COVID-19 endocrinopathy with hindsight from SARS

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Abstract

The current COVID-19 pandemic is probably the worst the world has ever faced since the start of the new millennium. Although the respiratory system is the most prominent target of SARS-CoV-2 (the contagion of COVID-19), extrapulmonary involvement are emerging as important contributors of its morbidity and lethality. This article summarizes the impact of SARS-CoV and SARS-CoV-2 on the endocrine system to facilitate our understanding of the nature of coronavirus-associated endocrinopathy. Although new data are rapidly accumulating on this novel infection, many of the endocrine manifestations of COVID-19 remain incompletely elucidated. We, hereby, summarize various endocrine dysfunctions including coronavirus-induced new onset diabetes mellitus, hypocortisolism, thyroid hormone, and reproductive system aberrations so that clinicians armed with such insights can potentially benefit patients with COVID-19 at the bedside.

COVID-19; endocrine system; SARS; SARS-CoV-2; virus

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly transmissible and pathogenic novel coronavirus that emerged in late 2019 and has caused a pandemic of acute respiratory disease, named “coronavirus disease 2019” (COVID-19), which threatens human health and public safety. At this time of writing, the total confirmed cases are approaching 60 million round the world, with total number of reported deaths well exceeding a million (1). The contagion of COVID-19 has been named “severe acute respiratory syndrome coronavirus subtype 2” or “SARS-CoV-2”, not only because it assaults predominantly the respiratory system reminiscent of SARS and the Middle East respiratory syndrome (MERS), but also because genomic analysis revealed all three positive-sense, single-stranded RNA viruses to belong under the same genus, Betacoronavirus (2). From a phylogenetic perspective, SARS-CoV-2 and SARS-CoV are both of the same clade (3). Hence, the biology and clinical aspects of SARS can inform and serve as useful yardsticks for predicting and extrapolating the behavior of COVID-19.

Despite its name, there is cogent evidence that SARS-CoV has extrapulmonary manifestations (4). During the SARS outbreak in 2003, many patients suffered sequelae in the gastrointestinal tract (5), the cardiovascular system (6), the coagulation system (7), the immune system (8), the nervous system (9), and even the endocrine system (10). Indeed, it is very likely that systemic viremia and an over-reactive immune response contributed to the pathogenesis of the lesions in key endocrine glands (Fig. 1). In the same vein, there is wisdom of hindsight distilled from historical parallels in guiding the manner we tackle this ongoing crisis. By contrast, MERS, while exacting a higher fatality rate compared with SARS and COVID-19, had not been associated with overt endocrine sequelae; despite the broad tissue distribution of dipeptidyl peptidase-4 (DPP4) receptors which serves as the portal of cell entry for MERS-CoV, this coronavirus has not been detected in any endocrine tissues in an autopsy study correlating clinicopathologic, immunohistochemical, ultrastructural, and molecular findings (11). Combining our experience combating both SARS and COVID-19 at the forefront with updated literature, we present this timely article devoted to features of SARS-induced endocrinopathy to better

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understand and predict COVID-19 effects on target organs of the endocrine system.

**RELEVANT CORONAVIRUS STRUCTURAL AND MOLECULAR BIOLOGY**

Coronavirus virion particles are spheroidal with dimensions ~80–120 nm across, and possess morphologically characteristic clubbed-shaped peplomers otherwise termed “S” spike glycoproteins extending 17–20 nm outward from the lipid bilayer surface envelope reminiscent of a “crown” on electron microscopy and atomic force microscopy (12–14) (Fig. 2A). To aid further understanding of the predilection of SARS-CoV and SARS-CoV-2 for the human host, it is necessary to appreciate the structural details of the S spike glycoprotein. Each S protein comprises three monomers fused as a trimer to form the spike (15). The molecularly divergent distal “bulb” amino-terminal half portion is the S1 fragment critical for binding to host cell surface receptors (16) whereas the highly conserved “stalk-like” carboxy-terminal half portion is the S2 fragment of the spike protein that has both an ectodomain and a transmembrane domain responsible for fusion to the host cell membrane (17) (Fig. 2B). Cathepsins are involved in the cleavage of S into S1 and S2 subunits to expose S2 for fusion to cell membrane via host proteases (18). This process is accomplished by the synergistic activity of cathepsins along with other host proteases, cell surface transmembrane protease serine (TMPRSS) proteases, furin, trypsin, and factor Xa, following which the internalized virus undergoes replication within the infected host cell and finally exits the cell via a lysosomal-based exocytosis pathway to complete its life cycle (Fig. 2C). The lipid bilayer multi-spanning M glycoprotein through which the S spike protein structure is inserted and anchored represents the largest constituent of the virion. The coronavirus M protein is interestingly the first polytopic viral membrane ever to be described in the virology field (19), and its glycosylation status plays a role in organ tropism (20) and possesses a capacity of alpha-interferon induction (21). The E protein of SARS-CoV is an integral membrane protein whereas the N protein is a phosphoprotein that binds to viral RNA in a helical nucleocapsid conformation and enhances replication efficiency (22).

