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Endocrine Disorders and COVID-19

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Abstract

The multifaceted interaction between coronavirus disease 2019 (COVID-19) and the endocrine system has been a major area of scientific research over the past two years. While common endocrine/metabolic disorders such as obesity and diabetes have been recognized among significant risk factors for COVID-19 severity, several endocrine organs were identified to be targeted by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). New-onset endocrine disorders related to COVID-19 were reported while long-term effects, if any, are yet to be determined. Meanwhile, the "stay home" measures during the pandemic caused interruption in the care of patients with pre-existing endocrine disorders and may have impeded the diagnosis and treatment of new ones. This review aims to outline this complex interaction between COVID-19 and endocrine disorders by synthesizing the current scientific knowledge obtained from clinical and pathophysiological studies, and to emphasize considerations for future research.

INTRODUCTION

The ongoing pandemic of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has claimed more than six million lives globally. Over the last two years, substantial research has sought to identify mechanisms of viral entry [angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease/serine subfamily 2 (TMPRSS2) for "priming" of the spike protein] and viral spreading. They have also described pathological effects of the virus in various tissues and organs, host immune responses, markers and characteristics of poor prognosis, and certain risk factors linked to adverse outcomes (1).

Endocrine disorders including obesity and diabetes have been among the risk factors for severe COVID-19 (2–6), and endocrine organs such as pancreas, adrenal glands, and testes have been identified as potential targets for SARS-CoV-2 (7, 8). New-onset endocrine disorders related to COVID-19 have also been reported (9–11), and the issue of whether hormonal dysfunctions will be among the long-term effects of the disease is to be clarified (12, 13). In addition, disruptions in health care during the pandemic may have led to delays in the care and possibly diagnosis of endocrine disorders (14). All these issues may constitute a significant burden for both patients and physicians in the upcoming years.

The main focus of this review is what is known and remains to be learned about COVID-19's prognosis in patients with pre-existing endocrine and metabolic disorders, whether COVID-19 aggravates these disorders, and whether patient care should differ from usual during SARS-CoV-2 infection. The topic of COVID-19 and diabetes has been recently reviewed in this journal (15) and is not covered here. We address new early and late endocrine complications of COVID-19, molecular and pathophysiological mechanisms identified thus far, and what remains to be clarified in the future.

COVID-19 AND OBESITY

Obesity has been a major issue during the COVID-19 pandemic, which is unsurprising considering its worldwide prevalence of 13% among adult population (16) and its well-described unfavorable effects during critical illnesses (17). A significant amount of clinical research indicates that obesity is related to higher COVID-19 severity and possibly fatality (2, 5, 18–21), a fact supported by Mendelian randomization studies (22). Obesity might leave subjects vulnerable to SARS-CoV-2 infection; it has been observed that infected patients had a greater overall rate of obesity than the general population (2, 3). In addition to body mass index (BMI), increased visceral adipose tissue has been proposed as a predictor of COVID-19 severity (23).

The data linking obesity to disease severity has been more conclusive than data linking obesity to mortality (**Table 1**). Several meta-analyses indicated that obesity increases the risk of COVID-19 severity but not mortality (2, 4, 24). As the pandemic evolved, obesity was shown to be an independent risk factor for COVID-19-related death (18, 25). Moreover, a "dose-response relationship" linking BMI to COVID-19 severity (18) and mortality (19) was suggested. On the other hand, studies reported a J-shaped mortality curve, indicating an increased risk of death for both underweight and overweight patients, with a BMI of 25–29 kg/m^2 having the lowest risk (19, 26). This finding is in line with the "obesity paradox" (27) previously described in critically ill non-COVID-19 patients (28).

