CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

Title	Is adipose tissue a reservoir for viral spread, immune activation and cytokine amplification in COVID-19?
Authors	Ryan, Paul MacDaragh;Caplice, Noel M.
Publication date	2020-04-21
Original Citation	Ryan, P. M. and Caplice, N. M. (2020) 'Is adipose tissue a reservoir for viral spread, immune activation and cytokine amplification in COVID-19?', Obesity, 28(7), pp.1191-1194. https://doi.org/10.1002/oby.22843
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1002/oby.22843
Rights	© 2020, the Obesity Society. Published by John Wiley & Sons, Inc. This is the peer reviewed version of the following article: Ryan, P. M. and Caplice, N. M. (2020) 'Is adipose tissue a reservoir for viral spread, immune activation and cytokine amplification in COVID-19?', Obesity, doi: 10.1002/oby.22843, which has been published in final form at https://doi.org/10.1002/oby.22843. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.
Download date	2026-10-30 11:36:01
Item downloaded from	https://hdl.handle.net/10468/9886

UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

DR. PAUL MACDARAGH RYAN (Orcid ID : 0000-0001-7251-6725)

Article type : Review

Is Adipose Tissue a Reservoir for Viral Spread, Immune Activation and Cytokine Amplification in COVID-19

Paul MacDaragh Ryan, Noel M Caplice

Centre for Research in Vascular Biology,
APC Microbiome Ireland,
University College Cork,
Cork University Hospital
Cork, Ireland

Perspective Paper

Accepted Article

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/oby.22843

This article is protected by copyright. All rights reserved

Accepted Article

Address for correspondence:
Prof. Noel M Caplice M.D., Ph.D.
Centre for Research in Vascular Biology,
APC Microbiome Ireland
Cork University Hospital,
University College Cork,
Cork, Ireland
Tel: int + 353 871201487
Email: n.caplice@ucc.ie

Funding: No extramural funding was sought for this manuscript.

Conflict of Interest: Dr. Ryan and Prof. Caplice have nothing to disclose.

This article is protected by copyright. All rights reserved

ABSTRACT

Coronavirus disease 2019 (COVID-19), the worst pandemic in more than a century, has claimed >125,000 lives worldwide to date. Emerging predictors for poor outcome include advanced age, male gender, pre-existing cardiovascular disease and risk factors including hypertension, diabetes and more recently obesity. Herein, we posit new obesity-driven predictors of poor COVID-19 outcome, over and above the more obvious extant risks associated with obesity including cardiometabolic disease and hypoventilation syndrome in intensive care patients. We outline a theoretical mechanistic framework whereby adipose tissue in subjects with obesity may act as a reservoir for more extensive viral spread with increased shedding, immune activation and cytokine amplification. We propose studies to test this reservoir concept with a focus on specific cytokine pathways that might be amplified in subjects with obesity and COVID-19. Finally, we underscore emerging therapeutic strategies that might benefit subsets of patients in which cytokine amplification is excessive and potentially fatal.

Accepted Article

This article is protected by copyright. All rights reserved

Coronavirus disease 2019 (COVID-19) has now infected over 2 million people worldwide, with a death toll of more than 125,000 people. Emerging risk factors for poor outcome in this disease include age, male gender, cardiovascular co-morbidities including hypertension, prior cardiovascular disease, diabetes and more recently obesity (1). The Center for Disease Control and Prevention (CDC, Atlanta, USA) has now reported a 3-fold increase in death in New Orleans compared to New York and speculation has grown as to whether these worrying mortality statistics might in part be attributable to higher levels of morbid obesity (2). In this perspective paper we develop a theoretical framework that describes why subjects with obesity may be at increased risk of poor outcomes compared to non-obese counterparts (3). We propose a mechanism for adverse consequences of virus seeding to adipose tissue (AT) with potential for prolonged viral shedding and extended cytokine activation in a voluminous and richly vascularized organ that is already perturbed in a metabolic and inflammatory sense in human subjects with obesity (4). We present a rationale for testing this concept in COVID-19 patients through prospective studies of subjects with and without obesity with accessible adipose tissue and plasma to determine whether or not an inflammatory and cytokine signature presages a systemic cytokine storm and clinical decline.

