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Mini-Review

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# Impact of COVID-19 on the Endocrine System: A Mini-review

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**Abbreviations:** ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; fT3, free T3; fT4, free T4; GC, germ cell; HPG, hypothalamic-pituitary-gonadal; ITU, intensive treatment unit; NTIS, nonthyroidal illness syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T2DM, type 2 diabetes mellitus; TMPRSS2, transmembrane serine protease 2

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## Abstract

The coronavirus disease 2019 (COVID-19) pandemic continues to exert a significant impact on global health care systems, causing devastating mortality and morbidity. As time passes and our understanding of this novel respiratory virus deepens, it is increasingly clear that its effects extend beyond that of the respiratory system. The coronavirus responsible for COVID-19, severe acute respiratory syndrome coronavirus 2, obtains cellular access through the angiotensin-converting enzyme 2 (ACE2) receptor in a process requiring the transmembrane serine protease 2 (TMPRSS2) protein. Both ACE2 and TMPRSS2 are widely expressed in many endocrine glands. This, along with several case reports of thyroid and pituitary disruption in patients with COVID-19, has resulted in significant interest in its impact on the endocrine system. Indeed, as mortality is abated by the increasing availability of effective vaccines, there is increasing focus on the long-term effects on health in COVID-19 survivors. This review summarizes data investigating the effects of COVID-19 on each of the endocrine axes to guide appropriate investigations and optimal management.

**Key Words:** COVID-19, SARS-CoV-2, adrenal insufficiency, adrenal function, thyroid function, thyroid gland, endocrine

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its variants will affect global health care systems over the upcoming years. Furthermore, the effects of coronavirus disease 2019 (COVID-19) extend beyond the respiratory system, and can be protracted, with ~10% of patients experiencing persistent symptoms at 8 weeks following initial infection (1). It is therefore vital to deepen our understanding of the disruption of COVID-19 on physiological function.

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Whilst early case reports first indicated a potential clinical impact on the endocrine system, there now exists a larger body of research describing the effects of COVID-19 on pituitary, thyroid, adrenal, gonadal, and pancreatic endocrine function. However, the contribution of endocrine dysfunction to the symptoms experienced by patients with COVID-19 remains to be fully elucidated. Endocrine disorders are eminently treatable, and their diagnosis and management can result in significant improvements in health and quality of life. Thus, in this review, we appraise the available data investigating the impact of COVID-19 on the endocrine system to aid clinicians in instituting appropriate investigation and management of affected patients.

### The Endocrine System is Vulnerable to SARS-CoV-2

The SARS-CoV-2 coronavirus, which causes COVID-19, gains cellular access through the angiotensin-converting enzyme 2 (ACE2) receptor. The homotrimeric spike glycoprotein, composed of S1 and S2 subunits, protrudes from the virus surface and is critical for its binding to ACE2 (2, 3). Upon binding to ACE2, the S1 subunit is dissociated with the ACE2 receptor, in a process that requires the presence of transmembrane serine protease 2 (TMPRSS2) (4) (see Fig. 1). It is known that TMPRSS2 drives oncogenic transcription in prostate cancer, and that TMPRSS2 is regulated by androgens. Indeed, androgen deprivation or antagonism both attenuate SARS-CoV-2 S-mediated cellular entry in vitro (5). The resultant conformational change affords the S2 subunit the increased stability necessary for membrane fusion (Fig. 1) (6). Binding to the ACE2 receptor is obligatory for SARS-CoV-2 cellular entry. In in vitro studies, the SARS-CoV-2 virus was unable to access HeLa cells that did not express ACE2 proteins (7), and raising antiserum to human ACE2 prevented cellular access by SARS-CoV-2 (4). Additionally, unlike other coronaviruses, SARS-CoV-2 does not appear to use other receptors for cellular access, such as dipeptidyl peptidase 4 or aminopeptidase N (4, 7).

In humans, ACE2 mRNA is expressed in several endocrine glands, including the pancreas, thyroid gland, ovaries, and testes (8) (Fig. 2). Crucially, TMPRSS2 mRNA is also expressed in the pancreas, thyroid gland, ovaries, and testes (8). Thus, the endocrine system not only possesses the requisite ACE2 receptor, but also the TMPRSS2 protein necessary to afford the SARS-CoV-2 virion cellular access. In summary, there is cumulative evidence that the endocrine system is particularly vulnerable to both destruction and alteration in function because of COVID-19.

## The Pituitary Gland

### Background and Pathophysiology

Although the ACE2 receptor is present in the normal pituitary gland (9), it is not a region of high expression of ACE2 mRNA or protein (8, 10). Moreover, postmortem pituitary tissue from patients with pituitary neuroendocrine tumors also display low ACE2 expression (10). Nevertheless, SARS-CoV mRNA was detected within the pituitary gland at autopsy (11), and postmortem investigation of 5 patients who died of SARS demonstrated reduced somatotrope, thyrotrope, and corticotrope cell number and

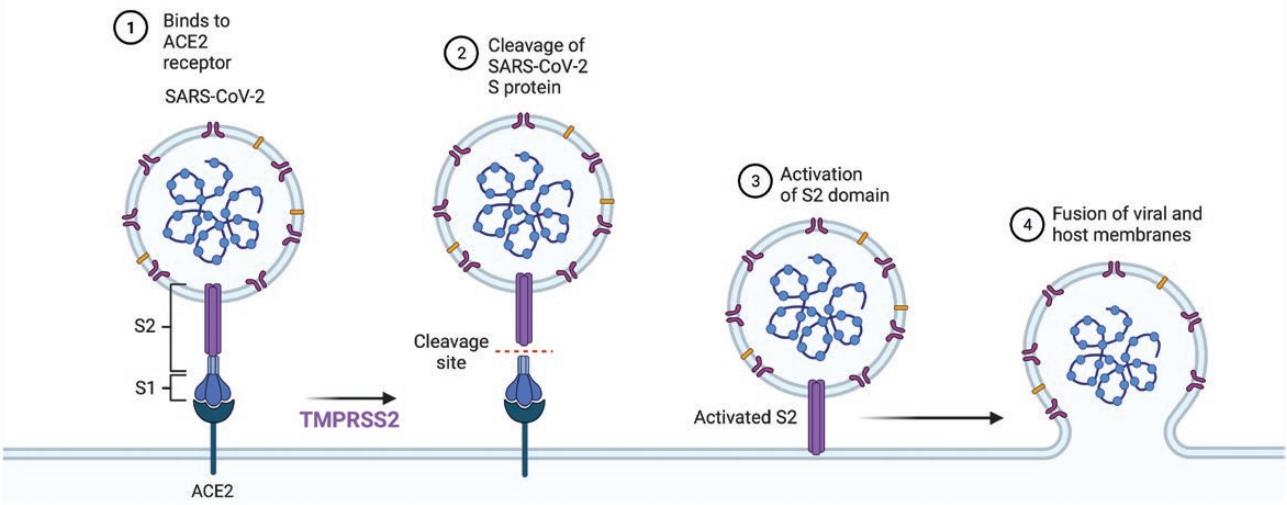


**Figure 1.** Binding of the SARS-CoV-2 virus to the ACE2 receptor. The SARS-CoV-2 spike protein binds to ACE2. In the presence of transmembrane serine protease receptor 2 (TMPRSS2), the S1 subunit dissociates inducing a conformational change that increases S2 subunit stability, permitting membrane fusion. Created with Biorender.com.