Observational studies assessing the relationship between obesity and poor COVID-19 outcomes suggested that certain factors accompanying obesity might be significant. For example, a dose-response meta-analysis reported that older age, but not sex or comorbidities, may increase the risk of severe COVID-19 in patients with obesity (18). In contrast, research in the United

Table 1 Selected studies evaluating COVID-19 outcomes in patients with obesity

Reference	Study design	*n*	Obesity prevalence	COVID-19 severity	COVID-19 mortality
5	Nationwide (UK)	17,278,392	Class I obesity 14% Class II obesity 5% Class III obesity 3%	NA	HR: 1.92 (CI 1.72–2.13) for class III obesity
29[a]	Multicenter (US)	3,222	36.8% 24.5% Class III	Class III obesity, aOR: 2.30 (CI 1.77–2.98) for death or MV	
2	Meta-analysis	68,214	Pooled obesity prevalence rates in non-ICU versus ICU patients: 0.30 (CI 0.21–0.39) versus 0.41 (CI 0.36–0.45)	OR: 1.30 (CI 1–1.69) for hospitalization OR: 1.51 (CI 1.16–1.97) for ICU admission OR: 1.77 (CI 1.34–2.35) for MV requirement	OR: 1.28 (CI 0.76–2.16)
24	Meta-analysis	7,224	30.8%	aOR: 1.75 (CI 1.33–2.30) for ICU admission aOR: 1.73 (CI 1.29–2.32) for MV requirement	aOR: 1.23 (CI 0.92–1.64)
4	Meta-analysis	17,687	NA	SRR: 1.31 (CI 0.94–1.84)	SRR: 1.06 (CI 0.76–1.49)
18	Meta-analysis	109,881	19.2% for mortality analysis	OR: 1.19 (CI 1.08–1.30) for each 2 kg/m^2 rise in BMI	OR: 2.68 (CI 1.65–4.37)
19	Meta-analysis	112,682	NA	NA	Pooled RR in dose-response meta-analysis: 1.016 (CI 1.008–1.025)
3	Multicenter (US)	7,606	Class I obesity 21% Class II obesity 11% Class III obesity 11%	Class I, OR: 1.28 (CI 1.09–1.51) Class II, OR: 1.57 (CI 1.29–1.91) Class III, OR: 1.80 (CI 1.47–2.20) for in-hospital death or MV Class III obesity, HR: 1.26 (CI 1.00–1.58) for mortality	
25	Nationwide (UK)	11,074,708	NA	NA	White, HR: 1.73 (CI 1.59–1.91) Black, HR: 3.01 (CI 2.32–3.90) South Asian, HR: 5.25 (CI 4.06–6.79) Others, HR: 3.89 (CI 2.72–5.54) BMI 40 kg/m^2 versus White patients with a BMI of 22.5 kg/m^2

[a]Patients between the ages of 18 and 34 years were included in this study.

Abbreviations: aOR, adjusted OR; BMI, body mass index; COVID-19, coronavirus disease 2019; HR, hazard ratio; ICU, intensive care unit; MV, mechanical ventilation; NA, not available; OR, odds ratio; RR, relative risk; SRR, summary relative risk; UK, United Kingdom; US, United States.

States showed that class III obesity increases the risk of mechanical ventilation (MV) and death, particularly in young people (3, 29) (**Table 1**). Moreover, obesity-related comorbidities including diabetes and cardiovascular diseases are predictors of poor COVID-19 outcomes (4–6).

Nevertheless, after adjusting for comorbidities, obesity remained an independent risk factor for COVID-19 severity and mortality (3).

Ethnic origin may play a role in phenotypic expression of COVID-19 and obesity. Although patients with obesity from all ethnicities had an elevated mortality risk, patients from Black, Asian, and other ethnic minority groups were shown to have a greater risk of hospitalization and mortality than the White population (3, 5, 25), in correlation with increasing BMI (25). A population-based study including 12.6 million adults in the United Kingdom showed a J-shaped association between BMI and mortality for all ethnic groups and a steeper slope for non-White ethnicities (25).

Beyond the impact of obesity on COVID-19 prognosis, "stay home" measures during the pandemic resulted in physical inactivity, stress, sleep deprivation, and unhealthy eating behavior, which could escalate obesity in individuals regardless of SARS-CoV-2 infection status (30). The elderly, considering their disadvantage due to age-related hormonal and immunological changes, may particularly be at risk of "sarcopenic obesity" (31).