Evidence for association of obesity with worse COVID-19 outcome

Obesity was not specifically reported in the initial cohort studies of COVID-19 from Wuhan, China (5) but regional epidemiological data from the USA suggests that at least 25% of patients who die of this disease have obesity, which is similar to reported rates of cardiovascular disease in the same high risk group (21%) (6). More recently, a small retrospective study of 85 subjects with COVID-19 identified obesity as a risk factor for admission to ICU with patients requiring increased medical attention (3). Moreover, in the influenza A subtype H1N1 pandemic, obesity was also strongly associated with a worse disease outcome and death (7). Together these data raise the question of whether there is a mechanistic link between obesity and disease survival, and whether obesity over and above its endocrine or cardiometabolic associations might independently contribute to COVID-19 risk.

Likely mechanisms involved in poor outcomes in subjects with obesity

It is clear that obesity could contribute to both diabetic and cardiovascular risk of COVID-19 and these elements of risk, in addition to more recently thrombosis, have been well described in the scientific literature (8, 9, 10, 11, 12). Moreover, obesity is an independent risk for hypoventilation syndrome in ICU patients (13) and, thus, could contribute to respiratory failure in

This article is protected by copyright. All rights reserved

patients with acute respiratory distress syndrome (ARDS) (14). Here, we propose additional unheralded pathophysiologic aspects of increased AT burden in morbid obesity that may amplify the pro-inflammatory response to extensive viral infection. AT should be viewed as a highly active organ interfacing immune, endocrine and metabolic homeostasis throughout the body (15). In subjects with obesity there is marked dysregulation of myeloid and lymphoid responses within AT with associated dysregulation of cytokine profiles (15). Intrinsically bound to this are endocrine and metabolic derangements including insulin resistance, and adipokine dysregulation with dysfunctional lipid and fatty acid metabolism (16). In highly vascularized adipose tissue, endothelial and smooth muscle cells as well as resident macrophages exhibit additional perturbations in response to an activated renin angiotensin system (RAS) at a local level with attendant depletion and dysfunction of the counter-regulatory angiotensin converting enzyme 2 (ACE2) Mas receptor system (17, 18). This makes AT, particularly in visceral distributions, pro-immunogenic, metabolically active and highly integrated into the cardiovascular system, with the capability to drive acute disease through augmented inflammation at an organ level in the heart, vasculature, pancreas, liver and kidneys (19). This “pre-activation state” of AT in obesity makes this organ a potential target for further immune amplification by external pathogens such as viruses.

Viral spread to AT and potential for activation of resident inflammation and cytokine pathways

Currently there is no evidence for direct SARS-CoV-2 infection of AT, although ACE2 receptor expression represents a basis for viral tropism in several cells within this tissue (20) including adipocytes, smooth muscle cells and endothelial cells (21). Moreover, many AT-resident cells are proven targets for multiple viruses including adipocytes (H1N1, Type A influenza and adenovirus 36 (7, 22, 23)), adipo-stromal cells (Adenovirus 36 (24), CMV (25)), endothelial cells (SARS-CoV (26)), macrophages (influenza A, SARS-CoV, adenovirus36, HIV (26, 27)) and lymphocytes (SARS-CoV, HIV (25, 26)). Although SARS-CoV-2 was detected only at low levels in blood in a small human study (28), we cannot exclude hematogenous spread to AT given very high virus affinity for its target cell receptor. Alternative routes of SARS-CoV-2 spread to AT include local egress of virus, from organs known to be infected, to adjacent visceral fat deposits such as intrathoracic fat (lungs), epicardial fat (heart), peri-renal fat (kidneys) and mesenteric fat (intestines). Finally, shared viral tropism for lung epithelium and adipose tissue has already been shown for H5N1 virus infection (29) and AT significantly prolongs the duration of viral shedding in humans with obesity infected with influenza (22). Were similar tropism of SARS-CoV-2 to occur

This article is protected by copyright. All rights reserved

within AT of COVID-19 subjects with obesity there exists the potential for prolonged viral shedding in this organ with extended activation of local “pre-activated” immune systems and resident cytokine signalling pathways.