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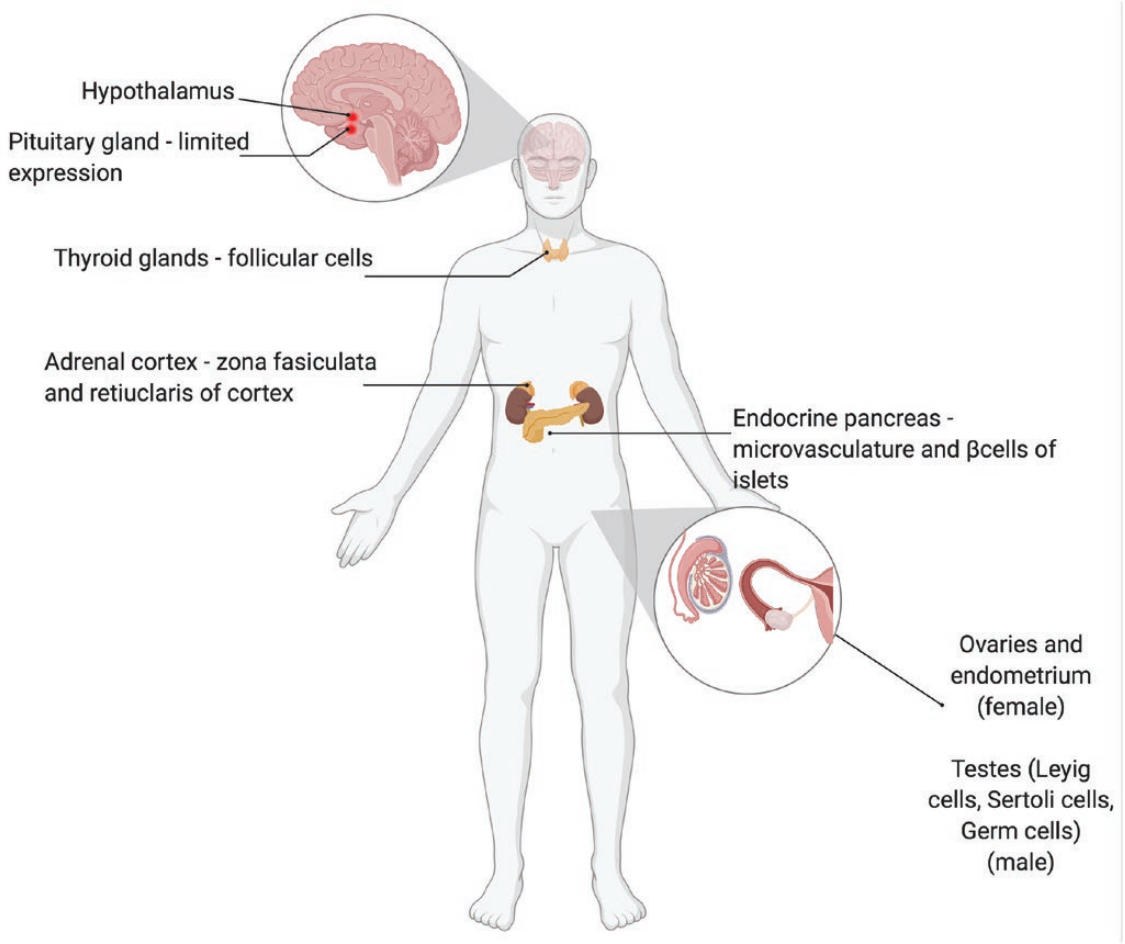


**Figure 2.** Location of ACE2 receptor within the endocrine system. Displayed are the areas of the endocrine gland that have been demonstrated as possessing ACE2 mRNA or protein. Created with Biorender.com.

immunoreactivity staining for GH, TSH, and ACTH (12). However, whilst direct damage to the pituitary gland by SARS-CoV-2 has not been demonstrated, clinical reports suggest that there may be some perturbation in pituitary gland function.

## Acute and Subacute Effects

The pituitary gland has a rich vascular supply; because vascular endothelium has a high expression of ACE2 receptors (9), it is vulnerable to damage during COVID-19 infection. Furthermore, pituitary apoplexy may be precipitated by conditions that alter platelet function and coagulation (13). Severe illness and sepsis result in a prothrombotic state (14), but more specifically, patients with COVID-19 have hypercoagulability (15) that is distinct, characterized by thrombocytopenia, high fibrinogen, and D-dimer levels, but only minor changes in prothrombin and antithrombin times (16). Thus, it is conceivable that there is an increased risk of pituitary apoplexy in patients with pituitary tumors with COVID-19 infection, which has been suggested by several case reports. Whilst some of these reports had other risk factors for apoplexy, such as pregnancy (17), and most were in patients with preexisting pituitary macroadenomas (18-20), some were in patients with microadenomas (21, 22), which is typically less commonly associated with apoplexy.

## Persistent Effects

Whilst there is a paucity of data detailing pituitary function following COVID-19, central hypothyroidism was observed in 4.9% of patients at 3 to 6 months post-SARS, with the majority of patients reverting to euthyroidism by 9 months postinfection (23). By contrast, our group has reported data from 70 survivors of COVID-19, of variable severities, finding that thyroid function remained within the reference range for the majority of patients, with no evidence of central hypothyroidism (24).

In summary, despite a theoretical risk, to date there remains little clinical evidence of direct damage to the

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pituitary gland by SARS-CoV-2. However, the inflammatory state after COVID-19 in combination with unique increased hypercoagulability that characterizes acute infection could theoretically precipitate pituitary apoplexy in patients with a preexisting macroadenoma.

## The Thyroid Gland

### Background and Pathophysiology

Patients diagnosed with SARS had reduced thyroid function. Furthermore, at postmortem, both follicular and parafollicular cells of the thyroid gland were extensively damaged in patients who died of SARS (25). Additionally, ACE2 mRNA is present in thyroid follicular cells, highlighting the potential of thyroid cellular access by SARS-CoV-2 (26), but, to date, no evidence of intracellular SARS-CoV-2 has been documented (27).

### Acute and Subacute Effects

Early in the pandemic, several cases of subacute thyroiditis were reported (28-31). Among patients admitted to intensive treatment unit (ITU), those with COVID-19 were more likely to have thyrotoxicosis (32). Likewise, those with COVID-19 admitted to a high-intensity ITU had a lower TSH compared with those admitted to low-intensity ITU (Table 1) (32). Interestingly, 6 patients with thyroiditis/thyrotoxicosis after COVID-19 were followed-up at a mean of 55 days. None of them had ever experienced neck pain, and rather than lymphocytosis, had the characteristic lymphopenia associated with COVID-19 (32). In patients with COVID-19 not requiring intensive care admission, overt thyrotoxicosis was observed in 10.8%, and 0.7% of patients had hypothyroidism (33). However, the majority of patients (74.6%) had normal TSH values (33) (Table 1). Notably, thyrotoxicosis was related to IL-6 levels, suggesting that those with a greater inflammatory response were more likely to develop thyrotoxicosis (33) (Table 1). By contrast, in a cohort of 334 patients with COVID-19, we observed that no patients had overt thyrotoxicosis, although TSH and fT4 values were reduced compared with baseline (34) (Table 1).

In addition to subacute thyroiditis, case reports have emerged of Graves' thyrotoxicosis in patients with COVID-19 (35, 36), 1 of whom had no previous documentation of autoimmune thyroid disease. Viral infections may trigger the presentation of autoimmune thyroid disease (37); however, it has been posited that the cytokine milieu induced by SARS-CoV-2 renders it a particular trigger for autoimmune thyroid disease (36). IL-6 levels are characteristically raised by COVID-19 and are elevated in Graves' disease (38).

