

COVID-19 and Obesity: Epidemiology, Pathogenesis and Treatment

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Xinyu Zhu^{1,2,*}

Liu Yang^{1,2,*}

Kai Huang^{1,2} 

¹Department of Cardiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China; ²Clinical Center for Human Genomic Research, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China

*These authors contributed equally to this work

Abstract: The growing prevalence of overweight and obesity has been a worldwide public health issue. During the COVID-19 pandemic, obesity is associated with a higher risk of severity and a worse clinical outcome of SARS-CoV-2 infection. This may be because of the chronic low-grade inflammation, impaired immune response and metabolic disorders in obese patients. In this narrative review, we have summarized the association between obesity and COVID-19 and discussed the potential pathogenesis and treatment in these patients. This work may provide practical suggestions on the clinical management of obese COVID-19 patients.

Keywords: COVID-19, obesity, SARS-CoV-2

Introduction

The coronavirus disease (COVID-19) has emerged as a global pandemic since its outbreak in December 2019. According to WHO, by Sep 28, 2020, there have been 33,137,748 confirmed cases worldwide, 3.01% of which were deceased (998,372). It has brought a great challenge to the disease prevention and control system around the world.

Obesity is a common metabolic disorder worldwide. It was estimated that nearly 2 billion people are overweight¹ and the prevalence in children and adolescence rose in a dramatic trend between 1975 to 2016 (0.7% to 5.6% in boys and 0.9% to 7.8% in girls).² It has been reported that obese patients are more vulnerable to COVID-19, accompanied with worse clinical outcomes. Moreover, the sudden lifestyle change caused by the pandemic also increases the likelihood of developing obesity. Due to the restriction in grocery shopping and outdoor activities during lockdown quarantine, people tend to increase the consumption of carbohydrate sources with a high glycemic index and live a more sedentary lifestyle. These changes in lifestyle render weight gain and increase the risk of developing obesity.^{3,4} Here we reviewed the impact of obesity in COVID-19. This paper will provide a comprehensive understanding on the role of obesity in the pathogenesis of COVID-19 and provide suggestions on the clinical management of COVID-19 in obese patients.

Characteristics of COVID-19 Epidemiology

COVID-19 is caused by the infection of a coronal virus named SARS-CoV-2. This is a 26–32 kilobases long, positive-sense RNA virus, belonging to the family

Correspondence: Kai Huang
Department of Cardiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Ave, Wuhan, Hubei 430022, People's Republic of China
Email: hushuang1003@163.com

Coronaviridae.⁵ SARS-CoV-2 shows a close relationship with another two coronaviruses from the same family: SARS-CoV (about 79%) and MERS-CoV (about 50%), both of which have caused epidemics, namely, SARS and MERS.⁶ The estimated basic reproductive number for SARS-CoV-2 was 2.68 (95% credible interval 2.47–2.86) and the epidemic doubling time was 6.4 days (95% credible interval 5.8–7.1).⁷

It is widely accepted that SARS-CoV-2 spread via person-to-person transmission through direct contact or droplets of saliva. The estimated mean incubation period is 6.4 days (95% credible interval: 5.6–7.7), ranging from 2.1 to 11.1 days.⁸ It has been confirmed that face masks and eye gear protects against the spread of COVID-19.^{9,10} Social distancing and frequent hand hygiene are also beneficial for disease prevention.¹¹ According to the World Health Organization (WHO), people of all ages are generally susceptible to this virus. Health workers and people who closely interact with patients or their family members are considered to be at high risk of infection.

Clinical Manifestations

According to the published data, the mean age of COVID-19 patients is 51.97 years old, 55.9% of which are male.¹² The most common symptoms of COVID-19 infection are fever (88.7%), cough (57.6%) and dyspnea (45.6%).¹² Other symptoms include expectoration, fatigue, headache, hemoptysis and diarrhea. Of all the COVID-19 patients, 32.8% present with acute respiratory distress syndrome (ARDS) and 20.3% are admitted into the intensive care unit (ICU). Laboratory findings show lymphopenia (43.1%), increase in C-reactive protein (58.3%), lactate dehydrogenase (LDH) (57.0%), erythrocyte sedimentation rate (ESR) (41.8%) and reduction in albumin (75.8%). The chest Computed Tomography (CT) scan demonstrates that the pneumonia compromise is predominantly bilateral, with images showing ground-glass opacity.¹³