**CELL INVASION GATEWAYS FOR COVID-19 AND SIMILARITIES TO SARS**

**Angiotensin-Converting Enzyme-2**

Coronaviruses exploit host cell membrane protein receptors to gain entry into the interior of the cell. The most well-described gateway for both SARS-CoV and SARS-CoV-2 is angiotensin-converting enzyme-2 (ACE2). ACE2 is a type I transmembrane zinc-dependent monokarboxyptidase with homology to ACE, a key player in the renin-angiotensin-aldosterone system (RAAS) and a target for the treatment of hypertension because it cleaves angiotensin-II into angiotensin-(1–7) which binds Mas-receptors to negatively regulate the RAAS (23). Unlike MERS-CoV, which engages surface dipeptidylpeptidase-subtype 4 (DPP4) and sialoside attachment receptors for host cell entry (24),

![Figure 1. The endocrine system as a target of betacoronaviruses (e.g., severe acute respiratory syndrome coronavirus, SARS-CoV).](image-url)
SARS-CoV and SARS-CoV-2 seek out ACE2 as receptors for cell invasion (25). ACE2 is abundantly expressed in human kidneys, adrenals, adipose tissues, thyroid, endothelium, pancreas, testis, ovary, and pituitary (26, 27). ACE2 possesses highly similar binding motifs for the S protein indispensable for SARS-CoV and SARS-CoV-2 invasion (25, 28, 29).

ACE2 interaction with the spike protein was first made available for SARS-CoV shortly after the 2002–2004 SARS outbreak, and had since been steadily built up for more than a decade, before being accumulated explosively in response to the 2019 SARS-CoV-2 pandemic (25, 29–34). Such information details both similarities and differences between SARS-CoV and SARS-CoV-2 in their receptor binding (29, 31). These two viruses both utilize their receptor-binding domains (RBDs), residing at the C-terminal half of the S1 fragment to bind ACE2 with nanomolar affinities; the binding sites on ACE2, located at the N-terminal peptidase domain, are nearly identical. Major differences lie within the two viruses’ respective 70 residue-long receptor-binding motifs (RBMs), which are extended insertions grafted onto the core of RBD, sharing ~50% sequence identity and adopting different conformations upon ACE2 binding (Fig. 2, A and B). Consequently, the viruses’ ACE2 binding affinities are folds apart (20–30 folds), with SARS-CoV-2 being the tighter binder (25, 31, 32, 35–37), which corroborates with the drastically higher transmissibility of SARS-CoV-2 (38).
SARS-CoV and MERS-CoV as examples, moderate changes in their RBM sequences have led to zero cross-reactivity against the receptor for the other (39).

Transmembrane Protease Serine-2

TMPRSS2 facilitates cellular entry of SAR-CoV and SARS-CoV-2 into the host. TMPRSS2 is an androgen-regulated gene (40, 41) involved in the priming of the viral spike protein. This process is critical for virulence as it diminishes viral recognition by neutralizing antibodies and also helps in activating SARS-CoV-2 for virus cell fusion. That the activated androgen receptor regulates the transcriptional activity of the TMPRSS2 gene could partly explain the differential susceptibility of males for COVID-19 (42, 43). TMPRSS2 works synergistically along with “a disintegrin and metalloproteinase domain-containing protein-17” (ADAM17) required for the shedding of ACE2 (44). It has been shown that single nucleotide polymorphisms (SNPs) in TMPRSS2 might influence SARS-CoV-2 entry into the cell (45). Some newly reported target sites of COVID-19 mediated by TMPRSS2 are hepatobiliary and pancreatic tissues (46), which deserves further mention below.

