Impact of COVID-19 on the Endocrine System – a mini-review

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Abstract

The Corona Virus Disease 2019 (COVID-19) pandemic continues to exert a significant impact on global healthcare 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, SARS-CoV-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 summarises data investigating the effects of COVID-19 on each of the endocrine axes to guide appropriate investigations and optimal management.

Key Terms: COVID-19, SARS-CoV-2, adrenal insufficiency, adrenal function, thyroid function, thyroid gland, endocrine.

Introduction

SARS-CoV-2 and its variants will impact on global healthcare systems over the upcoming years across the world. Furthermore, the effects of 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.

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 an S1 and S2 subunit, 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 Figure 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 (Figure 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 anti-serum to human ACE2 prevented cellular access by SARS-CoV-2 [4]. Additionally, unlike other coronaviruses, SARS-CoV-2 does not appear to utilise other receptors for cellular access, such as dipeptidyl peptidase 4 (DPP4) or aminopeptidase N (APN) [4,7].

In humans, ACE2 mRNA is expressed in several endocrine glands including the pancreas, thyroid gland, ovaries and testes [8] (see Figure 2). Crucially, TMPRSS2 mRNA 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 due to 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, post-mortem pituitary tissue from patients with pituitary neuroendocrine tumours also display low ACE2 expression [10]. Nevertheless, SARS-CoV mRNA was detected within the pituitary gland at autopsy [11], and post-mortem investigation of five patients who died of SARS, demonstrated reduced somatotrope, thyrotrope and corticotrope cell number and immunoreactivity staining for growth hormone (GH), thyroid stimulating hormone (TSH) and adrenocorticotropic hormone (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 Sub-acute effects

The pituitary gland has a rich vascular supply; as vascular endothelium has 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, characterised 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 tumours 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 pre-existing 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 3-6 months post-SARS with the majority of patients reverting to euthyroidism by 9 months post-infection [23]. By contrast, our group have 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 pituitary gland by SARS-CoV-2. However, the inflammatory state after COVID-19 in combination with unique increased hypercoagulability that characterises acute infection could theoretically precipitate pituitary apoplexy in patients with a pre-existing macroadenoma.

The Thyroid Gland

Background and Pathophysiology

Patients diagnosed with SARS had reduced thyroid function. Furthermore, at post-mortem, 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 Sub-acute Effects

Early in the pandemic, several cases of sub-acute thyroiditis were reported [28–31]. Amongst patients admitted to ITU, those with COVID-19 were more likely to have thyrotoxicosis [32]. Likewise, those with COVID-19 admitted to high intensity ITU had a lower TSH compared to 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 to baseline [34] (Table 1).

In addition to subacute thyroiditis, case reports have emerged of Graves' thyrotoxicosis in patients

with COVID-19 [35,36], one 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].

Non-thyroidal illness syndrome (NTIS) occurs during physiological stress, and is characterised by an initial reduction in total T3 (TT3) and fT3, with an increase in reverse T3 (rT3) but without a concomitant rise in TSH [39]. Persistent illness results in global reductions in TSH, fT4 and fT3 [40] due to a reduction in hypothalamic thyrotropin releasing hormone (TRH) [41]. It is therefore unsurprising that several studies have reported features consistent with NTIS in patients with COVID-19.

Patients with pneumonia due to COVID-19 were observed to have lower serum TSH and TT3 levels than other forms of pneumonia, although there was no difference in total T4 (TT4) 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 higher levels of 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 non-survivors (Table 1). Moreover, given that corticosteroid use is now gold-standard for patients requiring oxygen supplementation [47], it should be noted that exogenous steroids can reduce TSH levels [48] and peripheral conversion of T4 to T3, providing an additional mechanism for thyroid dysfunction.