Resident myeloid and lymphoid cells are plentiful in AT and obesity is associated with macrophage (30) and lymphocyte dysfunction (31). Expansion of distinct memory T lymphocytes within AT can also activate aberrant immune responses with wider tissue damage on viral challenge (31). A recent report from Wuhan suggests that SARS-CoV-2 induces a dysregulated immune response in severely ill COVID-19 subjects (32), characterised by reduced numbers of circulating memory T lymphocytes, as well as reduced helper / suppressor T cell and T Reg subtypes. It is tempting to speculate whether already dysfunctional immune responses in subjects with obesity may accentuate this SARS-CoV-2 effect on T cell function.

Specific inflammatory cytokine programmes such TNFα, IL1 and IL6 are known to be pre-activated in AT in the context of obesity (33) and, thus, viral infection may similarly amplify the already primed organ cytokine response in AT. The cytokine storm identified in multiple respiratory viral infections including COVID-19 exhibits diverse interferon, interleukin, chemokine, tumor necrosis factor and colony stimulating factor responses which are beyond the scope of this perspective, but comprehensively reviewed elsewhere (34). The intensity of inflammatory lung responses reflect the imbalance between proinflammatory cytokines (such as TNF and Il1β) and their soluble cognate receptors that inhibit cytokine effects in aqueous phase (35). IL10 produced by macrophages and T lymphocytes (Th2 and T regs) acts as a negative regulator of inflammation; whereas IL6 and its soluble receptor enhance activity of IL6 on target cells providing a mechanism for enhancement of TNF and IL-1β activity when these soluble cognate receptor are particularly high (35). Thus, a balance between pro- and anti-inflammatory mechanisms is critical in maintaining lung tissue homeostasis. It is conceivable that if one or more of these regulatory elements were absent or dysfunctional then this may contribute to a cytokine storm in the lung or in other tissues such as AT where aberrant cytokine activation exists. Temporal studies of cytokine dynamics in human “cytokine storm” models show IL6 sustains activation of multiple cytokine pathways for many days post initial immune insult (36). Interestingly, in early COVID-19 studies IL6 was a strong independent predictor of mortality (37). Human AT is a major source of IL6 and its receptor IL6R (38) and, thus, AT may provide a reservoir for IL6 activation and cascade signalling in viral infection (Figure). Viral spread from affected organs to adjacent AT may take days, with subsequent prolonged viral shedding

This article is protected by copyright. All rights reserved

contributing to the delayed cytokine storm and consequences for tissue injury in patients with COVID-19.

Testing AT inflammatory cytokine reservoir concept in COVID-19

Initial studies should aim to detect SARS-CoV-2 in AT upon autopsy of subjects who have died of COVID-19. Focus should be on analysis of specific cells that have evidence of infection by immunocytopathic and in situ viral detection techniques. Parallel studies should identify whether specific cell types in AT can support SARS-CoV-2 infection and replication ex vivo. With respect to cytokine storm, an integrated systems biology approach would enable multiple pathways to be assessed simultaneously. In this regard, cytokine and chemokine genomic data analysis in blood and AT would be an important first step. Moreover a weighted gene correlation network analysis of SARS-CoV-2 mediated transcriptional response in infected cells could also be used as a model for human AT analysis downstream (39). Interesting aspects of transcriptional network analysis could then be tested in appropriate animal models to determine pivotal components of the cytokine storm including key cytokine and chemokine genes that are conserved across species (40). These insights may allow rational diagnostics and therapeutic strategies to be developed. In line with this, IL6 inhibition has already been proposed as a treatment in COVID-19 and the results of trials of Tocilizumab are awaited (41). It would be interesting to examine whether subjects with obesity, who are expected to have higher circulating IL6 levels compared to lean counterparts, respond more favourably to IL6 inhibition strategies in COVID-19 in a post hoc analysis of this RCT. Similarly, tissue and systemic analysis of cytokine dynamics may identify likely responders and non-responders to such therapy.