Nonthyroidal illness syndrome (NTIS) occurs during physiological stress, and is characterized by an initial reduction in total T3 and fT3, with an increase in reverse T3 but without a concomitant rise in TSH (39). Persistent illness results in global reductions in TSH, fT4, and free T3 (fT3) (40) from a reduction in hypothalamic thyrotropin-releasing hormone (41). It is therefore unsurprising that several studies have reported features consistent with NTIS in patients with COVID-19.

Patients with pneumonia resulting from COVID-19 were observed to have lower serum TSH and total T3 levels than other forms of pneumonia, although there was no difference in total T4 values (42). These differences were resolved at recovery (42). Whilst a prospective study of 367 patients with mild-moderate COVID-19 failed to demonstrate overt thyrotoxicosis or hypothyroidism, 7.4% had NTIS and 8.2% had thyroid function tests consistent with different stages of thyroiditis (43) (Table 1). Notably, NTIS was associated with a higher SARS-CoV-2 viral load and inflammatory markers (Table 1) (43). Other studies have observed similar findings with an isolated low TSH or in combination with low fT3 being reported in patients with COVID-19 (44, 45) and the degree of reduction being associated with the severity of disease (45, 46). Finally, survivors of COVID-19 had lower TSH levels than nonsurvivors (Table 1). Moreover, given that corticosteroid use is now the gold standard for patients requiring oxygen supplementation (47), exogenous steroids can reduce TSH levels (48) and peripheral conversion of T4 to T3, providing an additional mechanism for thyroid dysfunction.

### Persistent Effects

Whilst thyroid function tests may be acutely altered during COVID-19, they return to baseline following recovery. We recently reported that, in a cohort of 70 survivors of COVID-19, thyroid function tests returned to normal by 3 to 6 months after COVID-19 infection (34), with no alteration in TSH, fT4, or fT3 values (24). Importantly, parameters of thyroid function did not associate with disease severity at presentation, markers of inflammation, or level of care required (24). "Long COVID" is characterized by symptoms including fatigue, myalgia, and "brain fog," and thereby has many similarities to thyroid dysfunction. Therefore, such findings have significant clinical relevance to both clinicians and patients.

In summary, for a proportion of patients with COVID-19, thyroid function may be disrupted acutely, either by subacute thyroiditis (which may present atypically, lacking the characteristic neck pain and lymphocytosis), NTIS, or even by triggering autoimmune disease, although the majority of patients are euthyroid. Large long-term studies are lacking;

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**Table 1.** The effect of COVID-19 on thyroid gland function

| Authors | Study design | Findings | Conclusion |
|---|---|---|---|
| Acute effects | | | |
| Muller et al (32) | Retrospective study<br>**Study population:**<br>n = 93 patients admitted to ITU in 2020 with COVID-19<br>n = 101 patients admitted to ITU in 2019 (pre-SARS-CoV-2 pandemic)<br>n = 52 COVID-19 LITU admission<br>TSH and fT4 measured within 2 days of admission | **Thyrotoxicosis: (TSH < 0.28 mIU/L and/or fT4 >21.9 pmol/L)**<br>-13/85 (15%) with COVID-19 in ITU<br>-1/41 (2%) with COVID-19 in low-intensity ITU<br>-1/78 (1%) with no COVID-19 in ITU<br>**Median (IQR) TSH (mU/L):**<br>ITU 2020 with COVID-19: 1.04 (0.47-1.80)<br>LITU 2020 with COVID-19: 1.43 (0.71-2.28)<br>ITU 2019 with no COVID-19: 1.43 (0.88-2.37)<br>**Mean ± SD fT4 (pmol/L):**<br>ITU 2020 with COVID-19: 18.6 ± 5.4<br>LITU 2020 with COVID-19: 13.5 ± 4.6<br>ITU 2019 with no COVID-19: 16.2 ± 2.4 | Patients with severe COVID-19 may present with thyrotoxicosis<br>fT4 and fT3 only measured when TSH <0.45 mU/L as per local policy<br>Thyrotoxicosis defined as TSH < 0.28 mU/L and/or fT4 >21.9 pmol/L |
| Lania et al (33) | Single-center, retrospective study<br>**Study population:**<br>n = 287 patients admitted with COVID-19, not requiring ITU admission<br>TSH measured as routine for all patients admitted with COVID-19 | **Thyrotoxicosis (TSH <0.34 mU/L and/or fT4 >17.29 pmol/L):** n = 58 (20.2%)<br>**Hypothyroidism (TSH >4.80 mU/L and/or fT4 <7.82 pmol/L):** n = 15 (5%)<br>**Euthyroid:**<br>n = 214 (75%)<br>TSH inversely correlated with age (rho −0.27; $P < 0.001$) and IL-6 (rho −0.41; $P < 0.001$).<br>Multivariable analysis: thyrotoxicosis associated with higher IL-6 (odds ratio: 3.25, 95% CI: 1.97-5.36; $P < 0.001$). | Patients with COVID-19 may present with thyrotoxicosis, which correlates with IL-6 levels<br>fT4 and fT3 only measured when TSH <0.45 mU/L or >4.80 mU/L per local policy |
| Brancatella et al (49) | Case series<br>4 female patients presenting with SAT following recovery from COVID-19 | Presentation at 16-36 days after resolution of COVID-19 symptoms<br>Presented with characteristic symptoms of SAT: neck pain, fever, palpitations<br>US: enlarged thyroid gland, diffuse hypoechogenicity<br>At 6 weeks, 50% were euthyroid, 50% were hypothyroid | Typical SAT is a possible and sometimes delayed presentation following acute COVID-19 |
| Das et al (50) | Single-center, prospective study<br>**Study population:**<br>74 consecutive patients admitted with COVID-19<br>Samples taken 0800-0900 in first 48 h of admission<br>Moderate/severe = $O_2$ sats < 94% on air, or with comorbidities, n = 35<br>Mild = $O_2$ sats <94% on air, and no comorbidities, n = 49 | **Sick euthyroid syndrome (fT3 <3.07 pmol/L, fT4 < 13.8 pmol/L with TSH ≤0.4-4.2mU/L):**<br>81% of patients with moderate/severe disease<br>73% of patients with mild disease<br>**Atypical thyroiditis (fT3 <3.07 pmol/L, fT4 >26.3 pmol/L, and TSH ≤0.4-4.2 mU/L):**<br>14% of patients with moderate/severe disease<br>2% of patients with mild disease | Patients with moderate/severe disease had greater incidence of sick euthyroid syndrome and atypical thyroiditis compared with those with mild disease. |



