COVID-19 and Obesity: Epidemiology, Pathogenesis and Treatment

This article was published in the following Dove Press journal:
Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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.

References

- Blüher M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol.* 2019;15(5):288–298. doi:10.1038/s41574-019-0176-8
- Bentham J, Di Cesare M, Bilano V, et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet.* 2017;390(10113):2627–2642. doi:10.1016/S0140-6736(17)32129-3
- Zupo R, Castellana F, Sardone R, et al. Preliminary trajectories in dietary behaviors during the COVID-19 pandemic: a public health call to action to face obesity. *Int J Environ Res Public Health.* 2020;17(19):1–15. doi:10.3390/ijerph17197073
- Barrea L, Pugliese G, Framondi L, et al. Does Sars-Cov-2 threaten our dreams? Effect of quarantine on sleep quality and body mass index. *J Transl Med.* 2020;18(1):1–11. doi:10.1186/s12967-020-02465-y
- Su S, Wong G, Shi W, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends Microbiol.* 2016;24(6):490–502. doi:10.1016/j.tim.2016.03.003
- Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* 2020;395(10224):565–574. doi:10.1016/S0140-6736(20)30251-8
- Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. *Lancet.* 2020;395(10225):689–697. doi:10.1016/S0140-6736(20)30260-9
- Backer JA, Klinkenberg D, Wallinga J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20 Jan–28 Jan 2020. *Eurosurveillance.* 2020;25(5):1–6. doi:10.2807/1560-7917.ES.2020.25.5.2000062
- Liang M, Gao L, Cheng C, et al. Efficacy of face mask in preventing respiratory virus transmission: a systematic review and meta-analysis. *medRxiv.* 2020. doi:10.1101/2020.04.03.20051649
- Chu DK, Akl EA, Duda S, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. *Lancet.* 2020;395(10242):1973–1987. doi:10.1016/S0140-6736(20)31142-9
- World Health Organization (WHO). Rational use of personal protective equipment for coronavirus disease 2019 (COVID-19). Who; 2020.
- Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. *Travel Med Infect Dis.* 2020;34:101623. doi:10.1016/j.tmaid.2020.101623
- Zhu N, Zhang D, Wang W, et al. Chest CT findings in 2019 novel coronavirus (2019-nCoV) infections from Wuhan, China: key points for the radiologist. *N Engl J Med.* 2020;382(8):727–733. doi:10.1056/NEJMoa2001017
- WHO. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases. Interim Guid; 2020. Available from: <https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117>.
- Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for typical 2019-nCoV pneumonia: relationship to negative RT-PCR testing. *Radiology.* 2020;200343. doi:10.1148/radiol.20200343
- Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ.* 2020;368. doi:10.1136/bmj.m606
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054–1062. doi:10.1016/S0140-6736(20)30566-3
- Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA.* 2020. doi:10.1001/jama.2020.6775
- Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev.* 2020. doi:10.1002/dmrr.3319
- Piva S, Filippini M, Turla F, et al. Clinical presentation and initial management critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Brescia, Italy. *J Crit Care.* 2020;58:29–33. doi:10.1016/j.jccr.2020.04.004
- Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 — COVID-NET, 14 States, March 1–30, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(15). doi:10.15585/mmwr.mm6915e3
- de Siqueira JVV, Almeida LG, Zica BO, Brum IB, Barceló A, de Siqueira Galil AG. Impact of obesity on hospitalizations and mortality, due to COVID-19: a systematic review. *Obes Res Clin Pract.* 2020;14(5):398–403. doi:10.1016/j.orcp.2020.07.005
- Tamara A, Tahapary DL. Obesity as a predictor for a poor prognosis of COVID-19: a systematic review. *Diabetes Metab Syndr Clin Res Rev.* 2020;14(4):655–659. doi:10.1016/j.dsx.2020.05.020
- Hussain A, Mahawar K, Xia Z, Yang W, S EL-H. Obesity and mortality of COVID-19. Meta-analysis. *Obes Res Clin Pract.* 2020;14(4):295–300. doi:10.1016/j.orcp.2020.07.002
- Barrasa H, Rello J, Tejada S, et al. SARS-Cov-2 in Spanish intensive care: early experience with 15-day survival in Vitoria. *Anaesth Crit Care Pain Med.* 2020;39(5):553–561. doi:10.1016/j.accpm.2020.04.001
- Simonnet A, Chetboun M, Poissy J, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity (Silver Spring).* 2020;28(7):1195–1199. doi:10.1002/oby.22831