Neuropilin-1

Neuropilin-1 (NRPI), a highly conserved type 1 transmembrane protein, plays important roles in the development of the nervous and cardiovascular system as well as in tumorigenesis through interaction with its established binding partners, such as vascular endothelial growth factor (VEGF) and semaphorin 3A (Sema3A). Cell entry of SARS-CoV-2 depends on priming by host cell proteases (47, 48). There is limited knowledge about the virus-host interactions that determine cellular entry of SARS-CoV-2. Viruses display considerable redundancy and flexibility because they can exploit weak multivalent interactions to enhance affinity. Although the focus to date has been almost entirely on the role of ACE2 in SARS-CoV-2 entry, the expression pattern of ACE2 does not match tissue tropism of SARS-CoV-2 (49). This raises the possibility that cofactors are required to facilitate virus-host cell interactions in cells with low ACE2 expression. In the case of SARS, the C-type lectin receptor CD209L (L-SIGN) was found to serve as an alternative gateway for the cellular entry of SARS-CoV by tethering to the

Figure 3. Angiotensin-converting enzyme-2 (ACE2) binding by the receptor-binding domains (RBDs) of severe acute respiratory syndrome coronavirus (SARS-CoV) (A) (PDB ID: 2AJF) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (B) (PDB ID: 6M0J). The RBD cores are in green, whereas the receptor-binding motifs (RBMs) are highlighted in gold. Major conformational differences between the RBDs are circled with dashed lines. In (C) the interaction between the C-terminus of SARS-CoV-2 S1 (residues 679–685, NSPRRAR, yellow sticks) and human transmembrane receptor Neuropilin-1 (electrostatic surface), based on recently published complex structure (PDB ID: 7JJC) (51) is illustrated. These figures are generated using PyMOL (36), with the APBS plugin for electrostatic surface calculations (35).
mannose glycans of the S-protein (50). Recently, by applying site-directed mutagenesis and monoclonal antibodies, it was shown that NRPI could represent such an ACE2 potentiating factor (51); the high expression of NRPI on epithelial cells strategizes it as an entry receptor (52). Reports demonstrated that the SARS-CoV-2 S protein binds to the βb2 ectodomain of the NRPI (Fig. 3C). The subsequent entry of SARS-CoV-2 into cells is facilitated by a polybasic amino acid sequence (68) termed the “C-end rule” (CendR) motif within NRPI (53). Corroborating evidence for its putative role as an entry receptor is its upregulation in COVID-19 biological samples versus healthy controls as shown by “omic” analyses (53). That SARS-CoV-2 shows a much greater infectivity relative to SARS-CoV is probably explained in part by NRPI binding to the CendR peptide in S1. Such a discovery meant that novel therapeutic approaches that target this mechanism could be developed. From the Human Protein Atlas, we find medium expression of NRPI in the parathyroids, adrenals, and testis, and low expression of NRPI in the thyroid. As VEGF is a natural endogenous ligand of NRPI, it is also possible that the pituitary could well be a target of SARS-CoV-2 since VEGF receptors are also present in the pituitary gland (54).