In summary we present a rationale for studying the relationship between obesity and COVID-19 disease severity. We provide a theoretical framework whereby viral systemic spread, entry and prolonged viral shedding in already “inflamed” AT may augment immune responses with consequences for cytokine cascade amplification. We highlight AT as an abundant source for local and systemic enrichment of cytokines, some already independently associated with increased COVID-19 mortality. Finally we suggest a series of research studies to identify whether a mechanistic link exists between AT, SARS-CoV-2 infection, organ seeding of infection, immune activation and the delayed cytokine storm known to presage rapid clinical decline in high risk COVID-19 patients.

References

This article is protected by copyright. All rights reserved

Accepted Article

1. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. *The New England journal of medicine* 2020.

2. Center for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19) - People Who Need Extra Precautions - People Who Are At Higher Risk: CDC; 2020 [cited 2020 06/04/2020]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html.

3. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A*, et al.* High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity (Silver Spring)* 2020.

4. O'Rourke RW. Inflammation in obesity-related diseases. *Surgery* 2009;**145:** 255-259.

5. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020.

6. Louisiana Department of Health. Louisiana Department of Health COVID-19 Updates for 3/31/2020 2020 [cited 2020 06/04/2020]. Available from: http://ldh.la.gov/index.cfm/newsroom/detail/5522.

7. Tsatsanis C, Margioris AN, Kontoyiannis DP. Association between H1N1 infection severity and obesity-adiponectin as a potential etiologic factor. *J Infect Dis* 2010;**202:** 459-460.

8. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J*, et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020;**e201585**.

This article is protected by copyright. All rights reserved

Accepted Article

9. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX*, et al.* Clinical Characteristics of Coronavirus Disease 2019 in China. *The New England journal of medicine* 2020;**[published online ahead of print]**.

10. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z*, et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet* 2020;**[published online ahead of print]**.

11. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F*, et al.* Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol* 2020.

12. Klok FA, Kruip M, van der Meer N, Arbous MS, Gommers D, Kant KM*, et al.* Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis Research* 2020;**Advance online publication**.

13. Marik PE, Chen C. The clinical characteristics and hospital and post-hospital survival of patients with the obesity hypoventilation syndrome: analysis of a large cohort. *Obes Sci Pract* 2016;**2:** 40-47.

14. Gong MN, Bajwa EK, Thompson BT, Christiani DC. Body mass index is associated with the development of acute respiratory distress syndrome. *Thorax* 2010;**65:** 44-50.

15. Mraz M, Haluzik M. The role of adipose tissue immune cells in obesity and low-grade inflammation. *J Endocrinol* 2014;**222:** R113-127.

16. Trim W, Turner JE, Thompson D. Parallels in Immunometabolic Adipose Tissue Dysfunction with Ageing and Obesity. *Front Immunol* 2018;**9:** 169.

This article is protected by copyright. All rights reserved

Accepted Article

17. Patel VB, Mori J, McLean BA, Basu R, Das SK, Ramprasath T*, et al.* ACE2 Deficiency Worsens Epicardial Adipose Tissue Inflammation and Cardiac Dysfunction in Response to Diet-Induced Obesity. *Diabetes* 2016;**65:** 85-95.

18. Pahlavani M, Kalupahana NS, Ramalingam L, Moustaid-Moussa N. Regulation and Functions of the Renin-Angiotensin System in White and Brown Adipose Tissue. *Compr Physiol* 2017;**7:** 1137-1150.

19. Chait A, den Hartigh LJ. Adipose Tissue Distribution, Inflammation and Its Metabolic Consequences, Including Diabetes and Cardiovascular Disease. *Front Cardiovasc Med* 2020;**7:** 22.

20. Uhlen M, Oksvold P, Fagerberg L, Lundberg E, Jonasson K, Forsberg M*, et al.* Towards a knowledge-based Human Protein Atlas. *Nat Biotechnol* 2010;**28:** 1248-1250.