Although we are still far from fully comprehending the pathophysiological link between obesity and COVID-19 severity, numerous potential mechanisms are proposed (**Figure 1**). First, obesity, particularly if severe, causes changes in respiratory anatomy and physiology, increasing the likelihood of atelectasis and a ventilation-perfusion mismatch, leading to hypoxemia (17). Second, increased BMI and waist circumference are associated with increased viscosity, higher levels of prothrombotic markers, and reduced fibrinolytic activity (32). Patients with obesity may be more prone to immune dysregulation when infected with SARS-CoV-2, because obesity is a chronic inflammatory condition with elevated cytokine production. In essence, obese COVID-19 patients have greater inflammatory markers than nonobese individuals, which may be an indirect sign of immune system hyperstimulation (32). Last, because adipocytes express ACE2, enlarged adipose

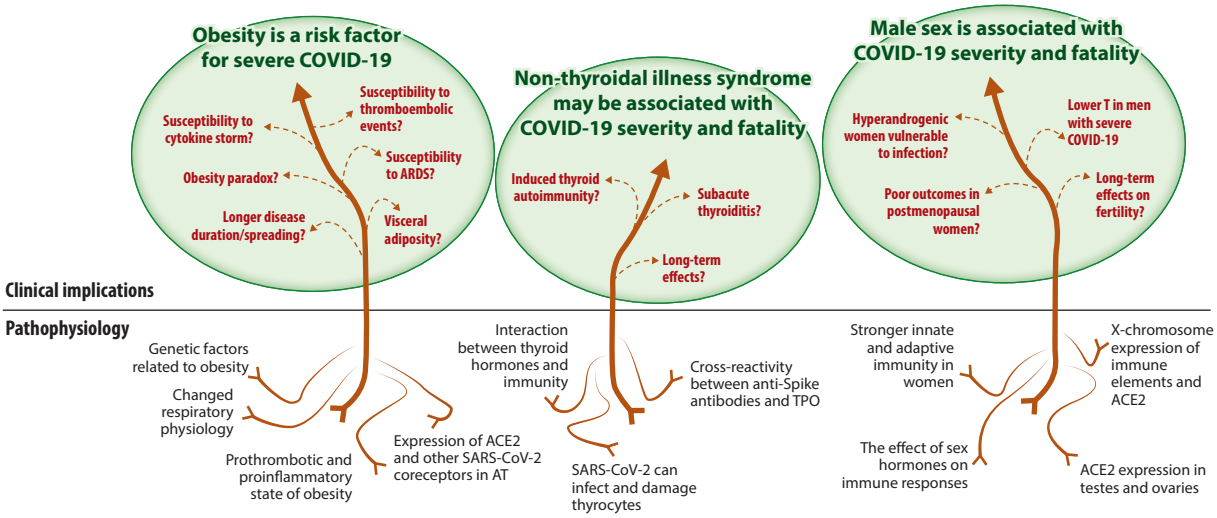

Figure 1

Endocrine disorders and COVID-19, from pathophysiology to clinical implications. The suggested pathophysiological underpinnings of the relationship between obesity, thyroid dysfunction, and sexual disparities are presented as roots below the line. Clinical implications, either supported with extensive research (*green*) or not (*red*), are presented as branches above the line. More research is needed to link pathophysiological data with clinical results in order to obtain reliable conclusions. Abbreviations: ACE2, angiotensin-converting enzyme 2; ARDS, acute respiratory distress syndrome; AT, adipose tissue; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; T, testosterone; TPO, thyroid peroxidase.

tissue might constitute a SARS-CoV-2 reservoir (30, 32). Studies have not determined if all these factors are relevant to the increased mortality risk in obese patients with COVID-19.