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**Table 1.** Continued

| Authors | Study design | Findings | Conclusion |
|---|---|---|---|
| Campi et al (44) | Single-center, prospective study<br>**Study population:**<br>n = 144 patients with COVID-19<br>Admitted to either ITU or non-ITU settings<br>115 met inclusion criteria (no previous thyroid dysfunction, no interfering medications [eg, amiodarone])<br>TFTs taken every 3-7 days during admission | Normal TSH at presentation and during admission: n = 76 (61%)<br>-n = 55 had normal fT4 and fT3<br>-n = 11 had low fT3 alone (4 of these on corticosteroids)<br>-n = 10 had low fT3 and fT4 (6 of these on corticosteroids)<br>Low TSH (<0.4 mU/L) at presentation but otherwise normal during admission: n = 12 (10%)<br>-n = 2 had normal fT4 and fT3<br>-n = 10 had normal fT4 and low fT3 (<2.9 pmol/L)<br>Normal TSH at presentation but reduced (<0.4 mU/L) during admission:<br>-n = 27 (24%)<br>-n = 12 had normal fT4 and fT3<br>-n = 13 had low fT3 alone (10 of these on corticosteroids)<br>-n = 2 had low fT3 and fT4 (both on corticosteroids)<br>fT3 predicted mortality<br>CRP, IL-6, and cortisol higher in patients with low TSH and fT3<br>TSH and fT3 restored by discharge | At presentation, majority of patients were euthyroid<br>Low TSH with normal fT4 and low fT3 = transient during admission.<br>Low TSH with normal fT4/low fT3 inversely correlated with CRP, IL-6, and cortisol, consistent with immune-mediated response, as opposed to destructive thyroiditis<br>Included patients who received corticosteroids as part of their treatment. |
| Khoo et al (34) | Cohort observational<br>**Study population:**<br>456 patients with suspected COVID-19<br>n = 334 COVID-19 confirmed<br>n = 122 COVID-19 not diagnosed<br>TFTs taken within first 48 h of admission<br>Subgroup of patients with COVID-19 with TSH preceding COVID-19 (n = 185)<br>Subgroup of patients with COVID-19 with fT4 preceding COVID-19 (n = 104) | Most patients (n = 289, 87%) were euthyroid at presentation<br>n = 20 had overt hypothyroidism (high TSH with low fT4)<br>n = 0 had overt hyperthyroidism (low TSH with high fT4)<br>Patients with COVID-19 had lower TSH and fT4 than those without COVID-19 ($P < 0.05$)<br>Admission TSH/fT4 levels were reduced compared with pre-COVID-19 values<br>By follow-up (median 79 days), TSH and fT4 returned to baseline (n = 50) | Most patients with COVID-19 euthyroid at presentation<br>No evidence of overt thyrotoxicosis/atypical thyroiditis<br>Thyroid dysfunction consistent with NTI/SES |
| Lui et al (43) | Prospective observational study<br>Study population:<br>n = 367 patients COVID-19 confirmed<br>TFTs taken within 24 h of admission | The majority of patients were euthyroid<br>No overt hyper-/hypothyroidism<br>n = 62 (16.9%) had abnormal TFTs<br>Of these:<br>n = 27 had NTI<br>n = 5 had preexisting autoimmune thyroid dysfunction<br>n = 30 had thyroiditis, 25 of whom were negative for autoantibodies<br>Patients with NTI were older, had worse symptoms, and more likely to have clinical deterioration<br>NTI independently predicted clinical deterioration in multivariable stepwise logistic regression (adjusted odds ratio 3.18, 95% CI 1.23-8.25, $P = 0.017$) | The majority of patients with COVID-19 are euthyroid<br>NTI is the most common thyroid dysfunction observed and is associated with clinical deterioration and poor prognosis |



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**Table 1.** Continued

| Authors | Study design | Findings | Conclusion |
|---|---|---|---|
| Lui et al (51) | Prospective observational study<br>**Study population:**<br>n = 191 consecutive patients with COVID-19<br>Blood tests taken on admission | n = 25 had abnormal TFTs<br>Of these, n = 14 (7.3%) had low TSH (<0.35 mU/L) and/or raised fT4 (>23 pmol)<br>n = 2 had thyroiditis (suppressed TSH with high normal fT4 and fT3) with positive autoantibodies consistent with Graves' disease<br>Compared with patients with normal fT3, those with low fT3 had:<br>Increased use of dexamethasone/supplementary oxygen ($P$ = 0.003)<br>Increased rates of prolonged hospital stay (≥14 days) $P$ = 0.018<br>Higher chance of deterioration in clinical severity ($P$ < 0.001)<br>Alterations in TSH not associated with deterioration in clinical severity | |
| Persistent effects | | | |
| Muller et al (32) | 8 patients with COVID-19 and deranged thyroid function tests (32)<br>Attended for US at mean of 55 (±8) days when negative for SARS-CoV-2 | - n = 2 (25%) had hypothyroidism.<br>US marked diffuse hypoechogenicity and heterogeneity consistent with autoimmune thyroiditis<br>- n = 6 (75%) had normal thyroid function and negative thyroid autoantibodies at follow-up. None reported neck pain. US: mild hypoechoic pattern, with evidence of reduced focal uptake on technetium-99m consistent with SAT | COVID-19 is associated with atypical subacute thyroiditis<br>Characterized by painless inflammation of thyroid gland |
| Clarke et al (24) | Prospective study<br>**Study population:**<br>70 patients with confirmed COVID-19<br>Assessment at ≥3 months after presentation<br>n = 68 complete TFTs | TFTs all within range at median of 210 days since admission<br>**Median (IQR):**<br>**TSH:** 1.32 (0.97, 2.09) mU/L<br>**fT4:** 12.30 (11.65, 13.08) pmol/L<br>**fT3:** 4.40 (4.08, 4.80) pmol/L<br>No difference in TFTs between those patients with fatigue at follow-up compared with those without | No evidence of persistent thyroid dysfunction in survivors of COVID-19 |

Presented are studies investigating the effects of COVID-19 on thyroid function test parameters.

Abbreviations: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; fT4, free T4; fT3; free T3; IQR, interquartile range; ITU, intensive treatment unit, LITU, low-intensity treatment unit; NTI, nonthyroidal illness; $O_2$ sats, oxygen saturations; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SAT, subacute thyroiditis, SES, sick euthyroid syndrome; TFT, thyroid function test; US, ultrasound.



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however, current evidence suggests that thyroid function returns to baseline with conservative management. The clinical relevance of such perturbations in thyroid function may therefore predominantly relate to their reflection of more severe disease and worse prognosis during acute presentation with COVID-19.

## The Adrenal Gland

### Background and Pathophysiology

Following the original SARS outbreak, it was reported that hypocortisolism (defined as either 8 AM cortisol ≤138 nmol/L, or stimulated cortisol ≤550 nmol/L following 250 mcg tetracosactide) affected 39.4% of patients at ≥3 months after acute infection (23). More recently, the ACE2 receptor has been identified by immunohistochemistry to be present in the adrenal cortex (52). It was highly prevalent in the zona fasciculata and reticularis (glucocorticoid and androgen production), but not in the zona glomerulosa (mineralocorticoid production) (52). Furthermore, TMPRSS2 was widely expressed throughout all 3 zones of the adrenal cortex (52). At autopsy, adrenal hemorrhage, ischemic necrosis, and focal inflammation were all described in patients who died of COVID-19 (52).

Finally, hyponatremia is commonly observed in patients with COVID-19, with 1 study finding up to 30% of patients with serum sodium values <135 mmol/L (53), and dysnatremia was associated with worse outcomes (54). Whilst there are several factors that account for this phenomenon, including the syndrome of inappropriate antidiuretic hormone and hypovolemia, if present adrenal insufficiency may also present with hyponatremia (55).

