m<sup>2</sup> to 35 kg/m<sup>2</sup> and over 35 kg/m<sup>2</sup> were 1.8 and 3.6 times more likely to be admitted to ICU, respectively, compared to those with a BMI < 30 kg/m<sup>2</sup>.<sup>110</sup> On the same line, the NHS intensive care national audit & research centre report declared that, 38% of patients admitted to ICU associated with Covid-19 were obese in the UK.<sup>111</sup> The retrospective study conducted in French showed that 76% of patients admitted to ICU for Covid-19 were at least overweight.<sup>112</sup> Researches from China also showed that the presence of obesity increases the risk of severe Covid-19 approximately 3fold with a consequent longer hospital stay.<sup>113</sup> We have summarized several factors responsible for the increased severity of COVID-19 in diabetes (Table 1).

#### 3.1.1 | Immune dysfunction in obesity

Obesity is an inflammatory state associated with chronic activation of the immune system, which negatively affects immune functions and host defence mechanisms, resulting in high rates of infectious complications and vaccine failure.<sup>13</sup> Besides, the altered pulmonary physiology, increased receptors for virus invasion, increased viral diversity and titers, and prolonged viral shed, together make the SARS-CoV-2 infection in obesity complicated.

### *Chronic inflammation state in obesity*

Chronic inflammation is a common feature of obesity mainly resulting from metabolic tissue stress induced by weight gain and AT dysfunction.<sup>114,115</sup> In obesity, the hypertrophic adipocytes are more prone to activating endoplasmic reticulum and mitochondrial stress responses, which promote the activation of a chronic, pro-inflammatory state within AT.<sup>114,116</sup> Persistent stress and inflammation within AT further lead to adipocyte apoptosis and the release of chemotactic mediators, leading to inflammatory leukocyte infiltration<sup>117</sup> and increased secretion of pro-inflammatory cytokines,<sup>118</sup> which further perpetuate the hypertrophy-induced dysfunctional state. Moreover, AT also secretes several pro-inflammatory cytokines, chemokines and adipokines releasing into the circulation, contributing to a systemic low-grade chronic inflammation.<sup>119</sup> Additionally, viruses could also express tropism for different tissues and cell types including ATs and adipocytes.<sup>120,121</sup> Considering the fact that SARS-CoV-2 uses an ACE2-dependent mechanism of cellular entry, which is also expressed by fat including ectopic reservoirs,<sup>122</sup> the SARS-CoV-2 might as well have a tropism for the AT, which further contributes to the intrapulmonary and systemic inflammation.<sup>123</sup> Subsequently, the inflammation-recruited immune cells differentiate into inflammatory subsets and secrete additional pro-inflammatory molecules, contributing to the maintenance of the local and systemic chronic inflammation state.<sup>124</sup> The obesity-related chronic inflammation could inhibit macrophage activation and migration, impair the generation of neutralizing antibody and memory T cells, and decrease the activation of effector cells of the immune system, which suppressed immune functions and host defences.<sup>125-128</sup> Given this, we hold the opinion that the local and systemic chronic inflammation in obesity contributes to the immune dysfunction, which increased the risk for Covid-19.

### *Imbalanced crosstalk between immune and metabolic systems*

By the secretion of adipokines, AT mediates the interactions between immune system and metabolic cells, suggesting that obesity may compromise the immune surveillance.<sup>129</sup> With the presence of obesity, complex interactions take place between immune and metabolic cells. Specially, the adipocyte-derived leptin could regulate the haematopoiesis of bone marrow, generation and development of T cells in the thymus, and determine T cell subsets in lymph nodes.<sup>130-132</sup> Leptin signalling is also important for nearly all parts of the innate immune response, including the expression of antiviral cytokines (IFN- $\alpha/\beta$ ), pro-inflammatory IL-6 and TNF- $\alpha$ , as well as the activation and stimulation of monocytes, DCs and macrophages.<sup>133</sup> In obese subjects, the relative deficiency in leptin and/or the leptin resistance of immune cells,<sup>134</sup> negatively affects the production and activation of T cells and impairs the immune responses.<sup>132,135</sup> Adiponectin, another key adipokine intimately associated with obese status, has in addition been shown to affect immunity. Whereas leptin plays a more significant role in preparing and initiating immune responses, adiponectin is essential for inflammatory resolution, with both anti-inflammatory and insulin-sensitizing properties.<sup>136</sup> Teoh et al<sup>137</sup> showed that adiponectin-deficient mice had an 8-fold greater risk of sepsis-related mortality than wild-type models, and that the loss of adiponectin

increased endothelial activation and inflammation. Therefore, the leptin resistance related to high leptin levels, together with the decreased adiponectin levels in obesity contribute to the heightened pro-inflammatory cytokine production as well as the poor responsiveness to infection stimuli.