In conclusion, obesity is associated with COVID-19 severity and possibly mortality in men and women at all ages. More data are needed to determine particularly if and how obesity raises the risk of infection and severe COVID-19. Limited data suggest that antiobesity medications, including glucagon-like peptide-I receptor agonists and orlistat, might prove useful in COVID-19 (33, 34); these findings require confirmation.

COVID-19 AND ADRENAL GLANDS

Adrenal diseases, notably adrenal insufficiency (AI), do not appear to have a negative impact on COVID-19 outcomes. In an Italian cohort including 279 patients with AI, only 31% of moderate COVID-19 cases (4.3% had positive polymerase chain reaction test results) required an increase in glucocorticoid replacement dose, with no adrenal crises or hospitalizations (35). While there is very little evidence on Cushing's disease, it is reasonable to assume these patients may be at risk of severe COVID-19 and should take all precautions to avoid infection (14).

COVID-19, on the other hand, was associated with incidents of new-onset primary AI. Although no gross infarct or thrombi in the adrenal glands were reported in autopsy series (8, 36), bilateral adrenal hemorrhagic or nonhemorrhagic infarction was observed in these cases, some associated with antiphospholipid antibody syndrome (10). Moreover, retrospective examination of initial chest computed tomography scans revealed signs of acute adrenal infarction in almost a quarter of patients with moderate to severe COVID-19, with 88% of the cases being bilateral. Although no information on biochemical/clinical hypocortisolism was available, patients with adrenal infarction had greater odds of intensive care unit (ICU) admission and longer hospitalization, but not mortality (37).

Critical illness–related corticosteroid insufficiency (CIRCI), an impaired hypothalamic-pituitary axis (stress) response during critical illness (38), was not observed in COVID-19. Instead, limited available data suggested that patients with severe COVID-19 have much greater cortisol levels than those with mild disease (39). Likewise, COVID-19 patients showed higher serum cortisol concentrations than non-COVID-19 controls within 48 h of hospitalization, with higher cortisol related to lower survival rates (40). Nevertheless, severely or critically ill COVID-19 patients benefit from glucocorticoids, particularly dexamethasone, possibly owing to its anti-inflammatory actions (41).

Additionally, hypocortisolism was not detected in survivors of COVID-19, at least in short-term follow-up. A prospective study that evaluated COVID-19 survivors 3 months following infection ($n = 70$; 77% hospitalized, 22% needed noninvasive MV/ICU, 31% received dexamethasone) found that all patients, including the 64% who reported ongoing fatigue, responded effectively to tetracosactide stimulation (12).

Current knowledge on possible effects of COVID-19 on the adrenal glands has mainly been based on histopathological studies. Human adrenal cortex expresses ACE2 and TMPRSS2 (42). Consequently, SARS-CoV-2 expression and replication in adrenal glands were shown in animals (43) and humans (8). In fact, adrenal glands were already revealed as targets of SARS-CoV infection during the outbreak of SARS in 2003, and both vasculitis in small vessels and adrenalitis were demonstrated (44). Similarly, the main findings of post mortem histopathological examinations of adrenal glands in COVID-19 were microthrombi in small adrenal vessels (8, 36) and contradictory findings regarding adrenalitis (8, 45). Clinical and biochemical data in autopsy studies, necessary to determine clinical relevance of histopathological abnormalities, are not available.

Overall, our understanding is still incomplete concerning COVID-19's effects on the adrenal gland, the adrenal gland's reaction to COVID-19, and the course of COVID-19 in patients with

adrenal disorders. Although hypercortisolemia was shown instead of CIRCI in severe COVID-19, the patients evaluated upon admission were not re-evaluated later during hospitalization, which might have led to different conclusions. Nevertheless, currently available data show no sign of late hypocortisolism in COVID-19 survivors.