**CLINICO-PATHOLOGICAL SPECTRUM OF SARS AND COVID-19 ENDOCRINOPATHY**

**Hypothalamus-Pituitary-Adrenal Axis**

The lack of detailed postmortem studies contributed to the paucity of knowledge surrounding the pathogenesis of endocrinopathy associated with SARS and COVID-19. There is only a dearth of reports of involvement of the hypothalamus and pituitary by SARS (55, 56). Using light microscopy, electron microscopy, and real-time reverse transcription-polymerase chain reaction (RT-PCR), autopsy series previously confirmed SARS-CoV genome sequences associated with cytopathic effects in neuronal cytoplasm of the hypothalamus. Clinical observation of an impaired adrenocorticotropic hormone (ACTH) and TSH response to hypocortisolism and hypothyroidism, respectively, implied that the hypothalamus-pituitary-adrenal (HPA) axis was probably involved either directly by SARS-CoV or indirectly due to hypophysitis caused by autoimmunity triggered by the virus (55). Little has been documented on the hypothalamic-pituitary effects of COVID-19, though a French group has recently confirmed from autopsy findings that the hypothalamus is a highly probable target of SARS-CoV-2 based on its rich expression of ACE2 and TMPRSS2, especially in the paraventricular nucleus (57). CT and MRI imaging have also revealed evidence of COVID-19 infecting the brain with serious consequences (58). A Chinese group successfully detected the presence of SARS-CoV-2 genome in the cerebrospinal fluid in a patient with COVID-19, thereby confirming that SARS-CoV-2 does indeed infiltrate into the brain, and thence can involve any part of the brain, including the hypothalamus and pituitary (59). Although HPA axis compromised with hypocortisolism can contribute to mortality in SARS and COVID-19, an overly excessive endogenous cortisol response itself poses a cave, lest high cortisol be misinterpreted to portend a better prognosis. A group has shown via Cox proportional hazards regression analysis that cortisol stress responses were predictive of death. Kaplan–Meier survival analysis revealed a sharp dichotomy in death probability, with significantly better median survival for serum cortisol lower than 744 nmol/L during acute COVID-19 infection, a scenario correlative of illness severity. This should not be misconstrued as justification to avoid prescribing exogenous steroids when there are overwhelming life-saving indications as discussed in the next section (60). Several recent publications have also confirmed that the adrenals are a frequent site of COVID-19 related lesions in the body based on radiological and autopsy evidence (61–64).

**Hypothalamus-Pituitary-Thyroid Axis**

The thyroid is another endocrine gland reportedly disordered in SARS previously (56, 65) and now in COVID-19 (66). In 2004, a group from Guangzhou in China produced postmortem evidence of cytopathic effects of SARS-CoV on endocrine organs including the thyroid, parathyroid, pancreas, and adrenals using a combination of RT-PCR, immunohistochemistry, in situ hybridization, and transmission electron microscopy (67). Among those who deceased from SARS, the thyroids showed destruction of the follicular epithelium with extensive exfoliation of apoptotic cells into the follicular lumen. Thyroid follicular damage was occasionally very severe, associated with complete loss of parafollicular C-cells as shown by total absence of calcitonin immunostaining. This explains why serum T3 and T4 were decreased in 94% and 46%, respectively, in a group of patients with SARS during the acute phase of the disease, followed by persistence of low-serum T3 and T4 in 90% and 38% among convalescent cases (68). Autopsies of patients with SARS showed marked destruction of the follicular and parafollicular cells of the thyroid (65).

The ongoing COVID-19 pandemic yields interesting and important insights on SARS-CoV-2 and thyroid pathology. The available data suggest that the disease spectrum can range from direct viral destructive effects to immune-mediated mechanisms on the thyroid precipitated by COVID-19 (69–72). Leow et al. (56) showed previously that SARS-CoV could inflict pituitary lesions either directly or indirectly and contribute to secondary thyroid and adrenal insufficiency, which could be treated using levothyroxine and hydrocortisone replacement (56). It appears that the SARS-induced thyroid aberrations were largely transient and fully resolved after several months. Current published data indicate a similar pathophysiological phenomenon associated with COVID-19. Mounting evidence points to the fact that COVID-19 might have a greater impact on the hypothalamus-pituitary-thyroid axis than previously suspected. This is particularly so following the discovery of ACE-2 mRNA in thyroid cells (73). ACE-2 mRNA in thyroid follicular cells was confirmed by analyzing primary cultures of thyroid cells, where the expression is similar to those found in tissues. The finding accounts for the recently described COVID-19-related subacute thyroiditis or De Quervain’s thyroiditis that is often thought to have a viral origin (73); it can present with thyrotoxicosis before a hypothyroid phase sets in weeks to months later (74). Hence, subacute thyroiditis is now considered to be a sequela closely associated with COVID-19 (75). Other
reports also indicate autoimmune thyroiditis may develop after the “cytokine storm” induced by SARS-CoV-2 infection which could result in the development of primary hypothyroidism. Common thyroid manifestations of COVID-19 thus include overt thyrotoxicosis, Graves’ orbitopathy, and hypothyroidism. Graci et al. (76) in a recent report has even suggested that COVID-19 could be considered as an endocrine disorder, to make sense of the nonspecific response of the immune system to the SARS-CoV-2 virus, which is far different from infections such as influenza (77).