Diagnosis

According to WHO, a nasopharyngeal or oropharyngeal swab followed by a nucleic acid amplification test is the standard assessment for the diagnosis of COVID-19.¹⁴ Patients with laboratory confirmation of SARS-CoV-2 infection, irrespective of clinical signs and symptoms are considered confirmed cases. However, due to the shortage of nucleic acid amplification kits in some areas and potential false-negative results, patients with acute respiratory illness and recent exposure to a confirmed or probable case should also be suspected for COVID-19. A chest CT scan may be helpful for diagnosis.¹⁵

Treatment

There is currently no cure for COVID-19. Treatment that may be beneficial includes corticosteroids, immunoglobulin, oxygen support (high-flow nasal cannula oxygen therapy, non-invasive or invasive mechanical ventilation), renal replacement therapy and extracorporeal membrane oxygenation (ECMO),^{16–18} depending on the disease severity and comorbidities. However, none of the currently available antiviral drug has been proven to be effective in the treatment of COVID-19. Therapy such as antibodies and immunoglobulin of cured patients are believed to be potentially beneficial for COVID-19 recovery, but solid evidence is still lacking.

Obesity is Associated with Disease Severity and Outcome

People with certain risk factors or comorbidities are more likely to develop severe disease conditions.¹⁹ According to the data from the US, 68% of the COVID-19 patients possessed at least one comorbidity,²⁰ among which obesity is the second most common (48.3%) in hospitalized patients.²¹ Although there is a lack of evidence to identify whether obesity increases the susceptibility of virus infection, several reports including Meta-analysis and systematic reviews have confirmed the correlation between obesity and worse outcome of COVID-19.^{22–24} The percentage of obesity in the COVID-19 patients admitted to intensive care units (ICU) or receiving invasive mechanical ventilation (IMV) is much higher than those who did not.^{25,26} Patients with obesity are prone to have symptoms of cough and fever^{27,28} and the presence of obesity increases the risk of severe COVID-19 illness after adjustment for other factors.²⁹ A cohort study that recruits 489,769 people in England has shown that higher BMI is associated with higher risk of severe COVID-19 (adjusted ORs: 1.40 for 25.0–29.9 kg/m², 1.73 for 30.0–34.9 kg/m², 2.82 for 35.0–39.9 kg/m², and 3.30 for ≥40.0 kg/m²).³⁰ Similar result was reported in Spain.³¹ More importantly, BMI >30 kg/m² was associated with an increased risk of death.²⁸ Taken together, these data imply that obesity is a risk factor for the severity and worse clinical outcome of COVID-19.

How Obesity Affects the Pathogenesis of COVID-19 Inflammation

Obesity, characterized by adipose tissue expansion, affects the inflammatory response. Adipocytes secrete pro-inflammatory cytokines, such as TNF α , interleukin (IL)-1, IL-6 and IL-10,³²

which results in elevated circulating levels of cytokines and chemokines in the plasma of obese patients.³³ Macrophages are the most abundant inflammatory cells in adipose tissue (AT). In such microenvironment, they tend to switch from an anti-inflammatory M2-polarized state to a proinflammatory M1 state,³⁴ which leads to a low-grade inflammation situation.³⁵ “Cytokine storm”, which is the hyperactivation of the inflammatory response with elevated interferon γ , IL-6, and other proinflammatory cytokines, also aggravates the severity of COVID-19.^{36,37} In addition, a higher portion of CD14⁺CD16⁺ inflammatory monocytes was found in severe patients than non-severe patients,³⁸ which also suggests an elevated level of inflammation in severe COVID-19 patients.

Immunity

The function of various immune cells is also altered in obese patients, which significantly affects the immune system. Laboratory findings suggest that the number of lymphocytes including CD4⁺ T cells, CD8⁺ T cells, B cells, and natural killer (NK) cells are dramatically decreased in COVID-19 patients.³⁹ Unfortunately, obesity impairs both T and B cell responses, therefore retards the adaptive immune response to infection.⁴⁰ The weakened immune system in obese patients may result in higher viral load, rapid viral replication and spreading.