COVID-19 AND THYROID FUNCTION

Thyroid diseases, in general, are not associated with COVID-19 severity, mortality, or susceptibility (46). Abnormal thyroid function tests [low thyroid-stimulating hormone (TSH) and free thyroxine (fT4) levels], on the other hand, were frequently observed in hospitalized COVID-19 patients (47). Non-thyroidal illness syndrome (NTIS), which is characterized by low free triiodothyronine (fT3), high reverse T3, low/normal TSH, and low fT4 levels (48), was detected in ~7% of COVID-19 patients admitted to the hospital (49). Low fT3 levels upon admission were associated with clinical deterioration (49), disease severity, and mortality (50). A risk ratio of 11.64 [95% confidence interval (CI) 4.88–27.78] for death in COVID-19 patients with NTIS was found in a recent meta-analysis (51) (**Figure 1**). Although symptomatic (9) and asymptomatic (52) subacute thyroiditis (SAT) during SARS-CoV-2 infection was reported, symptomatic SAT was actually an uncommon consequence of COVID-19. SAT in association with COVID-19 was similar to classical SAT (53), and no rise in the incidence of SAT was documented during the pandemic (54). Existing evidence suggests that thyroid function tests return to normal following recovery, and SARS-CoV-2 has no long-term effect on thyroid functions (12, 47).

NTIS in COVID-19 may be related to immune activation that affects thyroid hormone levels through downregulating the hypothalamic-pituitary-thyroid hormone axis, modifying enzyme activity in thyroid hormone metabolism, and influencing other unknown pathways (48, 55). Aside from that, infections can cause cell injury, resulting in autoantigens being produced by thyrocytes and triggering thyroid autoimmunity/autoinflammation in genetically susceptible subjects, which may appear in the clinic as SAT/Graves' disease (55). Thyroid follicular epithelial cell destruction (36), as well as cross-reactivity between antibodies against SARS-CoV-2 Spike protein and thyroid peroxidase (56), imply SARS-CoV-2 may induce thyroid autoimmunity (**Figure 1**). All these findings, however, need to be supported regarding clinical implications.

Overall, thyroid dysfunction is common among COVID-19 patients, particularly in the ICU, most likely as a sign of NTIS. While NTIS has been associated with mortality, thyroid tests tend to normalize upon recovery. Guideline recommendations should be followed for COVID-19 patients with pre-existing thyroid disorders (14, 57). No postponement of diagnostic and therapeutic interventions is currently recommended in patients with thyroid nodules (57).

COVID-19 AND THE REPRODUCTIVE SYSTEM

The importance of sex in COVID-19 outcomes has been recognized since the beginning of the pandemic, as male sex is linked to greater COVID-19 severity and mortality but not susceptibility (58). Overall, male sex is related to ~1.4-fold greater risk of COVID-19-related death compared to female sex (58, 59), while survival rates between postmenopausal women and men become more comparable (60).

COVID-19 may affect the reproductive system, as it may cause menstrual abnormalities in women (61) and orchitis or epididymitis in up to 20% of cases in men (7). Moreover, SARS-CoV-2 was identified in semen, with 6.9% and 1.4% of semen samples testing positive during infection and recovery phases, respectively (62). Additionally, lower levels of serum testosterone in men were associated with severe COVID-19 (63). Concerns about COVID-19's impact on male fertility were therefore raised in light of research showing reduced testosterone levels, oligozoospermia, and

sperm immobility in SARS-CoV-2-infected men (7, 62, 63). However, 87% of COVID-19 patients with low testosterone normalized their levels 7 months after recovery, and still-low testosterone levels were associated with comorbidities and higher interleukin-6 levels (adjusted for age and BMI) (13). Overall, current evidence is insufficient to conclude if low testosterone in men is the cause or consequence of severe COVID-19.

