Immunome Research
ISSN: 1745-7580
OPEN ACCESS Freely available online
Commentary

The Clinical Paradigm of SARS-CoV-2 Interaction with the Endocrine System: Direct Viral Invasion and Indirect Immune-Mediated Dysfunction

Kamyar Asadipooya*

Department of Medicine, Division of Endocrinology, Diabetes, and Metabolism, Barnstable Brown Diabetes and Obesity Center, University of Kentucky, Lexington, KY, USA

DESCRIPTION

The dramatic decline in Coronavirus Disease (COVID-19) mortality globally is indeed a multifactorial achievement driven by several key developments, such as medical advancement (vaccination and various treatment options), improved supportive care and clinical expertise, widespread immunity and resilience, and finally evolution of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) over time. However, the intersection of SARS-CoV-2, chronic illness, and the induction or acceleration of autoimmune diseases remain a challenging issue. For instance, long COVID, a type of post-COVID-19 condition with damage to multiple organs and unexplained symptoms, is due to direct invasion of organs by SARS-CoV-2, a persistent reservoir of SARS-CoV-2 in tissues, immune dysregulation, vascular injury, hypercoagulability, metabolic derangement, and impairments of the neurological, respiratory, and endocrine systems [1-3].

The canonical receptor of SARS-CoV-2 is Angiotensin-Converting Enzyme 2 (ACE2), which interacts with the host proteases, Transmembrane Protease Serine 2 (TMPRSS2) and A Disintegrin and Metalloprotease 17 (ADAM17), to facilitate viral particle attachment and engulfment. The other possible receptor for coronavirus is Dipeptidyl Peptidase 4 (DPP-4) or (T-cell antigen Cluster of Differentiation 26 (CD26)). The extensive tissue distribution of both ACE2 and DPP-4 acts as a systemic gateway, allowing SARS-CoV-2 to trigger multi-organ damage rather than remaining restricted to a localized respiratory infection. SARS-CoV-2 damages organs through a combination of direct viral cytopathic effects, severe localized and systemic inflammation, and widespread vascular complications, such as endothelial dysfunction, thrombosis and hypoxia. In addition, the disruption or downregulation of the major biological control, endocrine and nervous systems, creates a compounding feedback loop where the host loses its baseline capacity to self-regulate or adjust homeostasis. Thyroid dysfunction, diabetes, and transient or permanent effects on adrenal, gonadal, pituitary, and hypothalamic function have been reported following COVID-19. Additionally, electrolyte imbalances and mineral disorders, such as hypocalcemia, can occur and are associated with poorer outcomes. Furthermore, the interaction of SARS-CoV-2 spike protein with ACE2 can not only be used for cell entry but also impair immune function by affecting T and B cells responses. In fact, the immune responses following acute SARS-CoV-2 infection can cause further organ damage or trigger autoimmunity because of antigen similarities or immunological cross-reactivity. These could include autoimmune endocrine disorders such as Hashimoto's thyroiditis, Graves' disease, type 1 diabetes, and Addison's disease [3-7].

Generally, improving the efficacy of preventive and therapeutic approaches against COVID-19 can reduce risks of end-organ damage and long-term complications. The reduction in the efficacy of antiviral medications against SARS-CoV-2 is a complex, multifactorial process involving both host and viral factors. Underlying viral mechanisms include spike mutations, non-spike or other unrecognized mutations, and mechanisms that antagonize host non-coding Ribonucleic Acid (RNAs). Consequently, SARS-CoV-2 can mutate to evade both monoclonal antibodies and antiviral therapies [8,9]. Moreover, reducing viral entry into host cells with strategies that exhibit a low propensity for resistance will attenuate viral replication, tissue damage, and inflammatory responses. Therefore, advancing our understanding of cellular receptors and developing novel methods to interrupt viral entry remain critical frontiers in the long-term management of SARS-CoV-2. By expanding our focus beyond highly mutable viral structures to more stable host-cell targets, researchers can create broader, variant-resistant shields against infection. The major receptor (ACE2) and possible receptor (DPP-4) of SARS-CoV-2 exist in two forms: membrane-bound and soluble. The soluble form is produced through proteolytic cleavage by membrane-bound proteinases like matrix metalloproteinases and kallikrein-related peptidases [8,10-12]. In human body, membrane-bound of ACE2 provides protective roles against organ damage, by acting as the primary counter-regulatory brake on the classic Renin-Angiotensin-Aldosterone System (RAAS) pathway. But the shedding of ACE2 and subsequent increase in soluble ACE2

Correspondence to: Kamyar Asadipooya, Department of Medicine, Division of Endocrinology, Diabetes, and Metabolism, Barnstable Brown Diabetes and Obesity Center, University of Kentucky, Lexington, KY, USA, Email: kas224@uky.edu

Received: 12-Oct-2026, Manuscript No. IMR-26-45524; **Editor assigned:** 14-Oct-2026, PreQC No. IMR-26-45524 (PQ); **Reviewed:** 28-Oct-2026, QC No. IMR-26-45524; **Revised:** 04-Nov-2026, Manuscript No. IMR-26-45524 (R); **Published:** 11-Nov-2026, DOI: 10.35248/1745-7580.26.22.352

Citation: Asadipooya K (2026). The Clinical Paradigm of SARS-CoV-2 Interaction with the Endocrine System: Direct Viral Invasion and Indirect Immune-Mediated Dysfunction. Immunome Res. 22:352