### Acute and Subacute Effects

Adrenal insufficiency secondary to acute adrenal infarction (56) and adrenal hemorrhage (57-59) have been described in case reports following COVID-19 (60). However, underlying comorbidities, such as antiphospholipid syndrome, may have been contributory in some cases (56). Adrenal function remains preserved in most patients with acute COVID-19. We observed that serum cortisol within the first 48 hours of admission in patients presenting with COVID-19 was significantly raised (61). Furthermore, high cortisol concentrations were associated with increased mortality, consistent with activation of the cortisol endocrine axis in acute illness (62). Conversely, critical illness may result in critical illness-related corticosteroid insufficiency resulting from physiological stress suppressing the hypothalamic-pituitary-adrenal axis (63). However, we did not find an increased proportion of patients with a cortisol <276 nmol/L (10 μg/dL) (threshold used to define critical illness-related corticosteroid insufficiency) in patients with COVID-19 (62). By contrast, in a study of 28 patients with COVID-19, morning cortisol levels on days 1 and 2 were observed to be <300 nmol/L in 64.3% of patients, but no dynamic function testing was undertaken (64). Only 1 patient in this cohort required admission to intensive care, and the sample size was small, making it difficult to generalize from these findings. In 84 patients admitted with COVID-19, hypocortisolism (cortisol <414 nmol/L) was observed in 38.4% of patients with moderate/severe disease compared with 6.8% of those with mild disease (50). However, data from only 13 patients with moderate/severe COVID-19 were included in the analysis and no dynamic function testing was undertaken to confirm adrenal insufficiency. In summary, most patients have preserved adrenal function during the first 48 hours after admission with COVID-19, and elevated levels correlated with worse clinical outcomes, with no confirmed reports of adrenal insufficiency.

Exogenous steroid treatment may impair adrenal function by suppressing the hypothalamic-pituitary-adrenal axis. In July 2020, the RECOVERY trial reported that treatment with dexamethasone reduced 28-day mortality in patients requiring oxygen therapy (47). Thus, it is notable that in our cohort of 70 survivors of COVID-19, 31.4% had received dexamethasone, but none had evidence of adrenal insufficiency on dynamic testing at ≥3 months after presentation (24).

### Persistent Effects

Symptoms of fatigue (65), postural hypotension, and cognitive impairment are frequently reported by patients with long COVID as well as by patients with adrenal insufficiency (66, 67). Thus, we assessed the degree to which adrenal insufficiency could explain the often-debilitating symptoms experienced by patients after acute COVID-19. In a cohort of 70 survivors, all patients had adequate adrenal reserve at ≥3 months after presentation with COVID-19 on dynamic testing, but neither baseline nor stimulated cortisol level corresponded with symptoms of fatigue (neither frequency nor severity) (24). Thus, whilst the fatigue experienced by patients is significant for many survivors of COVID-19, it does not appear to be explained by insufficient adrenal function.

To conclude, adrenal function remains preserved in most patients, and increased cortisol levels within the first 48 hours of admission are associated with increased mortality. Whilst there are case reports of adrenal insufficiency in patients with COVID-19, related to acute vascular complications (eg, hemorrhage/thrombosis), corticosteroid

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production is not impaired. Furthermore, whilst symptoms of long COVID have similarity to those of adrenal insufficiency, there remains little robust evidence of glucocorticoid deficiency, even in patients treated with dexamethasone.

## The Gonads

### The Testes

#### Background and pathophysiology

Recently, using single-cell RNA sequencing, ACE2 receptors have been demonstrated in testicular germ cells, Leydig cells, and Sertoli cells (68). Furthermore, ACE2 and TMPRSS2 mRNA expression was up-regulated in patients with COVID-19 (69). However, whilst some studies have failed to demonstrate the presence of SARS-CoV-2 in the testes (70, 71), 1 study observed its presence in 2 patients using RT-quantitative PCR, with additional confirmation provided by immunohistochemistry (69). Coronavirus-like particles were also observed in the interstitial compartment of the testes of patients with COVID-19 at autopsy, providing evidence of direct testicular damage by SARS-CoV-2 (69). Histology of the testes of patients with COVID-19 demonstrated significant germ cell (GC) loss at postmortem, with a near-complete absence of GC in the seminiferous tubules, although strikingly Sertoli cells were spared (69). Interestingly, only 1 study has identified SARS-CoV-2 in the semen of men with COVID-19 (72), whereas the majority of studies have not (71, 73-77). In summary, there is evidence to suggest that not only are the testes susceptible to damage by SARS-CoV-2, but also that in some patients with COVID-19, significant morphological changes occur which could impair GC function.

#### Acute and subacute effects

In keeping with the histopathological findings, patients with COVID-19 have presented with testicular pain and either epididymo-orchitis or orchitis in isolation (78-80). Likewise, testicular pain was reported by 10.9% of patients with acute COVID-19 in 1 study (81) (Table 2). More than one-fifth (22.5%) of 142 men with acute COVID-19 infection had ultrasound evidence of orchitis or epididymo-orchitis at 1 week to 1 month posthospitalization, with the risk of epididymo-orchitis increasing with severity of COVID-19 and advancing age (82) (Table 2). By contrast, a study of 253 male patients did not find any features of acute orchitis in patients with COVID-19; however, this study relied on physical symptoms/examination for diagnosis rather than ultrasound and included a younger cohort with a shorter duration of follow-up (83) (Table 2).

Whilst evidence is mixed regarding the presence of SARS-CoV-2 in semen, COVID-19 may affect testicular function, by way of spermatogenesis, via mechanisms other than the direct effects of the virus in the testes. It is known that fever has a negative impact on spermatogenesis (84). In a small study of 18 men with COVID-19, those with moderate infection had reduced sperm concentration, total number of sperm per ejaculate, and total number of progressive complete motility compared with those with mild disease and healthy controls (77) (Table 2). Interestingly, men with fever had reduced semen volume and reduced motility compared with those without (77) (Table 2). Other studies have also reported both motility and normal morphology of sperm to be reduced in men with COVID-19 (75, 85). When compared with healthy age-matched controls, sperm concentration and total sperm count were reduced in 55 male patients who had recovered from COVID-19, compared with healthy controls at a median of 80 days postinfection (86).

Leydig cells are the predominant source of testosterone production in males. In a small study, men with untreated COVID-19 had reduced serum LH, FSH, and total testosterone compared with men treated with oral hydroxychloroquine and azithromycin (n = 10) or age-matched controls without COVID-19 (Table 2) (87). Likewise, in a study in China, 119 men with COVID-19 had higher serum LH, lower total testosterone:LH ratio, and lower FSH:LH ratio compared with age-matched controls, consistent with testicular damage (75) (Table 2). Finally, in a preprint from a study in Germany, men admitted to the ITU with COVID-19 had reduced total testosterone compared with age-matched men with coronary heart disease or healthy controls (88). Of those with low calculated free testosterone values (n = 28, 66.7%), 7 (25%) had elevated LH values, with the authors concluding that this was reflective of defective Leydig cell function (88). However, most men with low calculated free testosterone values had either low or normal serum LH values (88), suggesting that this hypogonadism could be due to hypothalamic-pituitary dysfunction, secondary to reduced GnRH pulsatility, a phenomenon known to occur with physiological stressors (89, 90). Finally, a recent prospective study observed that men with severe COVID-19 (n = 66) had lower median testosterone values than those with mild disease (admission median testosterone: 1.84 vs 5.24 nmol/L), and that testosterone concentrations were inversely related to cytokines, including IL-6, and C-reactive protein (CRP), suggesting that the hypogonadism is immune-mediated (91) (Table 2).