A primary care database study suggested that hyperandrogenism in women may cause susceptibility to SARS-CoV-2 infection (64), although confirmatory data are not yet available. Regarding female fertility, no change from baseline anti-Mullerian hormone levels was observed in women with mild COVID-19 (65). However, pregnancy was associated with a 2.5- to fivefold greater risk of severe COVID-19 and a 1.7-fold increased risk of death. The data are insufficient to conclude if pregnancy is also related to COVID-19 susceptibility (66, 67). Usual risk factors associated with COVID-19 severity, including higher BMI and pregestational comorbidities such as diabetes and older maternal age, were significant in pregnant women (66). In addition, COVID-19 may affect maternal and prenatal outcomes. The risks for pre-eclampsia/eclampsia, preterm birth, and fetal distress were reported as 1.76 (95% CI 1.27–2.43), 1.59 (95% CI 1.30–1.94), and 1.70 (95% CI 1.06–2.75), respectively (67). On the other hand, an increased risk for stillbirth but not preterm birth was shown (68). While vertical transmission of SARS-CoV-2 infection from mothers to neonates appears to be unlikely (69), immunoglobulin M positivity in cord blood was reported (70).

The putative underpinning mechanisms of male disadvantage in COVID-19 have been discussed from various perspectives (**Figure 1**) (71). Women have better innate and adaptive immune responses to infectious pathogens than men of similar age in general, especially in the premenopausal period (72). In accordance, female COVID-19 patients had larger amounts of cytokines and terminally activated $CD8^+$ T cells (73). Furthermore, women showed higher levels of immunoglobulin G antibodies than men with either SARS-CoV-2 infection or vaccination (74, 75), despite contradictory research reporting that male patients acquired higher levels of antibodies in the short-term response to infection (76).

Sex chromosomes and hormones may influence immunological responses (71). Certain elements of immunity are coded on the X chromosome, and transcriptional research indicates sex variations in immune responses (72). In addition, estrogen improves innate immunological responses, whereas testosterone suppresses them. Estrogen also promotes peripheral B cell activation, maturation, and survival (72). Nevertheless, based on present data, we cannot determine if the disparity in COVID-19 outcomes between pre- and postmenopausal women is simply attributable to sex hormones (60).

Another proposed reason for male disadvantage in COVID-19 is that chronic comorbid diseases associated with poor COVID-19 outcomes are more common in men than in premenopausal women (77, 78). Yet this may be not accurate because women are more likely to be undiagnosed for longer periods of time (78). On top of that, aging (menopause) and having metabolic comorbidities such as obesity and diabetes negate some of the benefits of female sex, even at younger ages (78).

Finally, the X chromosome expression of ACE2, the androgen sensitivity of both ACE2 and TMPRSS2 (79), and the fact that the glucocorticoid response to acute stress is more apparent in females have all been proposed as possible theories accounting for male disadvantage (71). Additionally, SARS-CoV-2 may target the reproductive organs, since both testes and ovaries express ACE2 (and possibly TMPRSS2) (7, 80), but only testes autopsy specimens showed SARS-CoV-2 presence (81), which could explain orchitis cases.

Overall, higher risk of severe disease and death in men has been well established in population-based COVID-19 studies. Interestingly, hypogonadism instead of higher androgen levels is

associated with severe COVID-19 in men, raising the question of whether low testosterone is simply a consequence of critical illness or potentially associated with obesity. On the other hand, clinical studies were not able to fully determine if menopause or hyperandrogenism in women have impacts on COVID-19 outcomes.

COVID-19 AND PITUITARY FUNCTION

Pituitary disorders are uncommon, so obtaining data on the COVID-19 course in such patients is challenging. Even so, hypopituitarism (mainly central hypocortisolism) appears not to have an impact on COVID-19 outcomes (35). On the other hand, COVID-19 might be associated with new-onset hypopituitarism via pituitary apoplexy (PA) and hypophysitis. At the time of this review, PA has been reported in ten COVID-19 patients and hypophysitis in two (11, 82, 83). While SARS-CoV-2 might have caused PA via endothelial dysfunction, viral tropism to pituitary gland, or thromboembolic effects, most of these patients already had risk factors for developing PA: eight had macroadenomas, three had hypertension, and one was pregnant (11, 35). Besides, ACE2 expression is low in both healthy pituitary glands and pituitary neuroendocrine tumors (84).