### *Interferes with cellular responses*

Both T cell and B cell responses present reduced efficacy in the obese host, which increases the infection susceptibility and impairs the resolution of Covid-19. Increasing evidence described the deficiencies in activation and function of CD4+ and CD8+ T cells in obese hosts,<sup>44,132,138,139</sup> with more IL-5 production and lower IFN- $\gamma$  production. Particularly, obesity-related metabolic dysregulation has been regarded as the driver of poor effector T cell and helper T cell function, as well as impaired memory T cell responses in obesity, owing to the altered T cell metabolism.<sup>140</sup>  $\gamma\delta$  T cells also decrease in number with increasing obesity status, while the remaining cells show increased differentiation that impaired their antiviral functionality and response to antigen presentation.<sup>141</sup> Karlsson et al<sup>142</sup> also indicated that the failure to maintain CD8+ memory T cell responses in obesity impairs the vaccine efficacy and increase mortality following challenge influenza infection. Interestingly, Misumi et al<sup>143</sup> observed that obesity increases memory T cell frequencies within ATs, leading to a unique form of viral pathogenesis involving memory T cell-dependent adipocyte destruction. On the side, increased visceral adiposity in obesity also attracts increased B cell amounts, contributing to systemic chronic inflammation through interactions with T cells.<sup>144</sup>

### *Complement system overactivation*

With the observation of a better respiratory function and reduced IL-6 secretion in complement-deficient models, experts have regarded the complement system as an important host mediator of SARS-CoV-induced disease.<sup>145</sup> Interestingly, excess fat has been shown associated with the hyperactivation of complement system,<sup>146</sup> potentially capable of inducing inflammatory sequelae ultimately developing a condition described as "cytokine storm".<sup>28</sup> Additionally, eculizumab, an antibody with complement system modulatory activity, is now being studied in a clinical trial (ClinicalTrials.gov Identifier: NCT04288713) to assess its effect on the adverse outcomes associated with Covid-19.

## **3.1.2 | Altered pulmonary mechanics and physiology in obesity**

Increasing evidence suggest that obesity could result in altered lung mechanics and physiology, including altered topographical distribution of ventilation, reduced lung volumes, decreased compliance, abnormal ventilation and perfusion distribution and respiratory muscle inefficiency.<sup>15,147,148</sup> Specially, obese individuals allocate a disproportionately high percentage of total body oxygen consumption to respiratory work, resulting in a reduced functional residual capacity and expiratory volume.<sup>149</sup> These changes could further induce or

aggravate the asthma or asthma-like symptoms such as dyspnea and wheeze.<sup>15</sup> Subsequent ventilation-perfusion abnormality further decreases the ventilatory reserve, making the obese more prone to respiratory failure.<sup>149</sup> Furthermore, obesity is shown to be strongly and independently associated with a higher prevalence of pulmonary embolism.<sup>150</sup> Therefore, the presence of increased airway resistance, impaired gas exchange, chronic inflammation of the respiratory tract, and increased risk of pulmonary embolism due to obesity may together affect the outcome of lung injury. This may increase the risk of acute respiratory failure or even multiple organ failure after Covid-19.

### 3.1.3 | High ACE2 expression in obesity

ACE2 is secreted by mature adipocytes and presented in the white and brown ATs.<sup>151</sup> In obese individuals, the adipocyte size increases and the white AT becomes hypertrophied due to macrophages infiltration with the increased secretion of pro-inflammatory cytokines.<sup>152</sup> Although current studies suggested that the levels of ACE2 expressed by adipocytes and adipose progenitor cells were similar between non-obese and obese subjects,<sup>153,154</sup> obese subjects have more adiposes so as to increase the number of ACE2-expressing cells, thus increasing the total amount of ACE2.<sup>66,68</sup> Pinheiro et al<sup>154</sup> further showed that, the obesity-related inflammation in the ATs leads to RAS up-regulation, which may contribute to the establishing metabolic disorders and increased susceptibility to infections. In contrast, the mild to moderate food restriction is associated with down-regulation of key RAS components.<sup>154</sup> As has been noted, SARS-CoV-2 uses ACE2 as its functional host-cell receptor to invade hosts.<sup>61</sup> Seen in this light, we assumed that the obese-induced overexpression of ACE2, as a functional receptor for SARS-CoV-2 invasion, may play a key role in the increased susceptibility to Covid-19, and the increased risk for progression to acute respiratory failure or even multiple organ failure.