#### Persistent effects

Despite acute reduction in testosterone in men with COVID-19, there remains little evidence of a persistent effect beyond recovery. Serum LH, FSH, and total testosterone values were all within normal limits at a median of

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**Table 2.** The effect of COVID-19 on male gonadal function

| Authors | Study design | Findings | Conclusion |
|---|---|---|---|
| Testes—acute effects | | | |
| Ediz et al (81) | Prospective observational study<br>**Study population:**<br>91 males diagnosed with COVID-19<br>Aged 18-75 y<br>Questionnaire to assess for testicular pain, and blood tests (CRP, D-dimer, neutrophil, lymphocyte count) | 10 of 91 patients reported testicular pain<br>No difference in blood parameters between groups<br>No difference in age between groups | Limited by recall bias and absence of confirmatory US scan<br>Testicular pain may affect up to 10% of patients with COVID-19 |
| Chen et al (82) | Retrospective observational study<br>**Study population:**<br>142 hospitalized male patients<br>58.3 years (range, 24-91 y)<br>Scrotal US scan at 1 week-1 month after initial symptoms/admission | n = 32 (22.5%) acute orchitis, epididymitis, or epididymo-orchitis on scrotal US imaging<br>Risk of acute scrotal infection increased with age.<br>Incidence 53.3% in men >80 y.<br>Risk of epididymo-orchitis increased in severe COVID-19 compared to nonsevere COVID-19 ($P = 0.04$). | Infection with SARS-CoV-2 results in US findings orchitis<br>Increased risk with increasing age and severity of COVID-19 |
| Alkhatabeh et al (83) | Retrospective observational study<br>**Study population:**<br>253 hospitalized male patients<br>Assessed by urology team every 2 days during admission up until 21 days | Mean age, 43 y<br>No patient had any symptoms or signs of epididymo-orchitis | No association between COVID-19 and symptoms or signs of orchitis<br>Limited assessment undertaken |
| Holtmann et al (77) | Prospective cohort study<br>**Study population:**<br>18 males recovered from COVID-19<br>14 healthy male volunteers<br>n = 14 mild COVID-19<br>n = 4 moderate COVID-19<br>n = 14 healthy controls<br>Freshly collected semen analyzed | SARS-CoV-2 not detected in semen of either those recovered or healthy controls<br>Sperm concentration:<br>**Mild:** 95.9 ± 50.5 × $10^6$/mL<br>**Moderate:** 16.2 ± 22.45 × $10^6$/mL<br>**Control:** 89.5 ± 69.6 × $10^6$/mL<br>$P < 0.05$<br>Total no. of sperm per ejaculate:<br>**Mild:** 243.7 ± 140.4 × $10^6$<br>**Moderate:** 11.9 ± 13.4 × $10^6$<br>**Control:** 233.1 ± 234.4 ×$10^6$<br>$P < 0.05$<br>Total no. of immotile<br>**Mild:** 86.6 ± 66.5 × $10^6$<br>**Moderate:** 7.2 ± 9.4 × $10^6$<br>**Control:** 109.1 ± 121 × $10^6$<br>$P < 0.05$<br>**Sperm concentration:**<br>**No fever:** 100.9 ± 31.1 × $10^6$/mL<br>**Fever:** 60.0 ± 66.8 × $10^6$/mL<br>$P < 0.05$<br>**Total no. of sperm per ejaculate:**<br>**No fever:** 283.6 ± 124 × $10^6$<br>**Fever:** 119.0 ± 147.5 × $10^6$<br>$P < 0.05$<br>**Total no. of immotile**<br>**No fever:** 98.01 ± 67.6 × $10^6$<br>**Fever:** 45.7 ± 60.6 × $10^6$<br>$P < 0.05$ | SARS-CoV-2 not detected in semen<br>Sperm quality reduced in patients with moderate COVID-19 compared with those with mild disease, or healthy controls<br>Sperm quality reduced in patients with COVID-19 who experienced fever compared with those who did not |

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**Table 2.** Continued

| Authors | Study design | Findings | Conclusion |
|---|---|---|---|
| Ruan et al (86) | Prospective study<br>**Study population:**<br>N = 74 males aged 20-50 y recovered from COVID-19<br>Semen, blood tests collected at median of 80 days after COVID-19 confirmation<br>N = 55 males with semen for analysis<br>Compared with 145 age-matched healthy controls | No evidence of SARS-CoV-2 mRNA in semen, urine, or expressed prostatic secretions<br>**Sperm concentration:**<br>**COVID-19:** 66.41 ± 31.82 × $10^6$/mL<br>**Healthy controls:** 81.31 ± 50.60 × $10^6$/mL<br>*P* = 0.04<br>**Total sperm count:**<br>**COVID-19:** 197.40 ± 123.80 × $10^6$/mL<br>**Healthy controls:** 261.40 ± 189.20 × $10^6$/mL<br>*P* = 0.02<br>**Total motility:**<br>**COVID-19:** 48.89 ± 13.72%<br>**Healthy controls:**56.38 ± 10.83%<br>*P* = < 0.001<br>No significant difference in semen parameters between mild/moderate/severe disease | Semen quality was reduced with increasing time from positive COVID-19 test |
| Temiz et al (87) | Prospective observational study<br>**Study population:**<br>Males 18-60 y<br>n = 10 age-matched healthy controls<br>n = 10 patients with COVID-19 pretreatment<br>n = 10 patients with COVID-19 posttreatment (oral hydroxychloroquine and azithromycin) | **Serum LH (IU/L):**<br>**COVID-19 pretreatment**<br>2.98 ± 1.65<br>**COVID-19 posttreatment**<br>3.22 ± 3.83<br>**Controls**<br>4.46 ± 2.06<br>*P* = 0.04<br>**Serum FSH (IU/L):**<br>**COVID-19 pretreatment**<br>2.04 ± 1.36<br>**COVID-19 posttreatment**<br>3.15 ± 0.70<br>**Controls**<br>3.92 ± 2.35<br>*P* = 0.01<br>**Total testosterone (nmol/L):**<br>**COVID-19 pretreatment**<br>3.92 ± 4.44<br>**COVID-19 posttreatment**<br>7.84 ± 6.45<br>**Controls**<br>10.05 ± 6.48 | Patients with COVID-19 pretreatment had significantly lower serum LH, FSH, and total testosterone compared with controls<br>Patients with COVID-19 posttreatment had similar LH, FSH, and total testosterone compared with controls<br>Findings of reduced LH, FSH, and total testosterone consistent with stressor effect on HPG axis |
| Ma et al (75) | Prospective observational study<br>**Study population for semen analysis:**<br>n = 12 males with confirmed COVID-19<br>n = 1 mild COVID-19<br>n = 11 moderate/severe COVID-19<br>**Study population for hormonal parameter analysis:**<br>n = 119 males with confirmed COVID-19<br>n = 273 age-matched controls | Most patients (n = 8) had normal semen parameters<br>**Serum LH (IU/L):**<br>**COVID-19**<br>6.36 (4.63-8.37)<br>**Healthy controls**<br>3.38 (2.48-4.52); *P* < 0.0001<br>**Testosterone:LH ratio**<br>**COVID-19**<br>0.68 (0.43-0.96)<br>**Healthy controls**<br>1.24 (0.92-1.84)<br>*P* < 0.0001<br>**Multiple regression analysis:**<br>Serum testosterone:LH negatively associated with WCC and CRP | Multiple regression analysis showed WCC negatively correlated with total testosterone:LH, suggesting those with more significant disease had an element of testicular resistance<br>Authors suggest this was immune mediated |

