Obesity and higher risk for severe complications of COVID-19: What to do when the two pandemics meet

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has spread around the globe, infecting more than ten million individuals, with more than 500,000 dead; about one half of the infected people have recovered. Despite this fact, a subgroup of individuals affected by COVID-19 is at greater risk of developing worse outcomes and experience a high rate of mortality. Data on the association between obesity and
COVID-19 are growing; the available studies, have reported a high prevalence of overweight and obesity in patients experiencing a severe COVID-19 course, with serious complications requiring hospitalization and admission to intensive care units. This paper attempts to highlight potential mechanisms behind the greater vulnerability to COVID-19 of individuals with obesity. The presence of uncontrolled chronic obesity-related comorbidities, particularly pulmonary diseases, can present a primary fertile soil for respiratory tract infection. Combined with immune system impairments, such as alteration in the T-cell proliferation and macrophage differentiation, and the high pro-inflammatory cytokine production by the adipose organ, this may worsen the general condition toward a systemic diffusion of infection. Prevention remains the first line of intervention in these patients that can be achieved by adhering to social distancing and adopting hygiene precautions, combined with a healthy lifestyle. Patients with obesity require preferential access dedicated to primary care services to ensure they are regularly taking their medications for the treatment of any concurrent chronic diseases. Finally, their physicians must promptly manage any medical signs or symptoms in the case of suspected severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) infection to prevent the risk of severe outcomes.

**Keywords:** COVID-19, obesity, pandemic, overweight, severe complications, mortality
In this direction, recent studies found that obesity is a condition associated with severe complications and higher mortality in COVID-19 disease.\textsuperscript{5,6} This paper attempts to highlight potential mechanisms behind the greater vulnerability to COVID-19 of individuals with obesity. Moreover, we aim to elucidate if special strategies should be adopted to prevent the infection or to improve the prognosis in this patient population.

THE HEAVY BURDEN OF OBESITY

Obesity is best described as an increase in fat deposition in the adipose tissue.\textsuperscript{7} The World Health Organization (WHO), however, uses BMI to define obesity in adults\textsuperscript{7}; individuals with a BMI $\geq 30$ kg/m\textsuperscript{2} are classified as affected by obesity.\textsuperscript{8} The prevalence of obesity has dramatically increased in the last three decades: it has become one of the most serious health conditions worldwide, to the extent that it is now considered a pandemic.\textsuperscript{8} Moreover, it is widely known that obesity is associated with several medical complications (i.e., high blood pressure, dyslipidemia, insulin resistance, type 2 diabetes mellitus, coronary artery disease, pulmonary diseases, and several cancer types) and psychosocial comorbidities (i.e., depression, eating disorders, impairment of health-related quality of life: HRQoL), and an increased rate of mortality worldwide.\textsuperscript{8}

THE BI-DIRECTIONAL INTERACTION BETWEEN OBESITY AND COVID-19 DISEASES

Even though the underlying mechanisms are still unclear, increasing evidence suggests an association between obesity and infectious diseases.\textsuperscript{9} Several factors have been identified that appear to increase the risk of acquiring infection with worse outcomes, especially pulmonary infections, in people with obesity.\textsuperscript{10} Growing data are now available in the COVID-19 scenario, where obesity seems to increases the risk of hospitalization\textsuperscript{6} and admission to intensive care units (ICU) for COVID-19\textsuperscript{11}, and has been considered as a risk factor for greater severity of the disease and higher mortality.\textsuperscript{5,11} Notably, obesity appears to be the main predictor of severe COVID-19 symptoms in younger people.\textsuperscript{12} In patients under the age of 60, those with obesity had almost double the risk of being admitted to critical care compared to normal-weight patients.\textsuperscript{12} Similarly, data from the H1N1 pandemic, which occurred a decade ago, also offer useful lessons, due the considerable similarity with COVID-19.\textsuperscript{13} In fact, in 2009, more than 50\% of H1N1 cases in adults in California were affected by obesity.\textsuperscript{14} Moreover, obesity was associated with a higher admission rate and a longer stay in ICU\textsuperscript{15}, and eventually with a higher rate of mortality due to the H1N1 infection.\textsuperscript{16} All of these are strong indications of the close association between obesity and poorer outcomes in H1N1.\textsuperscript{17} At that time, several hypotheses were formulated regarding the association between H1N1 and obesity which in our opinion can be extensible to the COVID-19 disease. We briefly mention here the most plausible explanation.