### 3.1.4 | Viral evolution in obesity

Under the influenza virus infection, researchers observed that obesity is associated with increased disease severity, prolonged viral shed, elevated viral titers in exhaled breath, and increased viral diversity.<sup>155-157</sup> Latest data suggested that, the obesogenic microenvironment, characterized by an impairment of the IFN response, permits the emergence of potentially pathogenic variants with increased replication ability and enhanced virulence, leading to a more diverse viral quasispecies.<sup>155</sup> Besides, obesity has been implicated in altering within-host viral evolution, together with the prolonged infections, delayed clearance and increased shedding, potentially promoting the viral transmission.<sup>158</sup>

### 3.1.5 | Obesity-related comorbidities

In addition to the detrimental effects, obesity is a confirmed cause of diabetes and CVDs,<sup>159-161</sup> which were also considered as the risk factors for developing severe Covid-19-19.<sup>3-6,16-19</sup>

It should be mentioned that, in evaluating obesity as a risk factor for poor outcomes associated with Covid-19, age should be considered as a possible influential factor. Kass et al<sup>162</sup> have examined the correlation between BMI and age in 265 Covid-19 patients admitted to ICU in the USA. Interestingly, they found a significant inverse correlation between age and BMI, in which younger patients admitted to hospital were more likely to be obese. This suggested that, in populations with a high prevalence of obesity, Covid-19 will affect younger populations more than previously reported. Therefore, public notification to younger adults, lowering the threshold for virus testing in obese subjects, and maintaining greater vigilance for this at-risk population should reduce the prevalence of severe Covid-19 disease.<sup>162</sup>

## 3.2 | Impact of covid-19 on obesity

Previous researches have suggested that some virus play a role in the development of obesity and obesity-related metabolic disorders. Adenovirus infection has been found associated with a sharp increase in body weight.<sup>121,163,164</sup> Possible mechanisms via which adenovirus infection induces obesity were summarized as follows: First, the virus-induced inflammation via increase in macrophage chemoattractant protein 1 (MCP-1) activated by NF- $\kappa$ B (nuclear transcription factor kappa B).<sup>120</sup> Second, a suppression of leptin production in the adipocytes leading to lipid accumulation by the decreased lipolysis, a downregulation of the adipocyte genes associated with lipid oxidation and fatty acid synthesis.<sup>165</sup> Third, the increase in glucose uptake by fat cells leading to an energy surplus in the cells glucose-dependent.<sup>121,165</sup> Next, an up-regulation of adipogenesis due to enhanced adipocyte proliferation and differentiation.<sup>166</sup> Fifth, the modulation of hypothalamic monoamines leading to the reduction of corticosterone, which result in the reduction in metabolic activity.<sup>121</sup> On the side, acute respiratory infection has also been linked to the rapid development of transient IR, both in otherwise healthy euglycemic normal weight or overweight individuals.<sup>167</sup> Mice infected by the influenza virus have shown a metabolic imbalance resembling an insulin-resistant condition, with a metabolic shift toward an increase in glycolytic rate, a reduction in the mitochondrial pyruvate dehydrogenase complex activity, and a decrease in ATP production.<sup>168</sup> Although the effects of Covid-19 on obesity have not yet been well described, the adenovirus and influenza experience should serve as a caution for the care of obesity. Additionally, islet inflammation mediated by islet macrophages has recently emerged as a key feature of obesity.<sup>169</sup> Under the Covid-19 infection, the chronic inflammatory processes tend to be more easily activated, which may contribute to the IR as well as  $\beta$ -cell dysfunction that characterizes T2D. Besides, with the cases of viral encephalitis, brain tissue edema, neuronal degeneration, and cerebrobasilar disease caused by SARS-CoV-2 attacking the nervous system increasingly reported, researchers recognized the destructive effects of SARS-CoV-2 on the nervous system.<sup>170,171</sup> Whether SARS-CoV-2 has an impact on obesity involving the central as well as peripheral effects, is an interesting field to explore. Besides, the



inability to go to work and exercise, emotional stress, and financial hardship will provide the perfect milieu for the obesity pandemic to rage even faster.<sup>172</sup> Possible impacts of Covid-19 infection on obesity were summarized in Table 2.