Copyright: © 2026 Asadipooya K. This is an open-access article distributed under the terms of the Creative Commons Attribution License, that permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

facilitates endocytosis and infectivity of SARS-CoV-2 [12,13]. Basically, the increase in ACE2 or DPP-4 shedding and attachment of soluble forms to the viral particles increases SARS-CoV-2 infectivity through the changes in the biophysical properties of the virus (heavier viral particles), cytoskeletal deformation of the cell membrane, and escape of virus form neutralizing antibodies [14,15]. Consistent with this observation, data show that spironolactone and sitagliptin (DPP-4 inhibitor) can improve the outcomes of COVID-19 by reducing hospitalization rates, which is probably due to reducing virus entry and modulating inflammation [8,16]. However, several novel approaches have shown promising results. These include recombinant soluble ACE2 [17] , monoclonal antibodies [18], biomedically engineered recombinant proteins that compete with the SARS-CoV-2 spike protein for ACE2 receptor attachment [19], dual-targeting engineered binding proteins that block viral entry while reducing complement-mediated inflammation [20], oligodeoxynucleotides [21], and nanosponges [22]. Nevertheless, these therapies may need to be personalized based on the specific SARS-CoV-2 variant.

SOURCE OF FUNDING

There is no funding support for this project.

DISCLOSURES

The author has declared that no conflict of interest exists.

REFERENCES

1. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: Major findings, mechanisms and recommendations. Nat Rev Microbiol. 2023;21(3):133-46.
2. Peluso MJ, Deeks SG. Mechanisms of long COVID and the path toward therapeutics. Cell. 2024;187(20):5500-5529.
3. Asadipooya K, Sriramula S. Endocrine complications of covid-19: Diabetes, musculoskeletal, thyroid, pituitary, adrenal, and gonadal disorders. J Endocr Soc. 2026;10(1):bvag219.
4. Moss P. The T cell immune response against SARS-CoV-2. Nat Immunol. 2022;23(2):186-193.
5. Baldari CT, Onnis A, Andreano E, Del Giudice G, Rappuoli R. Emerging roles of SARS-CoV-2 Spike-ACE2 in immune evasion and pathogenesis. Trends Immunol. 2023;44(6):424-434.
6. Lapuente D, Winkler TH, Tenbusch M. B-cell and antibody responses to SARS-CoV-2: Infection, vaccination, and hybrid immunity. Cell Mol Immunol. 2024;21(2):144-58.
7. Adiguzel Y, Bogdanos DP, Shoenfeld Y. Molecular/antigenic mimicry and immunological cross-reactivity explains SARS-CoV-2-induced autoimmunity. Autoimmun Rev. 2025;24(7):103811.
8. Asadipooya K, Asadipooya A, Adatorwovor R. Combination of spironolactone and DPP-4 inhibitors for treatment of SARS-CoV-2 infection: A literature review. Arch Virol. 2024;169(6):122.
9. Chen N, Zhang B, Chen X, Zhang H, Yu Z. Non-coding RNAs: Master regulators in the battle between host antiviral defense and viral replication. Front Immunol. 2026;17:1908472.
10. Röhrborn D, Eckel J, Sell H. Shedding of dipeptidyl peptidase 4 is mediated by metalloproteases and up-regulated by hypoxia in human adipocytes and smooth muscle cells. FEBS Lett. 2014;588(21): 3870-3877.
11. Nargis T, Kumar K, Ghosh AR, Sharma A, Rudra D, Sen D, et al. KLK5 induces shedding of DPP4 from circulatory Th17 cells in type 2 diabetes. Mol Metab. 2017;6(11):1529-39.
12. Guo X, Cao J, Cai JP, Wu J, Huang J, Asthana P, et al. Control of SARS-CoV-2 infection by MT1-MMP-mediated shedding of ACE2. Nat Commun. 2022;13(1):7907.
13. Wang J, Zhao H, An Y. ACE2 shedding and the role in COVID-19. Front Cell Infect Microbiol. 2021;11:789180.
14. Li L, Liu X, Zhou Y, Wang J. On resistance to virus entry into host cells. Biophys J. 2012;102(9):2230-2233.
15. Rotem A, Serohijos AWR, Chang CB, Wolfe JT, Fischer AE, Mehoke TS, et al. Evolution on the biophysical fitness landscape of an RNA virus. Mol Biol Evol. 2018;35(10):2390-400.
16. Davarpanah MA, Adatorwovor R, Mansoori Y, Ramsheh FSR, Parsa A, Hajiani M, et al. Combination of spironolactone and sitagliptin improves clinical outcomes of outpatients with COVID-19: A prospective cohort study. J Endocrinol Invest. 2024;47(1):235-43.
17. Zhang Z, Zeng E, Zhang L, Wang W, Jin Y, Sun J, et al. Potent prophylactic and therapeutic efficacy of recombinant human ACE2-Fc against SARS-CoV-2 infection in vivo. Cell Discov. 2021;7(1):65.
18. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV antibody combination and outcomes in outpatients with covid-19. N Engl J Med. 2021;385(23):e81.
19. Lei C, Qian K, Li T, Zhang S, Fu W, Ding M, et al. Neutralization of SARS-CoV-2 spike pseudotyped virus by recombinant ACE2-Ig. Nat Commun. 2020;11(1):2070.
20. Pu F, Guo Y, Pan X, Liu X, Yang F. Dual-targeting engineered binding proteins block SARS-CoV-2 infection and complement activation. Antiviral Res. 2026;254:106515.
21. Acuña JA, Gabriel B, Ayyanathan K, Miller J, Li Y, Whig K, et al. DNA oligonucleotides block viral entry of SARS-CoV-2 omicron variants. PLoS Pathog. 2026;22(7):e1014461.
22. Chen Z, He Z, Guo H, Shi M, Liang R, Liu L, et al. Intelligent programmable membrane nanosponge for early virus blocking. Adv Sci (Weinh). 2026:e77592.