Firstly, the presence of uncontrolled chronic obesity-related comorbidities (e.g., type 2 diabetes, cardiovascular and renal diseases, among others)\textsuperscript{18} makes this population more vulnerable. Especially comorbidities with pulmonary complications may present a primary fertile soil for respiratory tract infection\textsuperscript{10}, such as 1) restrictive lung diseases, 2) lower operating lung volumes, 3) obstructive sleep apnea, 4) increased risk of pulmonary embolism, and 5) dysregulated pulmonary immune response.

Secondly, immune system impairments due to the increased and abnormal fat deposition in individuals with obesity may add insult to injury, facilitating a systemic diffusion of infection\textsuperscript{19,20}, and make the condition difficult to tame or/treat. These include: 1) impaired cross-communication between adipocytes and the immune system, due to dysregulated secretion of adipokines (leptin and adiponectin) affecting the
functionality of several immune cells 2) altered T-cell proliferation and macrophage differentiation (i.e., decreased CD8+ T cells, reduced natural killer [NK] cell activity and antigen presentation of dendritic cells), 3) increased cytokine production (i.e., Interleukin 6; Interferon gamma; Tumor Necrosis Factor alpha). Interestingly, disturbed NK cell function has been proposed as a determinant of the high incidence of H1N1 infections in individuals with obesity.21 Recently, in the same direction, Diao and colleagues from Wuhan reported similar findings in patients with COVID-19; T-cell counts were found to be dramatically reduced, and the surviving T cells appeared to be functionally exhausted.22

Finally, the increased incidence of nosocomial infections in patients with obesity when compared with their normal weight counterparts23, the lack of full knowledge about optimum antimicrobial doses suitable for patients with obesity that fit their body mass24, the poor wound recovery with impaired repair of damaged epithelial surface25, the elevated levels of oxidative stress as well as inflammation26, and the logistic barriers in the management of individuals with obesity during hospitalization, may also lead to difficulties in treating these patients in time, with possible life-threatening consequences.27

CONCLUSION

Individuals with obesity, especially those in the severe obesity classes or those with related comorbidities, are at a higher risk of developing more serious symptoms and complications due to COVID-19. The two conditions may reciprocally and negatively influence each other. Effective strategies that prevent this group of individuals from being infected (i.e., adhering to social distancing and adopting the recommended hand washing and hygiene precautions) undoubtedly form the first line of defense.28 These precautions should be combined with a healthy lifestyle based on healthy eating and appropriate hydration, regular and moderate physical activity, and adequate rest and sleep.28

Weight-management programs (i.e., internet-based self-administered intervention) are of utmost importance.29 They provide an indispensible opportunity to avoid any additional weight gain that may lead to clinical deterioration of obesity and its correlated comorbidities.30 Last but not least, patients with obesity need a preferential access dedicated to primary care services. Polypharmacy is usually an issue for these patients,31 which by itself increases the risk of adverse drug events, drug–drug interactions, and non-adherence to medication.32–34 To keep these comorbidities under control, general practitioners must ensure that these patients are regularly and correctly taking medications for the treatment of chronic conditions such as diabetes, high blood pressure, and dyslipidemia. Careful management of any medical signs or symptoms and prompt intervention in cases of suspected SARS-CoV2 infection is necessary for early diagnosis of COVID-19 to prevent the progression of the disease towards severe outcomes. Such precautions are needed both at home and during hospital care.