### 3.3 | Treatment attention in obesity under Covid-19

Regarding the treatment of obese individuals under Covid-19 infection, there are a few points to note. First, the efficacy of antivirals and vaccines could be reduced in obese patients,<sup>173</sup> which is not only result from the obese-induced chronic inflammation, but also the altered viral life cycle and increased viral diversity complementing the already weakened immune response.<sup>155,173</sup> Whether the dosage of antivirals or vaccines should be adjusted in obese patients is a question worth thinking about. Specially, pharmacokinetics studies of oseltamivir showed that obese subjects clear the drug faster than non-obese subjects, but this increase in the clearance rate was non-obvious with potentially insignificant biological impact.<sup>174</sup> This suggests that dose adjustment for obese patients may be not necessary from a pharmacokinetic perspective, but the question remains concerning whether the dosage is appropriate to control viral replication.<sup>175</sup> Second, based on the tendency of prolonged shedding and spread of the virus in obese subjects,<sup>116,157</sup> whether quarantine should be prolonged in obese subjects relative to non-obese subjects should be seriously and comprehensively considered. Third, a balanced diet or a mild caloric restriction, instead of excessive dieting to lose weight, seems more important in obese patients with Covid-19 for the immunity considered.<sup>177</sup> Mild-to-moderate physical exercise is recommended, not only aiming at losing weight but also at quickly improving immune modulation.<sup>177,178</sup> Fourth, different treatments for Covid-19 may have differential impacts on the obesity. In regarding to the antiviral agents, the use of hydroxychloroquine have been shown to reduce body weight, improve obesity-induced lipotoxicity and IR, though the peroxisome proliferator-activated receptor gamma pathway.<sup>179</sup> On the side, although there were decreases in total weight and BMI with the chloroquine treatment, researchers observed increases in total body fat in patients infected with hepatitis C virus.<sup>180</sup> As the initially first-line agent in the management of Covid-19, lopinavir/ritonavir has been shown to induce lipodystrophy and metabolic syndrome, which leads to reduced weight, but increased plasma levels of lipids and insulin.<sup>181,182</sup> Besides, it was reported that remdesivir has protective effects against high fat diet -induced non-alcoholic fatty liver disease, by regulating hepatocyte dyslipidemia and inflammation.<sup>183</sup> However, long-term antiviral treatment with azithromycin,<sup>184</sup> and both short- and long-term corticosteroids uses as the supporting treatment under severe circumstances,<sup>185,186</sup> have been shown to significantly increase body weight. Given the differential impacts of various treatments on obese patients, attention should be paid on stratification by BMI while evaluating safety and efficacy outcomes in the coming clinical trials.

## 4 | CONCLUSIONS

The outbreak of the Covid-19 has become an evolving worldwide health crisis. With the rising prevalence of obesity and diabetes has come an increasing awareness of their impacts on infectious diseases. In diabetes, the chronic exposure to an abnormal metabolic environment may lead to persistent derangements in innate and adaptive immunity, aggravation of inflammatory storm, abnormalities in lung physiology and microcirculation, and increase of virus infectivity and virulence, which may together increase the risk for Covid-19 poor prognosis. At present, whether diabetes increases the susceptibility to Covid-19 infection still lacks evidence. In addition to deleterious effects on host immunity, obesity is also associated with altered pulmonary mechanics and physiology, increased ACE2 expression, increased viral diversity and titers and prolonged viral shed, which may further increase the susceptibility to Covid-19 and promote the progression to respiratory failure. How Covid-19 affects obesity and diabetes still lacks robust data. Covid-19 infection might promote IR and obesity, worsen preexisting diabetes or even induce new-onset diabetes, thus forming a vicious circle. An individualized strategy for BG management should be developed according to the clinical typing of Covid-19 and condition of diabetes. The use of ACEis/ARBs, DPP4is and other antidiabetic drugs merits reconsideration during the Covid-19 outbreak. The clinical treatment for severe Covid-19 cases is still difficult, future studies on the pathogenesis of SARS-CoV-2 and developing specific therapeutic drugs are desperately needed.

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### CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

### AUTHOR CONTRIBUTIONS

Conceptualization, Yangang Wang; writing-original draft preparation, Yue Zhou, Jingwei Chi; writing-review and editing, Yue Zhou, and Wenshan Lv. All authors approved the final draft and agreed to submit it for publication.

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