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

Authors	Study Design	Findings	Conclusion
Acute Effects			
Muller et al [32]	Retrospective study **Study population:** n=93 patients admitted to ITU in 2020 with COVID-19 n=101 patients admitted to ITU in 2019 (pre-SARS-CoV-2 pandemic) n=52 COVID-19 low intensity ITU (LITU) admission TSH and fT4 measured within 2 days of admission	**Thyrotoxicosis: (TSH<0.28 mIU/L and/or FT4 >21.9 pmol/L)** - 13/85 (15%) with COVID-19 in ITU - 1/41 (2%) with COVID-19 in low intensity ITU - 1/78 (1%) with no COVID-19 in ITU **Median (IQR) TSH (mU/L):** ITU 2020 with COVID-19: 1.04 (0.47-1.80) LITU 2020 with COVID-19: 1.43 (0.71-2.28) ITU 2019 with no COVID-19: 1.43 (0.88-2.37) **Mean ±SD fT4 (pmol/L):** ITU 2020 with COVID-19: 18.6±5.4 LITU 2020 with COVID-19: 13.5±4.6 ITU 2019 with no COVID-19: 16.2 ± 2.4	Patients with severe COVID-19 may present with thyrotoxicosis fT4 and fT3 only measured when TSH <0.45mU/L as per local policy Thyrotoxicosis defined as TSH<0.28mU/L and/or fT4>21.9pmol/L
Lania et al [33]	Single centre, retrospective study **Study population:** n= 287 patients admitted with COVID-19, not requiring ITU admission TSH measured as routine for all patients admitted with COVID-19	**Thyrotoxicosis (TSH <0.34mU/L and/or fT4 >17.29pmol/L):** n=58 (20.2%) **Hypothyroidism (TSH >4.80mU/L and/or fT4 <7.82pmol/L):** n=15 (5%) **Euthyroid:** n=214 (75%) TSH inversely correlated with age (rho −0.27; P < 0.001) and IL-6 (rho −0.41; P < 0.001). 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 fT4 and fT3 only measured when TSH <0.45mU/L or >4.80mU/L as per local policy
Brancatella et al [49]	Case series 4 female patients presenting with SAT following recovery from COVID-	Presentation at 16-36 days after resolution of COVID-19 symptoms Presented with characteristic symptoms of SAT: neck pain, fever,	'Typical' SAT is a possible and sometimes delayed presentation following acute COVID-19

	19	palpitations US – enlarged thyroid gland, diffuse hypoechogenicity At 6 weeks', 50% were euthyroid; 50% were hypothyroid	
Das et al [50]	Single-centre, prospective study **Study population:** 74 consecutive pts admitted with COVID-19 Samples taken 0800-0900 in first 48hrs admission Moderate/severe = 0_2 sats<94% on air, or with comorbidities, n=35 Mild = 0_2 saturation <94% on air, and no comorbidities, n=49	**'Sick euthyroid syndrome' (fT3 <3.07pmol/L, fT4<13.8pmol/L with TSH ≤0.4-4.2mU/L):** 81% of pts with moderate/severe disease 73% of pts with mild disease **'Atypical thyroiditis' (fT3 <3.07pmol/L, fT4>26.3pmol/L and TSH ≤0.4-4.2mU/L):** 14% of pts with moderate/severe disease 2% of pts with mild disease	Pts with moderate/severe disease had greater incidence of sick euthyroid syndrome and atypical thyroiditis compared to those with mild disease.
Campi et al [44]	Single-centre Prospective study **Study population:** n=144 pts with COVID-19 Admitted to either ITU or non-ITU settings 115 met inclusion criteria (no previous thyroid dysfunction, no interfering medications eg amiodarone) TFTs taken every 3-7 days during	Normal TSH at presentation and during admission: n=76 (61%) - n=55 had normal fT4 and fT3 - n=11 had low fT3 alone (4 of these on corticosteroids) - n=10 had low fT3 and fT4 (6 of these on corticosteroids) Low TSH (<0.4mU/L) at presentation but otherwise normal during admission: n=12 (10%) - n=2 had normal fT4 and fT3 - n=10 had normal fT4 and low fT3 (<2.9pmol/L) Normal TSH at presentation but reduced (<0.4mU/L) during admission:	At presentation, majority of patients were euthyroid Low TSH with normal fT4 and low fT3 = transient during admission. 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 Included patients who received corticosteroids as part of their treatment.