**Reproductive Axis**

Next, on the list of endocrine gland targets of the coronavirus is the testis which has been established to express ACE2 and NRPI copiously (78). In addition, the MAS receptor is present on the acrosome and tail of human spermatozoa and plays a role in the acrosome reaction and the maintenance of sperm motility, thereby underscoring the role of ACE2 in sperm biology (79). The release of TMPRSS2 in prostasomes secreted into semen from the prostate during ejaculation together with ACE2 present on the sperm plasma membrane would thus allow SARS-CoV-2 to infect sperm cells (80). With respect to coronavirus invasion of the testis, there were men with symptoms consistent with acute orchitis in some male cases of SARS (81). Similarly, at least one case of orchitis has been reported in a young man with COVID-19 (82). Postmortem examination of men who succumbed to COVID-19 interestingly also revealed seminiferous tubular injury, vacuolation of Sertoli cells, reduced Leydig cells, and lymphocytic infiltrates in 11 of 12 deceased males, of whom one had demonstrable SARS-CoV-2 by RT-PCR within testicular tissues (83). How SARS-CoV-2 might inhibit sperm motility, permanently damage the testis, and negatively influence fertility remains undetermined. A subsequent study confirmed the frequent presence of SARS-CoV-2 in semen of men with acute COVID-19 as well as those convalescing from it (84). This finding, together with the significantly high rates of COVID-19 infection between sex partners, implies the possibility of a sexual route of transmission, though there is no current strong evidence supporting such a route of transmission as one of clinical concern as yet (85). In females, ACE2 is expressed in the ovary, uterus, placenta, vagina, and breast tissues. ACE2 is present in ovarian stroma, granulosa cells, and oocytes (86), and ACE2 mRNA has been shown to be detectable in the ovaries of premenopausal and postmenopausal women (87). Unlike males, TMPRSS2 appears to be absent in human oocytes which means that infection of the female germline by SARS-CoV-2 is rather improbable except in the situation where the ovum is fertilized by an infected spermatozoon. Despite such theoretical concerns, there have not been any published reports of teratogenic effects and embryopathy directly attributable to SARS-CoV-2 as yet in contrast to Zika virus infection (88).

**Endocrine Pancreatic Islets**

More recently, de novo onset of severe diabetes mellitus and diabetic ketoacidosis among patients with COVID-19 who were formerly healthy and nondiabetic stoked fears of permanent beta cell damage from a single episode of COVID-19 (89). This is not unfounded given the high expression of ACE2 in the pancreatic islets, and previous encounters of new-onset diabetes as a sequela of SARS (90). Importantly, the downregulation of ACE2 by SARS-CoV-2 can lead to unopposed angiotensin-II activity on AT-1 receptors that suppresses insulin secretion (91). In addition, because it was reported a decade ago that an abnormal allele of NRPI in pancreatic beta cells led to type 1 diabetes, this could imply that the binding of the S protein of SARS-CoV-2 to NRPI in pancreatic islets might potentially cripple the insulin secretory pathway and trigger insulin-dependent diabetes or even overt diabetic ketoacidosis (92). A global CoviDiab registry has just been initiated to examine beta cell injury and insulinopenia in those without pre-existing diabetes in whom SARS-CoV-2 is the only etiologic factor (93). These data suggest the importance of proactive monitoring for such endocrine dysfunction among COVID-19 patients (10).

**Clinical Course of COVID-19 Among Patients with Pre-existing Endocrine Issues**

Available reports indicate that individuals with pre-existing endocrine disorders are at higher risk of suffering greater disease severity during COVID-19. Interestingly though, patients with pre-existing hypothyroidism and receiving thyroid hormone therapy were not found to be associated with an increased risk of hospitalization (94). However, patients with other endocrine conditions such as hypocortisolism and diabetes mellitus appeared to have poorer prognosis. Risk factors for hospital admission among patients with COVID-19 with diabetes include older age, higher HbA1c level, hypertension, cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, malignancy, chronic kidney disease (CKD 3A, 3B, 4), and insulin-treated patients were more likely to require hospital admission (95).