CONFLICTS OF INTEREST

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DATA AVAILABILITY STATEMENT

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COMPLIANCE WITH ETHICAL STANDARDS

Not applicable.

REFERENCES

1. Gralinski LE, Menachery VD. Return of the coronavirus: 2019-nCoV. Viruses. 2020;12(2):135. https://doi.org/10.3390/v12020135
2. Park M, Cook AR, Lim JT, Sun Y, Dickens BL. A systematic review of COVID-19 epidemiology based on current evidence. J Clin Med. 2020;9(4):967. https://doi.org/10.3390/jcm9040967
3. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020;323(18):1775–1776. https://doi.org/10.1001/jama.2020.4683
4. Coronavirus Disease 2019. Centres for Disease Control and Prevention (CDC): [cited 2020 May 30]. Available from: https://www.cdc.gov
5. Palaiodimos L, Kokkinidis DG, Li W, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metab Clin Exp. 2020;108:154262. https://doi.org/10.1016/j.metabol.2020.154262
6. Petrilli CM, Jones SA, Yang JJ, et al. Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City. BMJ. 2020;369:m1966. https://doi.org/10.1101/2020.04.08.20057794
7. Apovian CM. Obesity: Definition, comorbidities, causes, and burden. Am J Manag Care. 2016;22(7 Suppl):s176–85.
8. El Ghoch M, Fakhoury R. Challenges and new directions in obesity management: Lifestyle modification programmes, pharmacotherapy and bariatric surgery. J Popul Ther Clin Pharmacol. 2019;26(2):e1–4. https://doi.org/10.15586/jptcp.v26i2.599
9. Huttunen R, Syrjanen J. Obesity and the risk and outcome of infection. Int J Obes (Lond). 2013;37(3):333–40. https://doi.org/10.1038/ijo.2012.62
10. Fernandez C, Manuel A. Obesity, respiratory disease and pulmonary infections. Ann Res Hosp. 2017;1(5):9. https://doi.org/10.21037/arh.2017.08.06
11. 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. https://doi.org/10.1002/oby.22831
12. Lighter J, Phillips M, Hochman S, et al. Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission. Clin Infect Dis. 2020;ciaa415. https://doi.org/10.1093/cid/ciaa415
13. Neumann G, Noda T, Kawaoka Y. Emergence and pandemic potential of swine-origin H1N1 influenza virus. Nature. 2009;459(7249):931–9. https://doi.org/10.1038/nature08157
14. Louie JK, Acosta M, Samuel MC, et al. A novel risk factor for a novel virus: Obesity and 2009 pandemic influenza A (H1N1). Clin Infect Dis. 2011;52(3):301–12. https://doi.org/10.1093/cid/ciq152
15. Diaz E, Rodriguez A, Martin-Loeches I, et al. Impact of obesity in patients infected with 2009 influenza A (H1N1). Chest. 2011;139(2):382–6. https://doi.org/10.1378/chest.10-1160
16. Fezeu L, Julia C, Henegar A, et al. Obesity is associated with higher risk of intensive care unit admission and death in influenza A (H1N1) patients: A systematic review and meta-analysis. Obes Rev. 2011;12(8):653–9. https://doi.org/10.1111/j.1467-789X.2011.00864.x
17. Van Kerkhove MD, Vandemaële KA, Shinde V, et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: A global pooled analysis. PLoS Med. 2011;8(7):e1001053. https://doi.org/10.1371/journal.pmed.1001053
18. Khaothong L, McCowen KC, Blackburn GL. Obesity and its comorbid conditions. Clin Cornerstone. 1999;2(3):17–31. https://doi.org/10.1016/S1098-3597(99)90002-9
19. Francisco V, Pino J, Campos-Cabaleiro V, et al. Obesity, fat mass and immune system: Role for leptin. Front Physiol. 2018;9:640. https://doi.org/10.3389/fphys.2018.00640
20. Bahr I, Spielmann J, Quandt D, Kielstein H. Obesity-associated alterations of natural killer cells and immunosurveillance of cancer. Front Immunol. 2020;11:245. https://doi.org/10.3389/fimmu.2020.00245
21. Nave H, Beutel G, Kielstein JT. Obesity-related immunodeficiency in patients with pandemic influenza H1N1. Lancet Infect Dis. 2011;11(1):14–15. https://doi.org/10.1016/S1473-3099(10)70304-2
22. Diao B, Wang C, Tan Y, et al. Reduction and functional exhaustion of T cells in patients with
coronavirus disease 2019 (COVID-19). Front Immunol. 2020;11:827. https://doi.org/10.3389/fimmu.2020.00827