21. Gupte M, Thatcher SE, Boustany-Kari CM, Shoemaker R, Yiannikouris F, Zhang X*, et al.* Angiotensin converting enzyme 2 contributes to sex differences in the development of obesity hypertension in C57BL/6 mice. *Arterioscler Thromb Vasc Biol* 2012;**32:** 1392-1399.

22. Maier HE, Lopez R, Sanchez N, Ng S, Gresh L, Ojeda S*, et al.* Obesity Increases the Duration of Influenza A Virus Shedding in Adults. *J Infect Dis* 2018;**218:** 1378-1382.

23. Bouwman JJ, Visseren FL, Bouter KP, Diepersloot RJ. Infection-induced inflammatory response of adipocytes in vitro. *Int J Obes (Lond)* 2008;**32:** 892-901.

24. Ponterio E, Cangemi R, Mariani S, Casella G, De Cesare A, Trovato FM*, et al.* Adenovirus 36 DNA in human adipose tissue. *Int J Obes (Lond)* 2015;**39:** 1761-1764.

This article is protected by copyright. All rights reserved

Accepted Article

25. Zwezdaryk KJ, Ferris MB, Strong AL, Morris CA, Bunnell BA, Dhurandhar NV*, et al.* Human cytomegalovirus infection of human adipose-derived stromal/stem cells restricts differentiation along the adipogenic lineage. *Adipocyte* 2016;**5:** 53-64.

26. Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. *The American journal of pathology* 2007;**170:** 1136-1147.

27. Bouwman JJ, Diepersloot RJ, Visseren FL. Intracellular infections enhance interleukin-6 and plasminogen activator inhibitor 1 production by cocultivated human adipocytes and THP-1 monocytes. *Clin Vaccine Immunol* 2009;**16:** 1222-1227.

28. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G*, et al.* Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA* 2020.

29. Nishimura H, Itamura S, Iwasaki T, Kurata T, Tashiro M. Characterization of human influenza A (H5N1) virus infection in mice: neuro-, pneumo- and adipotropic infection. *J Gen Virol* 2000;**81:** 2503-2510.

30. Boutens L, Stienstra R. Adipose tissue macrophages: going off track during obesity. *Diabetologia* 2016;**59:** 879-894.

31. Misumi I, Starmer J, Uchimura T, Beck MA, Magnuson T, Whitmire JK. Obesity Expands a Distinct Population of T Cells in Adipose Tissue and Increases Vulnerability to Infection. *Cell Rep* 2019;**27:** 514-524 e515.

32. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y*, et al.* Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis* 2020.

This article is protected by copyright. All rights reserved

Accepted Article

33. Kern L, Mittenbuhler MJ, Vesting AJ, Ostermann AL, Wunderlich CM, Wunderlich FT. Obesity-Induced TNFalpha and IL-6 Signaling: The Missing Link between Obesity and Inflammation-Driven Liver and Colorectal Cancers. *Cancers (Basel)* 2018;**11**.

34. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. *Microbiol Mol Biol Rev* 2012;**76:** 16-32.

35. Park WY, Goodman RB, Steinberg KP, Ruzinski JT, Radella F, 2nd, Park DR*, et al.* Cytokine balance in the lungs of patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2001;**164:** 1896-1903.

36. Yiu HH, Graham AL, Stengel RF. Dynamics of a cytokine storm. *PLoS One* 2012;**7:** e45027.

37. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020.

38. Sindhu S, Thomas R, Shihab P, Sriraman D, Behbehani K, Ahmad R. Obesity Is a Positive Modulator of IL-6R and IL-6 Expression in the Subcutaneous Adipose Tissue: Significance for Metabolic Inflammation. *PLoS One* 2015;**10:** e0133494.

39. Li C, Bankhead A, 3rd, Eisfeld AJ, Hatta Y, Jeng S, Chang JH*, et al.* Host regulatory network response to infection with highly pathogenic H5N1 avian influenza virus. *J Virol* 2011;**85:** 10955-10967.