Contributory causes included addisonian crisis and impaired immunity (96), which makes these patients more vulnerable to SARS-CoV-2 infection (97). Serum biomarkers (IL-6, serum ferritin, CRP) and D-dimers are also higher in patients with SARS-CoV-2 with underlying diabetes (98). Although clinicians might be deterred from prescribing corticosteroids in accordance with earlier conservative treatment guidelines for COVID-19 (99), glucocorticoids should be instituted in those with features of hypocortisolism on a case-by-case basis, especially since addisonian crisis can be equally life threatening if missed or untreated (100). Intriguingly, emerging promising data from an ongoing clinical trial, randomized Evaluation of COVID-19 Therapy, otherwise codenamed RECOVERY (ClinicalTrials.gov Id: NCT04381936) showed that low-dose dexamethasone is a life-saving drug and reduced deaths by 20% for patients with COVID-19 requiring oxygen, and even lowered the risk of death for those on mechanical ventilation by ~30% which is very impressive. Although speculative, low-dose dexamethasone for patients with severe COVID-19 worldwide can thus be lifesaving if prescribed at the right timing during the disease course (101). An expected corollary of dexamethasone might be aversion of collateral damage to endocrine
glands via suppression of a cytokine-driven hyperinflammatory response during the course of COVID-19 infection.

Among pre-existing endocrine issues, diabetes mellitus probably tops the list, simply because diabetes itself is a worldwide pandemic and it confers an increased mortality in the face of COVID-19 (102). It has been found that SARS-CoV-2 virus is more prevalent and severe in people with diabetes. A recent case-control study demonstrated the virus infection could lead to significant insulin resistance, dehydration, and acute kidney injury. In rare cases, patients could also develop diabetic ketoacidosis (103). Hyperglycemia predisposes to bacterial and viral pathogens such as tuberculosis and influenza (104), since hyperglycemia could trigger the hyper-virulence of certain pathogens (105). In addition, glycemic control tends to be worse among diabetic patients treated with corticosteroids and lopinavir/ritonavir, which can result in cytokine-induced insulin resistance as well as hypokalemia, which can impair insulin secretion itself. Evidence also suggests a heightened tendency of ketoadiposis among patients with COVID-19 with pre-existing diabetes (93, 106).

Related to diabetes mellitus is obesity, in which a recent study revealed that obesity is correlated to higher odds of mechanical ventilation and in-hospital mortality after multivariable adjustment on analyzed data from patients with COVID-19 at 88 hospitals enrolled in the American Heart Association’s COVID-19 Cardiovascular Disease Registry (107). Notably, among patients ≤50 yr of age, BMI ≥40 kg/m² was linked to a profoundly elevated risk of death or mechanical ventilation (OR, 1.64 [95% CI, 1.23–2.11]), moderately increased odds in those aged 51–70 (OR, 1.40 [1.10–1.80]), but no significant increase in risk among patients >70 yr old (OR, 1.28 [0.83–1.95]). Venous thromboembolism and dialysis were also linked to higher BMI, all of which suggest that the generally lower probability of morbidity and mortality in younger people with COVID-19 may not necessarily apply to those with obesity.

The mechanisms of how increased adiposity complicates the clinical course of COVID-19 remain to be elucidated, but is likely to be multifactorial and related to the impact of excess fat on metabolism, immune response, and vascular function. Whether direct viral infection of adipocytes plays a mechanistic role in COVID-19 severity among obese people is open to question. In this regard, it is remarkable that adipose tissues show the highest level of NR1P1 mRNA transcripts among all the organs of the human body examined, as shown by a mean protein-coding transcripts per million (pTPM) of 101 in the Genotype-Tissue (GTEx) RNA-seq database and 388.6 Scaled Tags per Million in another public data set, the Functional Annotation of Mammalian Genomes 5 (FANTOM5) Cap Analysis of Gene Expression (CAGE).