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**Table 2.** Continued

| Authors | Study design | Findings | Conclusion |
|---|---|---|---|
| Dhindsa et al (91) | Prospective cohort study<br>**Study population:**<br>N = 90 males with COVID-19<br>(66 of 90 men had severe COVID-19) | **Median T on admission:**<br>**Severe COVID-19:** 1.84 nmol/L<br>**Nonsevere COVID-19:** 5.24 nmol/L<br>*P* = 0.008<br>In males with severe COVID-19:<br>Total testosterone lower on day 1 vs day 151 (*P* = 0.01)<br>Total testosterone negatively associated with<br>-CRP (*P* < 0.01)<br>-IL-6 (*P* < 0.04)<br>Estradiol and IGF-1 concentrations not associated with severity of COVID-19 | Lower total testosterone observed in acute infection in pts with severe COVID-19<br>Evidence of recovery with increased time from diagnosis<br>Total testosterone negatively associated with markers of inflammation |
| Testes—persistent effects | | | |
| Ruan et al (86) | Prospective study<br>**Study population:**<br>n = 74 males aged 20-50 y recovered from COVID-19<br>Semen, blood tests collected at median of 80 days after COVID-19<br>Compared with 145 age-matched healthy controls | Normal endocrine parameters at a median of 77 days postinfection | In men recovered from COVID-19, no evidence of persistent reduction in endocrine gonadal function |
| Moreno-Perez et al (92) | Cross-sectional study<br>Study population:<br>n = 143 male patients recovered from COVID-19<br>Median 77 days after symptom onset<br>n = 103 severe inpatients<br>n = 19 nonsevere (outpatient) | **Low serum testosterone:**<br>Defined as total testosterone <6.9 nmol/L or calculated free testosterone <0.22 nmol/L<br>**Sertoli cell dysfunction:**<br>Inhibin-B <89 ng/L<br>**Low serum testosterone:**<br>n = 41 (29%): rates not different in patients according to severity<br>n = 25 (18%): low inhibin-B<br>Multivariable analysis:<br>Obesity and hypokalemia associated with low testosterone<br>Age >65 y was independent predictor of Sertoli cell dysfunction<br>No relationship between prevalence hypogonadism/Sertoli cell dysfunction and symptoms of "post-COVID-syndrome" | Evidence of gonadal function is not uncommon in patients recovered from COVID-19<br>Prolonged studies required to determine persistent effects in longer term |

Presented are studies investigating the effects of COVID-19 on testicular function.
Abbreviations: COVID-19, coronavirus disease 2019; CRP; C-reactive protein; HPG, hypothalamic-pituitary-gonadal; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; US, ultrasound; WCC, white cell count.

80 days after acute infection in an uncontrolled study of 66 men who had recovered from COVID-19 (86) (Table 2), with recovery of testosterone toward baseline levels by 28 days after presentation (91).

Male hypogonadism is associated with the metabolic syndrome, altered body composition, and constitutional symptoms such as fatigue. A recent study from Spain of 143 men at a median of 77 days after initial presentation found that 28.7% had low total testosterone (<6.9 nmol/L), whereas 18.1% had low inhibin-B, but neither of these correlated with symptoms of "post-COVID syndrome" (92). Whilst a single testosterone value without preinfection levels for comparison is difficult to interpret, the absence of correlation with post-COVID syndrome is clinically relevant. Taken together, although the testes are vulnerable to damage by SARS-CoV-2 and there is evidence to suggest that patients with SARS-CoV-2 have reduced testosterone values compared with other critical illnesses, the evidence to date suggests that any fall in testosterone levels resolves spontaneously after recovery from acute illness.

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## The Ovaries

### Background and Pathophysiology

Whilst most studies have focussed on the male reproductive axis, reports of menstrual irregularity have raised the possibility of altered function of the female reproductive system. In a recent survey of 1031 women (mean age, 36.7 years), 46% had experienced a change in their menstrual cycle since the start of the pandemic, with new-onset menorrhagia, dysmenorrhea, or increased variability of cycle length (93). Whilst changes to psychological and overall physical health (including weight gain, reduced exercise, and low mood) could account for some of these findings (93), it is important to consider any effect of SARS-CoV-2 on ovarian function.

The female reproductive system possesses ACE2 receptors, albeit to a lesser degree than the male reproductive system, with ovarian ACE2 mRNA detected in both pre- and postmenopausal women (94). ACE2 is important in regulating angiotensin II and angiotensin (1-7), both of which have important roles in the regulation of follicular development (95, 96), oocyte maturation (97), and maintenance of the corpus luteum (98). Additionally, ACE2 (and TMPRRS2) have been identified in both the epithelial and stromal cells of the endometrium in the proliferative phase of the menstrual cycle, and stromal cell ACE2 expression was increased during the secretory phase (99). Correspondingly, progesterone treatment to ovariectomized mice increased expression of stromal cell ACE2, consistent with progesterone being a regulator of endometrial ACE2 (99).

### Acute and Subacute Effects

In a prospective study from China, median serum anti-Müllerian hormone was lower in patients with COVID-19 compared with controls ($P < 0.05$) (Table 3). Serum LH, total testosterone, and prolactin were higher in the follicular phase of women with COVID-19 compared with healthy controls. Prolactin is known to be increased during times of stress (100), which could account for this observation. In another cohort of 62 women with COVID-19, there were no significant changes in estradiol, testosterone, or IGF-1 during hospitalization and no differences in disease severity or inflammatory markers (91) (Table 3). Importantly, this study included women of all ages diagnosed with COVID-19; their menopausal status and other sex hormones were not provided, making it difficult to fully interpret these findings (91).

A further cross-sectional study of 177 premenopausal women diagnosed with COVID-19 found that more women with severe COVID-19 had cycle lengths lasting more than 37 days than those with mild disease (34% vs 19%, $P = 0.001$) (101). In those with available data (n = 91), there was no difference in serum anti-Müllerian hormone, LH, FSH, estradiol, progesterone, or testosterone compared with age-matched prepandemic historic controls (101) (Table 3).

### Persistent Effects

Unfortunately, there are scant data on the effects of COVID-19 infection on ovarian function beyond the noninfective impact of the pandemic such as increased psychological stress and weight gain. In an international survey of patients experiencing long COVID, 36.1% reported changes to their menstrual cycle following COVID-19, including new onset of irregular periods, abnormally heavy periods, and postmenopausal bleeding (102).

In summary, both the acute and chronic effects of COVID-19 on the female hypothalamic-pituitary-gonadal (HPG) axis remain unclear. Because the prevalence of COVID-19 appears to be equal between sexes (103), and the female reproductive axis is vulnerable to COVID-19, further research into the impact of the disease on the female HPG axis is needed. Whilst the widespread impact of the COVID-19 pandemic, and the vulnerability of the female HPG axis to psychological and physical stressors render it difficult to fully decipher the impact of SARS-CoV-2, this remains a key area for future research.

## The Endocrine Pancreas

### Background and Pathophysiology

Whilst a full discussion regarding the hyperglycemic effects of COVID-19 is beyond the scope of this mini-review, and has been skillfully covered by others (105, 106), this section will focus on the potential for islet cell destruction and subsequent impairment of glycemic control.

During the SARS pandemic, hyperglycemia in patients not previously known to be diabetic was reported, with 51.3% of 39 nondiabetic patients diagnosed with SARS, meeting diagnostic criteria for diabetes during their inpatient admission (107). Similarly, reports emerged of patients presenting with ketosis (108), new-onset hyperglycemia, and new diagnoses of diabetes (109, 110), with patients with type 1 or type 2 diabetes having an increased risk of mortality following COVID-19 (111). Indeed, such is the scale of the problem, that an international registry has been established to investigate the complex interaction between diabetes and COVID-19 (112).