There is also considerable interaction between immunity and inflammation. Several studies reported that proinflammatory T and B cell phenotypes are involved in inflammation of adipose tissue.⁴¹ For example, CD8⁺ T cells promote macrophage recruitment,⁴² while anti-inflammatory Th2 cells promoting macrophage differentiation into M2 reduce.⁴³ In the setting of obesity, pro-inflammatory T helper 1 (Th1) cells secrete IFN- γ and increase the level of inflammation. Moreover, low-grade inflammation in obesity could also induce a dysfunctional immune system in the disease.

Lipofibroblasts and Pulmonary Fibrosis

The most common feature of COVID-19 is severe acute respiratory syndrome induced by progressive consolidation of the lung. There has been a positive correlation between the duration of SARS-CoV infection and the degree of interstitial fibrosis.⁴⁴ Extensive pulmonary fibrosis is one of the main reasons for pulmonary consolidation, due to excessive extracellular matrix components produced by activated myofibroblasts. This poses an obstacle to gas exchange.

Pulmonary lipofibroblasts are a special type of adipocytes, which contain typical lipid droplets and reside close to type 2 alveolar epithelial cells in the alveolar interstitium.⁴⁵ Lipofibroblasts might be the result of ectopic fat deposition, and lipofibroblasts may play a vital role in the progress of COVID-19 in obese patients. When exposed to various stimulation such as hyperoxia and infection,⁴⁶ pulmonary lipofibroblasts can transdifferentiate into a myogenic phenotype called “myofibroblasts” to induce pulmonary fibrosis.⁴⁷ Although there is a lack of direct evidence of how lipofibroblasts affect pulmonary fibrosis after SARS-CoV-2 infection, it is reasonable to speculate that the number of lipofibroblasts positively correlates with the severity of pulmonary fibrosis.

Glucose Metabolism

A significant number of obese patients are accompanied with glucose metabolic disorder, which is considered a risk factor for poor outcomes of COVID-19. Notably, it is reported that SARS infection could induce hyperglycemia in some patients due to the transient impairment of pancreatic islet cell function by virus attack.⁴⁸ A similar effect may also occur after SARS-CoV-2 infection. This may partially explain why 52% of subjects with SARS-CoV-2 infection also had hyperglycemia.⁴⁹ The percentage of glucose metabolic disorder in obese COVID-19 patients may be even higher.

Hyperglycemia leads to several complications including osmotic diuresis, fluid and electrolyte imbalances, hyperosmolar nonketotic coma, worsening skeletal muscle catabolism, impaired wound healing, altered coagulability, and increased susceptibility to infections. Furthermore, hyperglycemia impairs the immune function of the host. These effects collectively impair the clinical outcome of COVID-19. Notably, proper blood glucose control decreases the mortality rate in critically ill patients,⁵⁰ which highlights the importance of blood glucose control in the management of obese COVID-19 patients.

The effect of antidiabetic drugs on the recovery of COVID-19 is beyond the scope of this study, which is reviewed elsewhere.^{51–54}

Lipid Metabolism

One of the reasons for obesity is the excessive lipid deposit in adipose tissue due to energy over-intake. Lipids have multiple functions in virus infection. In addition to being a source of energy, lipid droplets can be utilized as sites of virus assembly, such as hepatitis

C virus.⁵⁵ It is reasonable to speculate that lipids accumulating in adipocytes in obese patients may facilitate the replication of SARS-CoV-2 and ectopic fat depositing may contribute to organ injury during virus infection.

Lipid rafts enriched with sphingolipids, cholesterol and proteins are microdomains of the cell membrane. Notably, lipid rafts were found co-localized with angiotensin-converting enzyme 2 (ACE2), the receptor of SARS-CoV. It is shown that lipid rafts facilitate the binding of the virus to the ACE2 receptor in Vero E6 cells.⁵⁶ This suggests that lipid rafts play an important role in virus entry. Moreover, it is also reported that lipid rafts facilitate virus replication.⁵⁷ Depletion of cholesterol, one of the main content of lipid rafts, significantly suppresses virus production.⁵⁸ This implies the importance of lipid in the development of virus infection and COVID-19.