Correspondingly, a previous study on rats also demonstrated the expression of NR1P1 on the surface membranes of adipocytes and parenchymal nerves found within adipose tissues (108, 109). Adipose tissues also rank among the top ten tissues with the highest abundance of ACE2 mRNA based on a pTPM of 8.8 in GTEx and an estimated 5.6 scaled tags per million in FANTOM5 CAGE (110). Consistent with this is the finding of ACE2 protein expression in adipocytes (111) as well as TMPRSS2 within adipose tissues (112). There is thus biological plausibility for higher host susceptibility to more severe COVID-19 among those with greater adiposity relative to those who are lean.

As this COVID-19 pandemic evolves, an increasing number of infected patients are observed to be afflicted with a range of different endocrine disorders worldwide. Thus, collaborations between experts from different countries are crucial as the collective wisdom and best practices shared across geographical boundaries can help tackle this pandemic better, such as illustrated by a recent survey of clinical endocrinologists (113). This raises the following important research questions that demand further investigations:

- Does SARS-CoV-2 invade the hypothalamus directly and induce endocrine dysfunction, given the fact that other coronaviruses have been proven to exhibit neurotropism through their invasion into the central nervous system, and that human pluripotent stem cell-derived dopaminergic neurons can be infected by SARS-CoV-2 in vitro (114)?
- Is SARS-CoV-2 capable of migrating in a retrograde fashion along the olfactory pathway and spread trans-synaptically into the hypothalamus, as this is one established route of entry into the central nervous system exploited by other coronaviruses (115), and especially because anosmia is a very common feature of those infected by the SARS-CoV-2 virus?
- Are the parathyroid glands also susceptible to SARS-CoV-2, and if so, would hypocalcemia be a potential complication in certain cases of COVID-19?
- Do adipose tissue depots serve as a reservoir for the coronavirus among asymptomatic carriers with obesity, and whether SARS-CoV-2 undergoes a lytic or lysogenic cycle if it infects white adipocytes?
- Are there any drugs or biologics approved for the treatment of endocrine and metabolic diseases potentially able to be repurposed as antiviral agents against SARS-CoV-2?

It is imperative to address such questions with scientific rigor and unravel the molecular mechanisms, especially since this pandemic is still very rampant in many countries and reports of an increasing range of endocrinological aberrations associated with COVID-19 continue to be added to the current literature. Greater clarity of COVID-19-induced endocrinopathies will expectedly aid diagnostic pathways, therapeutic decisions, and drive clinical management with ultimate benefit to patients suffering from this viral assault.

**CONCLUSIONS**

Although COVID-19 is very widespread, much of its endocrine manifestations are still far from being fully elucidated. Knowledge of SARS-associated endocrinopathy forms a basis for better understanding COVID-19 endocrinopathy. Meanwhile, scholarly contributions on endocrine issues in COVID-19 should be facilitated, while peer-reviewed journals might consider publishing more worthy papers that add useful insights to the scarce literature in this emerging field. Physicians, endocrinologists, and even patients with different types of endocrine conditions can get more up-to-date information regarding the endocrine manifestations of COVID-19 or the effects of COVID-19 on any pre-existing
endocrine disorders from the various national, regional, and international endocrine societies and thyroid associations.

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No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

N. Kothandaraman, N. Karnani, and M.K.S.L. conceived and designed research; N. Kothandaraman and M.K.S.L. analyzed data; N. Kothandaraman, A.R., and M.K.S.L. interpreted results of designed research; N. Kothandaraman and M.K.S.L. edited and revised manuscript; S.S.V., N. Karnani, and M.K.S.L. drafted manuscript; N. Kothandaraman, A.R., B.X., W.S.Y., S.S.V., N. Karnani, and M.K.S.L. analyzed data; N. Kothandaraman, A.R., B.X., W.S.Y., S.S.V., N. Karnani, and M.K.S.L. interpreted results of designed research; N. Kothandaraman and M.K.S.L. edited and revised manuscript; N. Kothandaraman, A.R., B.X., W.S.Y., S.S.V., N. Karnani, and M.K.S.L. approved final version of manuscript.

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