SARS-CoV-2 is able to infect and replicate in human endocrine pancreas cells (113) and SARS-CoV-2 viral RNA has been detected in the β cells of patients with COVID-19

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**Table 3.** The effect of COVID-19 on female gonadal function

| Authors | Study design | Findings | Conclusion |
|---|---|---|---|
| Ovaries—acute effects | | | |
| Li et al (101) | Retrospective cross-sectional study<br>**Study population:**<br>n = 237 women aged 18-45 y with confirmed COVID-19<br>Of these:<br>n = 177 complete menstrual history<br>n = 91 serum bloods in early follicular phase<br>n = 91 age-matched controls | **Menstrual cycle:** n = 50 (28%) menstrual cycle disturbance (including change in cycle length)<br>**Serum AMH:** Not significantly different between healthy controls and those with COVID-19<br>Not significantly different between those with severe and non-severe COVID-19<br>**Serum E2 and progesterone:** Not significantly different between healthy controls and those with COVID-19 | Transient changes in menstrual function<br>No significant differences in endocrine parameters |
| Dhindsa et al (91) | Prospective cohort study<br>**Study population:**<br>n = 62 women mean age 63 y with COVID-19<br>Of whom:<br>60% severe disease<br>40% nonsevere disease<br>Serum T, E2, IGF-1 taken on admission and days 3, 7, 14, and 28 of admission | **Serum testosterone, E2, IGF1:** Not different between severe vs nonsevere COVID-19<br>**Serum testosterone, E2, IGF1 on day 0 and 3:** No correlation with cytokines including CRP or IL-6 | Endocrine parameters did not alter with COVID-19 disease severity<br>Endocrine parameters did not alter with inflammatory response |
| Ding et al (104) | Observational single-center study<br>**Study population:**<br>n = 78 women aged 43.5 y diagnosed with COVID-19<br>n = 17 diagnosed as severe COVID-19<br>n = 39 had blood taken in the follicular phase<br>Compared with:<br>151 healthy controls | **Menstrual cycle:** n = 51 (75%) normal menstrual cycle<br>**Serum AMH (ng/mL):**<br>**COVID-19:** 0.28<br>**Healthy controls:** 1.12, $P = 0.03$<br>**Serum FSH (IU/L):**<br>**COVID-19:** 6.35<br>**Healthy controls:** 7.81, $P = 0.02$<br>**Serum testosterone (ng/mL)**<br>**COVID-19:** 0.39<br>**Healthy controls:** 0.22, $P < 0.001$<br>**Serum PRL (ng/mL)**<br>**COVID-19:** 24.1<br>**Healthy controls:** 12.12, $P < 0.001$ | Menstrual cycle disturbed for 25% of patients with COVID-19<br>Serum AMH reduced in patients with COVID-19<br>Serum testosterone and prolactin increased in patients with COVID-19 |
| Ovaries—persistent effects | | | |
| Davis et al (102) | Retrospective study<br>International survey distributed via social media<br>**Study population:**<br>N = 17,929 women aged ≥18 y with menstrual cycle<br>COVID-19 or suspected COVID-19<br>Symptoms for >28 days | n = 6472 (36.1%) reported menstrual disturbance<br>26.1% had abnormally irregular cycles<br>19.7% had abnormally heavy cycles<br>Of 1123 women > 49 y: 4.5% postmenopausal bleeding/spotting. | Although no direct measure of ovarian function, disordered menstrual bleeding observed |

Presented are select studies investigating the effects of COVID-19 on ovarian function.
Abbreviations: AMH, anti-Müllerian hormone; COVID, coronavirus disease 2019; E2; estradiol; PRL, prolactin.



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at autopsy (114). Both the ACE2 receptor and TMPRSS2 protein have been detected in the microvasculature of the pancreas (115, 116); however, there is conflicting evidence regarding the presence of ACE2 receptors in β cells. Several studies have failed to demonstrate the presence of ACE2 in pancreatic β cells (115, 116), whilst others have observed increased ACE2 expression in pancreatic islets (107, 117). Recently, variable ACE2 expression was found in pancreatic β cells of patients who died of COVID-19, which correlated with the cytokine response (117).

### Acute and Subacute Effects

Ketoacidosis can occur in the context of insufficient pancreatic insulin secretion to meet the glycemic needs, and is typically observed in type 1 diabetes, secondary to autoimmune destruction of beta cells. However, ketoacidosis has also been reported in patients with T2 diabetes mellitus (T2DM) with COVID-19. Indeed, 1 meta-analysis found that 77% of patients diagnosed with ketoacidosis had T2DM (118). In the majority of cases, this appeared to be secondary to insulinopenia (119, 120); however, it is also possible that this is a consequence of the significant insulin resistance observed in patients with COVID-19 (106) leading to β-cell failure (119). Patients presenting with ketoacidosis during the SARS-CoV-2 outbreak were more likely to be older, have T2DM, and in nonwhite ethnic groups, than historic controls (121).

Additionally, new-onset type 1 diabetes has been reported following COVID-19 (122), with some remaining islet cell autoantibody negative (123, 124). Thus, the existence of autoantibody-negative, insulin-requiring diabetes following COVID-19, together with the histopathological findings, suggests that, at least in some individuals, COVID-19 could be associated with β-cell functional impairment or destruction.

Finally, along with the potential for β-cell destruction, a recent small study (n = 10-15 per group) from Italy suggested that COVID-19 may disrupt β-cell function in patients without known diabetes (125). Both patients with acute COVID-19 and those recovering from COVID-19 had an increased insulin response to arginine stimulation compared with healthy controls (125). suggesting that COVID-19 may cause β-cell hypersecretion, which could, in turn, result in relative secretory failure.

### Persistent Effects

Whilst the long-term effects of COVID-19 on hyperglycemia remain to be fully elucidated, 1 study found that by 6 months after admission, 63% of those diagnosed with hyperglycemia during their admission had recovered euglycemia (125). Nevertheless, more than one-third still had persistent hyperglycemia (blood glucose 100-199 mg/dL), and ~2% had overt diabetes (125). Similarly, at 3 years following SARS, 5% of patients diagnosed with new-onset diabetes during their admission still had diabetes (107).

To summarize, SARS-CoV-2 is associated with hyperglycemia and ketoacidosis occurring more frequently in older patients with T2DM, and can affect those not previously treated with insulin. Whilst this may be due to the stress response that occurs in severe illness (characterized by increased cortisol and glucagon, resulting in a relative insulin deficiency) direct damage to the β-cell structure and function is possible. Thus, further characterization of the effects of COVID-19 on dysglycemia in future research will be of clinical relevance.

## Conclusions

As we near the conclusion of the second year of the COVID-19 pandemic, it is apparent that its additional impact beyond the respiratory system is clinically important and may have additional effects on health and quality of life. The endocrine system is particularly vulnerable to perturbation from the COVID-19 infection, with thyroid dysfunction and hyperglycemia being widely reported. However, much remains to be investigated regarding the impact of COVID-19 on the endocrine system. Specifically, the trajectory of hyperglycemia that is well documented in the acute phase remains an important focus of investigation, with clear implications for the future metabolic health of COVID-19 survivors. Additionally, gonadal function appears to be vulnerable to disruption, and remains underresearched particularly in women, despite reports of change to menstruation and reproductive health. Finally, as the long-term effects of COVID-19 become an ever-increasing challenge to health care systems, the extent to which endocrine dysfunction contributes to long-COVID is currently unknown, and thus forms a priority area for future research.

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