23. Huttunen R, Karppelin M, Syrjanen J. Obesity and nosocomial infections. J Hosp Infect. 2013;85(1):8–16. https://doi.org/10.1016/j.jhin.2013.06.012

24. Mehuis E, Kayitare E, Vervaet C, Remon JP. Adjustment of dosing of antimicrobial agents for bodyweight in adults. Lancet. 2010;375(9719):983–4. https://doi.org/10.1016/S0140-6736(10)60439-4

25. O’Brien KB, Vogel P, Duan S, et al. Impaired wound healing predisposes obese mice to severe influenza virus infection. J Infect Dis. 2012;205(2):252–61. https://doi.org/10.1093/infdis/jir729

26. Epingeac ME, Gaman MA, Diaconu CC, Gad M, Gaman AM. The evaluation of oxidative stress levels in obesity. Rev Chim. 2019;70(6):2241–4. https://doi.org/10.37358/RC.19.6.7314

27. Miles J, Anderson DP, Engelke M, et al. Barriers to transition of obese patients from hospital to community. Am J Manag Care. 2012;18(6):e234–7.

28. El Ghoch M, Valerio A. Let food be the medicine, but not for coronavirus: Nutrition and food science, telling myths from facts. J Popul Ther Clin Pharmacol. 2020;27(SP1):4. https://doi.org/10.15586/jptcp.v27iSP1.682

29. Banos RM, Mensorio MS, Cebolla A, et al. An internet-based self-administered intervention for promoting healthy habits and weight loss in hypertensive people who are overweight or obese: A randomized controlled trial. BMC Cardiovasc Disord. 2015;15:83. https://doi.org/10.1186/s12872-015-0078-1

30. Johnson WD, Brashear MM, Gupta AK, Rood JC, Ryan DH. Incremental weight loss improves cardiometabolic risk in extremely obese adults. Am J Med. 2011;124(10):931–8. https://doi.org/10.1016/j.amjmed.2011.04.033

31. Assari S, Wisseh C, Bazargan M. Obesity and polypharmacy among African American older adults: Gender as the moderator and multimorbidity as the mediator. Int J Environ Res Public Health. 2019;16:2181. https://doi.org/10.3390/ijerph16122181

32. Ziere G, Dieleman JP, Hofman A, Pols HAP, van der Cammen TJM, Stricker BHC. Polypharmacy and falls in the middle age and elderly population. Br J Clin Pharmacol. 2006;61:218–23. https://doi.org/10.1111/j.1365-2125.2005.02543.x

33. Flaherty JH, Perry HM, Lynchard GS, Morley JE. Polypharmacy and hospitalization among older home care patients. J Gerontol A Biol Sci Med Sci. 2000;55:M554–9. https://doi.org/10.1093/gerona/55.10.M554

34. Dobrică EC, Gâman MA, Cozma MA, Bratu OG, Pantea Stoian A, Diaconu CC. Polypharmacy in type 2 diabetes mellitus: Insights from an internal medicine department. Medicina. 2019;55:436. https://doi.org/10.3390/medicina55080436