Hyponatremia has been observed in 20–60% of patients with COVID-19, as it is the most prevalent electrolyte abnormality in hospitalized patients in general (85). Still, hyponatremia was more common in COVID-19-related hospital admissions than in non-COVID-19-related admissions (28% versus 17.5%) (86), and it has been associated with COVID-19 severity and fatality [hazard ratio (HR) 1.4, 95% CI 1.10–16.62 for 30-day mortality] (85, 86). The etiology of hyponatremia in COVID-19 is poorly understood, but syndrome of inappropriate antidiuretic hormone secretion (SIADH) and hypovolemia are suspected. Hypernatremia, though uncommon relative to hyponatremia (~5%), can be detected in COVID-19 patients, particularly in the ICU, and is also associated with poor outcomes (85).

In conclusion, the fact that pituitary disorders are uncommon makes obtaining satisfactory evidence on COVID-19 outcomes in such individuals difficult. Long-term studies are needed to determine whether the COVID-19 pandemic resulted in increased time to diagnosis, as well as disease-related morbidity and mortality in this population. Although a causal link between COVID-19 and PA or hypophysitis, if any, cannot be established at this time, COVID-19 patients presenting with sudden-onset headache and/or neuro-ophthalmological symptoms should undergo pituitary examinations. Hyponatremia is common, and serum sodium levels should therefore be monitored in all hospitalized COVID-19 patients.

COVID-19 AND BONE AND MINERAL METABOLISM

Hypocalcemia has been observed in up to 60% of patients with COVID-19 and has been related to higher risk of hospitalization, ICU admission, and death [odds ratio (OR) 5.09, 95% CI 2.14–12.09 for ICU admission; OR 6.98, 95% CI 2.71–17.99 for mortality] (87). The suggested underlying pathophysiological mechanisms linking hypocalcemia and severe COVID-19 include viral utilization of host calcium for survival and action, calcium (and albumin) being a sign of general nutritional status, and altered fatty acid metabolism during severe COVID-19 that may lead to increased levels of unbound/unsaturated fatty acids that can bind circulating calcium (88). However, a major drawback in most of the hypocalcemia-related clinical data in COVID-19 is the absence of thorough investigation of contributing factors, such as vitamin D levels, which could be the root cause of hypocalcemia.

Vitamin D is involved in both innate and adaptive immune responses to bacterial and viral infections (89). Vitamin D deficiency mildly but significantly increased the risk of acute respiratory

tract infections (90). In accordance, vitamin D deficiency/insufficiency was linked to increased susceptibility to SARS-CoV-2 infection (OR 1.46, 95% CI 1.28–1.65). However, the risk of bias was high, since vitamin D measurements were recorded at the time of COVID-19 diagnosis. Still, a recent study designed to counteract this bias reached similar conclusions (91). Lower vitamin D also increased the risk of severe COVID-19 (OR 1.90, 95% CI 1.52–2.38) and death (OR 2.07, 95% CI 1.28–3.35), but in like manner, there was a significant risk of bias and heterogeneity, especially in mortality data (92).

Vitamin D supplementation as a therapy for COVID-19 still lacks sufficient evidence to establish benefits and risks (93). Nevertheless, available data suggest lower risk of SARS-CoV-2 infection (HR 0.66, 95% CI 0.57–0.77), severe COVID-19 (HR 0.72, 95% CI 0.52–1.0), and death (HR 0.66, 95% CI 0.46–0.93) in older vitamin D–sufficient adults than in those who are vitamin D–deficient (91). Vitamin D supplementation might therefore be considered, particularly in older adults (14).

Osteoporosis may be among the diseases whose diagnosis and care have been hampered by the COVID-19 pandemic, but the rates of fractures remained almost unchanged compared to previous years (94). Although vertebral fractures were observed as a common finding in a limited sample of older COVID-19 patients (95), they did not appear to be any different from non-COVID-19 patients (96). While data were inconsistent regarding the impact of vertebral fractures in COVID-19 outcomes (95, 97), COVID-19 patients admitted to the hospital with a hip fracture had a higher mortality rate (OR 5.94, 95% CI 4.02–8.77), most likely due to delayed surgery (98).