27. Cai Q, Chen F, Wang T, et al. Obesity and COVID-19 severity in a designated hospital in Shenzhen, China. *Diabetes Care*. 2020;43(7):1392–1398. doi:10.2337/dc20-0576
28. Hajifathalian K, Kumar S, Newberry C, et al. Obesity is associated with worse outcomes in COVID-19: analysis of early data from New York City. *Obesity (Silver Spring)*. 2020;28(9):1606–1612. doi:10.1002/oby.22923
29. Zheng KI, Gao F, Wang X-B, et al. Obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease. *Metabolism*. 2020;108:154244. doi:10.1016/j.metabol.2020.154244
30. Zhu Z, Hasegawa K, Ma B, Fujiogi M, Camargo CA, Liang L. Association of obesity and its genetic predisposition with the risk of severe COVID-19: analysis of population-based cohort data. *Metabolism*. 2020;112:154345. doi:10.1016/j.metabol.2020.154345
31. Fresán U, Guevara M, Elia F, et al. Independent role of morbid obesity as a risk factor for COVID-19 hospitalization: a Spanish population-based cohort study. *Obesity*. 2020. doi:10.1002/oby.23029
32. Divella R, De Luca R, Abbate I, Naglieri E, Daniele A. Obesity and cancer: the role of adipose tissue and adipo-cytokines-induced chronic inflammation. *J Cancer*. 2016;7(15):2346–2359. doi:10.7150/jca.16884
33. Park HS, Park JY, Yu R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF- α and IL-6. *Diabetes Res Clin Pract*. 2005;69(1):29–35. doi:10.1016/j.diabres.2004.11.007
34. Lumeng CN, Bodzin JL, Saltiel AR, Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization Find the latest version: obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J Clin Invest*. 2007;117(1):175–184. doi:10.1172/JCI29881.both
35. Zatterale F, Longo M, Naderi J, et al. Chronic adipose tissue inflammation linking obesity to insulin resistance and type 2 diabetes. *Front Physiol*. 2020;10. doi:10.3389/fphys.2019.01607
36. Muscogiuri G, Pugliese G, Barrea L, Savastano S, Colao A. Obesity: the “Achilles heel” for COVID-19? *Metabolism*. 2020;108:8–10. doi:10.1016/j.metabol.2020.154251
37. Shi Y, Wang Y, Shao C, et al. COVID-19 infection: the perspectives on immune responses. *Cell Death Differ*. 2020;27(5):1451–1454. doi:10.1038/s41418-020-0530-3
38. Zhou Y, Fu B, Zheng X, et al. Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. *Natl Sci Rev*. 2020;7(6):998–1002. doi:10.1093/nsr/nwaa041
39. Wang F, Nie J, Wang H, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. *J Infect Dis*. 2020;221(11):1762–1769. doi:10.1093/infdis/jiaa150
40. Green WD, Beck MA. Obesity altered T cell metabolism and the response to infection. *Curr Opin Immunol*. 2017;46:1–7. doi:10.1016/j.coi.2017.03.008
41. McLaughlin T, Ackerman SE, Shen L, Engleman E. Role of innate and adaptive immunity in obesity-associated metabolic disease. *J Clin Invest*. 2017;127(1):5–13. doi:10.1172/JCI88876
42. Nishimura S, Manabe I, Nagasaki M, et al. CD8⁺ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nat Med*. 2009;15(8):914–920. doi:10.1038/nm.1964
43. Winer S, Chan Y, Paltser G, et al. Normalization of obesity-associated insulin resistance through immunotherapy: CD4⁺ T cells control glucose homeostasis. *Nat Med*. 2009;15(8):921–929. doi:10.1038/nm.2001.Normalization
44. Tse GMK, To KF, Chan PKS, et al. Pulmonary pathological features in coronavirus associated severe acute respiratory syndrome (SARS). *J Clin Pathol*. 2004;57(3):260–265. doi:10.1136/jcp.2003.013276
45. Kruglikov IL, Scherer PE. The role of adipocytes and adipocyte-like cells in the severity of COVID-19 infections. *Obesity*. 2020. doi:10.1002/oby.22856
46. Rehan VK, Torday JS. The lung alveolar lipofibroblast: an evolutionary strategy against neonatal hyperoxic lung injury. *Antioxidants Redox Signal*. 2014;21(13):1893–1904. doi:10.1089/ars.2013.5793
47. El Agha E, Moiseenko A, Kheirollahi V, et al. Two-way conversion between lipogenic and myogenic fibroblastic phenotypes marks the progression and resolution of lung fibrosis. *Cell Stem Cell*. 2017;20(2):261–273.e3. doi:10.1016/j.stem.2016.10.004
48. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol*. 2010;47(3):193–199. doi:10.1007/s00592-009-0109-4
49. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507–513. doi:10.1016/S0140-6736(20)30211-7
50. Butler SO, Btaiche IF, Alaniz C. Relationship between hyperglycemia and infection in critically ill patients. *Pharmacotherapy*. 2005;25(7):963–976. doi:10.1592/phco.2005.25.7.963
51. Mirabelli M, Chiefari E, Puccio L, Foti DP, Brunetti A. Potential benefits and harms of novel antidiabetic drugs during COVID-19 crisis. *Int J Environ Res Public Health*. 2020;17(10). doi:10.3390/ijerph17103664
52. Qu H, Zheng Y, Wang Y, et al. The potential effects of clinical antidiabetic agents on SARS-CoV-2. *J Diabetes*. 2020;1753–0407.13135. doi:10.1111/1753-0407.13135
53. Chen X, Guo H, Qiu L, Zhang C, Deng Q, Leng Q. Immunomodulatory and Antiviral Activity of Metformin and Its Potential Implications in Treating Coronavirus Disease 2019 and Lung Injury. *Front Immunol*. 2020;11:7–12. doi:10.3389/fimmu.2020.02056
54. Katsiki N, Ferrannini E. Anti-inflammatory properties of antidiabetic drugs: A “promised land” in the COVID-19 era? *J Diabetes Complications*. 2020;34(12): 107723. doi:10.1016/j.jdiacomp.2020.107723
55. Heaton NS, Randall G. Multifaceted roles for lipids in viral infection. *Trends Microbiol*. 2011;19(7):368–375. doi:10.1016/j.tim.2011.03.007
56. Lu Y, Liu DX, Tam JP. Lipid rafts are involved in SARS-CoV entry into Vero E6 cells. *Biochem Biophys Res Commun*. 2008;369(2):344–349. doi:10.1016/j.bbrc.2008.02.023
57. Lu JC, Chiang YT, Lin YC, et al. Disruption of lipid raft function increases expression and secretion of monocyte chemoattractant protein-1 in 3T3-L1 adipocytes. *PLoS One*. 2016;11(12):1–21. doi:10.1371/journal.pone.0169005
58. Li GM, Li YG, Yamate M, Li SM, Ikuta K. Lipid rafts play an important role in the early stage of severe acute respiratory syndrome-coronavirus life cycle. *Microbes Infect*. 2007;9(1):96–102. doi:10.1016/j.micinf.2006.10.015
59. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virology*. 2005;2:1–10. doi:10.1186/1743-422X-2-69
60. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269–271. doi:10.1038/s41422-020-0282-0
61. Smit C, Peeters MYM, van den Anker JN, Knibbe CAJ. Chloroquine for SARS-CoV-2: implications of its unique pharmacokinetic and safety properties. *Clin Pharmacokinet*. 2020;59(6):659–669. doi:10.1007/s40262-020-00891-1
62. Wessels I, Maywald M, Rink L. Zinc as a gatekeeper of immune function. *Nutrients*. 2017;9(12):9–12. doi:10.3390/nu9121286
63. Gammoh NZ, Rink L. Zinc in infection and inflammation. *Nutrients*. 2017;9(6). doi:10.3390/nu9060624
64. De Luis DA, Pacheco D, Izaola O, Terroba MC, Cuellar L, Cabezas G. Micronutrient status in morbidly obese women before bariatric surgery. *Surg Obes Relat Dis*. 2013;9(2):323–327. doi:10.1016/j.soard.2011.09.015
65. Suliburska J, Cofta S, Gajewska E, et al. The evaluation of selected serum mineral concentrations and their association with insulin resistance in obese adolescents. *Eur Rev Med Pharmacol Sci*. 2013;17:2396–2400.