Treatment of COVID-19 in Obese Patients

Chloroquine

Chloroquine is widely used in the treatment of malaria. It suppresses virus infection by increasing endosomal pH to disturb membrane fusion and interfere with ACE2, the receptor of SARS-CoV.⁵⁹ Moreover, it has been reported that chloroquine inhibits the replication of SARS-CoV-2 in vitro.⁶⁰ However, the proper concentration, at which the great anti-virus effects take place with limited side effects, is still undetermined. In obese patients, there is an increase in the clearance of chloroquine, indicating a higher dose may be needed in these patients.⁶¹

Zinc

Zinc is an indispensable metal in maintaining the proper function of immune system.⁶² Deficiency of zinc increases the production of proinflammatory cytokines, such as IL-6 and TNF α , and reduce the effectiveness of immune response.⁶³ A significant deficiency of zinc was found in obese patients.^{64,65} Notably, zinc supplementation ease glucose metabolism and insulin resistance in individuals with prediabetes⁶⁶ and significantly decrease serum levels of CRP, TNF- α , and IL-6.⁶⁶

More importantly, combined with its ionophores, Zn²⁺ efficiently reduces the replication of SARS-CoV by suppressing the activity of RNA-dependent RNA polymerase (RdRp).⁶⁷ Interestingly, chloroquine could act as a zinc ionophore to increase zinc uptake by cells.⁶⁸ Lin and colleagues also reported that disulfiram-induced zinc

release destabilizes papain-like protease of MERS-CoV and SARS-CoV.⁶⁹ Therefore, it is reasonable to speculate that zinc will be beneficial for obese patients with SARS-CoV-2 infection. More studies are warranted to support this hypothesis.

Corticosteroids

Corticosteroids are often used in the treatment of viral pneumonia, since they modulate immune and inflammatory response through repressing the expression of pro-inflammatory genes and interacting with anti-inflammatory proteins.⁷⁰ Critically ill patients are more likely to receive corticosteroids, but the mortality rate is still higher in this group, due to various reasons.⁷¹ However, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial reported that 28-day all-cause mortality of COVID-19 patients who received 6 mg of dexamethasone per day for up to 10 days was lower than those who received usual care (21.6% vs 24.6%; age-adjusted rate ratio, 0.83 [95% CI, 0.74–0.92]; $P < 0.001$). This effect is more distinct in patients receiving invasive mechanical ventilation (29.0% vs 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; $p < 0.001$).⁷² It is reasonable to speculate that corticosteroids may also be beneficial for severe and obese COVID-19 patients. Notably, a common side effect of corticosteroids is to increase blood glucose, due to the increase in the hepatic gluconeogenesis and reduction in the insulin sensitivity. Additional monitoring on the level of blood glucose in obese patients is needed.

Antiviral Agents

There is a lack of solid evidence to show whether the pre-existing anti-viral agents are effective for SARS-CoV-2 infection. Ribavirin, a guanosine analog, is often used to treat respiratory syncytial virus or hepatitis C virus infection. Recently, it was reported that Ribavirin, in combination with IFN- α 2b, suppresses the progression and improves the clinical outcome of MERS in rhesus macaque model.⁷³ In a clinical trial, COVID-19 patients who received a combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin presented less median time from beginning of study treatment to recover (7 days [IQR 5–11]) than those who received lopinavir-ritonavir alone (12 days [8–15]).⁷⁴ This suggests a combination of interferon beta-1b and ribavirin may be beneficial in the treatment of COVID-19. In addition to Ribavirin, Sofosbuvir and Remdesivir may also be effective,⁷⁵ according to the sequence analyses. Remdesivir is an adenosine analog, which impairs the activity of RNA-dependent RNA-

polymerases.⁶⁰ In vitro studies showed its capability of killing SARS-CoV-2.⁶⁰ But the result of clinical studies remains controversial.^{76,77} Moreover, there is a lack of evidence to show whether the effect of antiviral agents in obese patients is different from lean people. More studies are needed to elucidate the effectiveness and safety of antiviral agents for obese COVID-19 patients.

In conclusion, the COVID-19 pandemic has caused an enormous threat to public health. Obesity increases the vulnerability of SARS-Cov-2 infection and is linked to a worse prognosis. Although the molecular mechanisms are not fully elucidated, which warrants additional studies, more attention should be paid to obese COVID-19 patients to decrease the comorbidities and to maximize the clinical outcomes.

Author Contributions

All authors made a significant contribution to the present work, including study design, execution, acquisition of data, analysis and interpretation. All authors carefully revised and critically reviewed the article; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that there are no conflicts of interest.

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