It was initially hypothesized that bisphosphonates could reduce the risk of COVID-19. However, several population-level studies have failed to prove this hypothesis and showed that osteoporosis medications are safe to use (94).

Overall, the long-term implications of the COVID-19 pandemic for osteoporosis and its sequelae are unknown, yet a rise in both might be expected, especially in older persons, because hospitalization, bed rest, and home confinement may have accelerated sarcopenia and bone loss (31). Vitamin D supplementation may therefore be beneficial in this population.

SARS-COV-2 VACCINES AND ENDOCRINE DISORDERS

There are no contraindications or special warnings for SARS-CoV-2 vaccines in patients with endocrine disorders in general (14), except that patients with AI and long-term users of exogenous glucocorticoids may need glucocorticoid dose adjustments (14). No vaccine-induced thrombotic events were reported in hypercortisolemic patients to date. However, SARS-CoV-2 vaccine-induced SAT and Graves' disease (new or recurrent) cases, and rarely ophthalmopathy, were described. While immunizations appear safe in SAT cases, there is no evidence on which to evaluate their safety in Graves' disease, particularly in active cases of Graves' disease (99).

Although limited, existing research shows that SARS-CoV-2 vaccination does not adversely affect human fertility (62), and vaccination for SARS-CoV-2 during pregnancy appears safe and effective (100).

CONCLUSIONS

COVID-19 and endocrinology have intersected across several contexts. For example, obesity, a global health problem, emerged as a major risk factor for poor COVID-19 outcomes. Meanwhile, the possibility of sex hormone involvement in male disadvantage opened the ground for research into antiandrogenic therapies in COVID-19 patients. Despite the disappointing results, research revealed that many endocrine organs can be targeted by SARS-CoV-2, with or without clear clinical consequences. Moreover, certain pre-existing conditions such as vitamin D deficiency

and potentially Cushing's syndrome might create vulnerability for COVID-19 infections. Public health measures taken during COVID-19 pandemic may adversely affect several endocrine disorders, and perhaps delay their diagnosis and treatment. Although endocrinological abnormalities, such as thyroid dysfunction (NTIS), hyponatremia (SIADH), and potentially male hypogonadism, can provide information on COVID-19 severity, most abnormalities are likely to revert to baseline following recovery. Although an abundance of hypotheses exists regarding the pathophysiological pathways linking endocrine disorders with COVID-19 outcomes, there has been a paucity of research to test these possibilities. Furthermore, it is unclear if COVID-19 is linked to long-term chronic or late-onset endocrine dysfunctions.

SUMMARY POINTS

1. Obesity is associated with increased COVID-19 severity and possibly lethality in both men and women of all age groups.
2. Although SARS-CoV-2 seems to target the adrenal glands, a paucity of data combining histological, radiological, and clinical findings results in inadequate understanding.
3. Abnormal thyroid function tests indicating non-thyroidal illness syndrome are common during severe COVID-19 and provide insight into the prognosis.
4. Male sex has been linked to greater COVID-19 severity and mortality, but not susceptibility. The role of sex hormones in these relationships still requires clarification.
5. Patients with hypopituitarism appear not to have an increased risk of severe COVID-19.
6. Hyponatremia and hypocalcemia are common electrolyte disorders among COVID-19 patients, and both seem to be associated with disease severity.
7. Vitamin D supplementation could be considered, particularly in the elderly, since vitamin D deficiency might be associated with increased susceptibility to SARS-CoV-2 infection.
8. Limited data suggest that COVID-19 has no long-term effects on thyroid, adrenal, and male gonadal functions.
9. SARS-CoV-2 vaccines appear to be safe in patients with endocrine disorders.
10. Overall, more research is required to precisely evaluate the relationships between hypothesized pathophysiological pathways and clinical phenotypes of COVID-19.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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