40. McDermott JE, Shankaran H, Eisfeld AJ, Belisle SE, Neuman G, Li C*, et al.* Conserved host response to highly pathogenic avian influenza virus infection in human cell culture, mouse and macaque model systems. *BMC Syst Biol* 2011;**5:** 190.

This article is protected by copyright. All rights reserved

41. Chinese Clinical Trial Registry. ChiCTR2000029765 - A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19) 2020 [cited 2020 06/04/2020]. Available from: http://www.chictr.org.cn/showprojen.aspx?proj=49409.

Accepted Article

This article is protected by copyright. All rights reserved

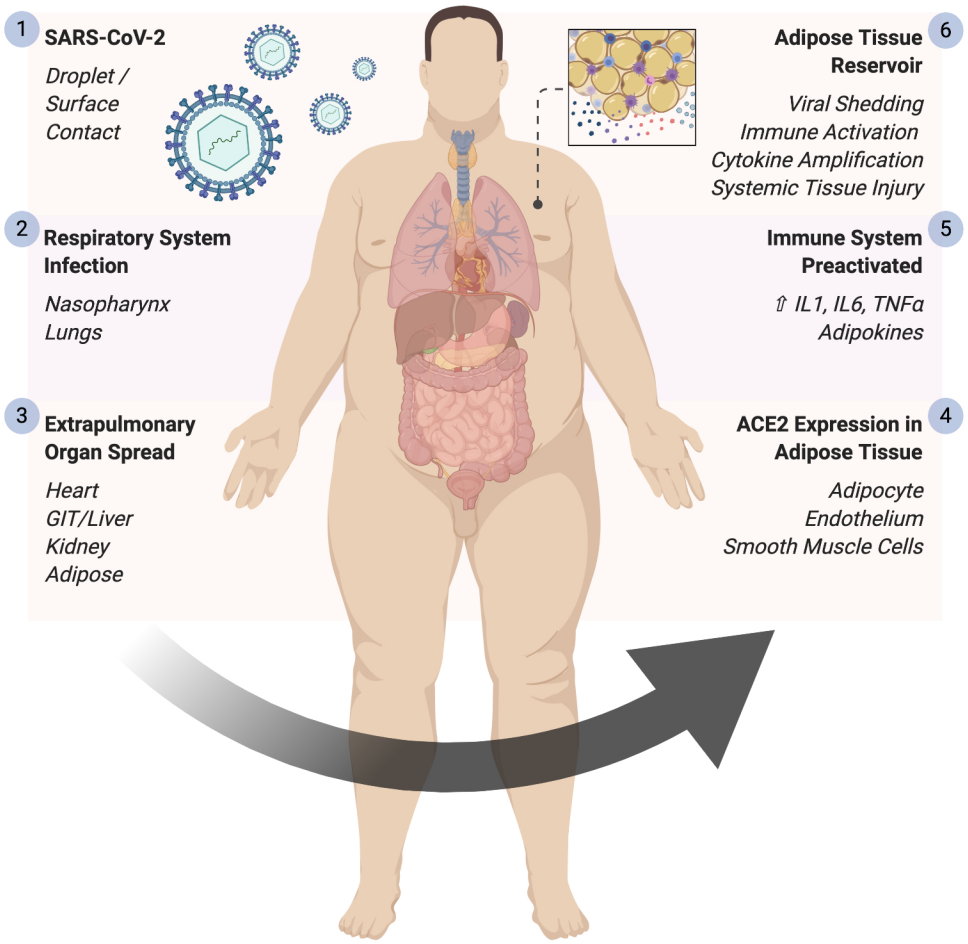
FIGURE LEGEND

Figure. Adipose Tissue as a Reservoir for SARS-CoV-2 Spread, Viral Shedding, Immune Activation and Cytokine Amplification. Schematic demonstrating the proposed centrality of adipose tissue in the dissemination of SARS-CoV-2 and the ensuing systemic immune activation. Created with Biorender.com.

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article



oby_22843_f1.jpeg

This article is protected by copyright. All rights reserved