66. Islam MR, Attia J, Ali L, et al. Zinc supplementation for improving glucose handling in pre-diabetes: a double blind randomized placebo controlled pilot study. *Diabetes Res Clin Pract.* 2016;115:39–46. doi:10.1016/j.diabres.2016.03.010
67. Te Velthuis AJW, van den Worml SHE, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn²⁺ inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog.* 2010;6(11):1–10. doi:10.1371/journal.ppat.1001176
68. Xue J, Moyer A, Peng B, Wu J, Hannafon BN, Ding WQ. Chloroquine is a zinc ionophore. *PLoS One.* 2014;9(10):1–6. doi:10.1371/journal.pone.0109180
69. Lin MH, Moses DC, Hsieh CH, et al. Disulfiram can inhibit MERS and SARS coronavirus papain-like proteases via different modes. *Antiviral Res.* 2018;150:155–163. doi:10.1016/j.antiviral.2017.12.015
70. Sierra H, Cordova M, Chen CSJ, Rajadhyaksha M. One hormone two actions: anti- and pro-inflammatory effects of glucocorticoids diana. *J Invest Dermatol.* 2015;135(2):612–615. doi:10.1038/jid.2014.371
71. Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. *J Infect.* 2020;81(1):e13–e20. doi:10.1016/j.jinf.2020.03.062
72. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med.* 2020. doi:10.1056/nejmoa2021436
73. Falzarano D, De Wit E, Rasmussen AL, et al. Treatment with interferon- α 2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. *Nat Med.* 2013;19(10):1313–1317. doi:10.1038/nm.3362
74. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet.* 2020;395:1695–1704. doi:10.1016/S0140-6736(20)31042-4
75. Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. *Life Sci.* 2020;248:117477. doi:10.1016/j.lfs.2020.117477
76. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multi-centre trial. *Lancet.* 2020;395(10236):1569–1578. doi:10.1016/S0140-6736(20)31022-9
77. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — final report. *N Engl J Med.* 2020;383(19):1813–1826. doi:10.1056/nejmoa2007764

Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

Dovepress

Publish your work in this journal

Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy is an international, peer-reviewed open-access journal committed to the rapid publication of the latest laboratory and clinical findings in the fields of diabetes, metabolic syndrome and obesity research. Original research, review, case reports, hypothesis formation, expert opinion

and commentaries are all considered for publication. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/diabetes-metabolic-syndrome-and-obesity-targets-and-therapy-journal>