	admission	n=27 (24%) - n=12 had normal fT4 and fT3 - n=13 had low fT3 alone (10 of these on corticosteroids) - n=2 had low fT3 and fT4 (both on corticosteroids) fT3 predicted mortality CRP, IL-6 and cortisol higher in pts with low TSH and fT3 TSH and fT3 restored by discharge	
Khoo et al [34]	Cohort observational **Study population:** 456 pts with suspected COVID-19 n=334 COVID-19 confirmed n=122 COVID-19 not diagnosed TFTs taken within first 48hrs of admission Subgroup of pts with COVID-19 with TSH preceding COVID-19 (n=185) Subgroup of pts with COVID-19 with fT4 preceding COVID-19 (n=104)	Most patients (n=289, 87%) were euthyroid at presentation n=20 had overt hypothyroidism (high TSH with low fT4) n=0 had overt hyperthyroidism (low TSH with high fT4) Pts with COVID-19 had lower TSH and fT4 than those without COVID-19 (P <0.05) Admission TSH/fT4 levels were reduced compared to pre-COVID-19 values By follow-up (median 79 days), TSH and fT4 returned to baseline (n=50)	Most pts with COVID-19 euthyroid at presentation No evidence of overt thyrotoxicosis/atypical thyroiditis. Thyroid dysfunction consistent with NTI/SES
Lui et al [43]	Prospective observational study **Study population:** n=367 pts COVID-19 confirmed TFTs taken within 24hrs admission	The majority of patients were euthyroid No overt hyper-/hypothyroidism n=62 (16.9%) had abnormal TFTs Of these: n=27 had NTI n=5 had pre-existing autoimmune thyroid dysfunction n=30 had thyroiditis, 25 of whom were negative for autoantibodies	The majority of patients with COVID-19 are euthyroid NTI is the most common thyroid dysfunction observed and is associated with clinical deterioration and poor prognosis

		Pts with NTI were older, worse symptoms and more likely to have clinical deterioration NTI independently predicted clinical deterioration in multivariable stepwise logistic regression (adjusted odds ratio 3.18, 95% CI 1.23–8.25, P = 0.017)	
Lui et al [51]	Prospective observational study **Study population:** n=191 Consecutive patients with COVID-19 Blood tests taken on admission	n=25 had abnormal TFTs Of these, n=14 (7.3%) had low TSH (<0.35mU/L) and/or raised fT4 (>23pmol) n=2 had thyroiditis (suppressed TSH with high normal fT4 and fT3) with positive autoantibodies consistent with Graves' Compared to pts with normal fT3, those with low fT3 had: Increased use of dexamethasone/supplementary oxygen (P=0.003) Increased rates of prolonged hospital stay (≥14 days) P=0.018 Higher chance of deterioration in clinical severity (P<0.001) Alterations in TSH not associated with deterioration in clinical severity	
Persistent Effects			
Muller et al [32]	8 pts with COVID-19 and deranged thyroid function tests from above [32] Attended for ultrasound at mean of 55 (±8) days when negative for SARS-CoV-2	- n=2 (25%) had hypothyroidism. US - marked diffuse hypoechogenicity and heterogeneity consistent with autoimmune thyroiditis - 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 Characterised by painless inflammation of thyroid gland

Clarke et al [24]	Prospective study **Study population:** 70 pts with confirmed COVID-19 Assessment at ≥ 3 months post presentation n=68 complete TFTs	TFTs all within range at median of 210 days since admission **Median (IQR):** **TSH:** 1.32 (0.97, 2.09) mU/L **fT4:** 12.30 (11.65, 13.08) pmol/L **fT3:** 4.40 (4.08, 4.80) pmol/L No difference in TFTs between those patients with fatigue at follow-up compared to those without	No evidence of persistent thyroid dysfunction in survivors of COVID-19

Table 1: The effect of COVID-19 on thyroid gland function. Presented are studies investigating the effects of COVID-19 on thyroid function test parameters. ITU; intensive care unit, TFTs; thyroid function tests, TSH; thyroid stimulating hormone, fT4; free thyroxine, fT3; free triiodothyronine, SAT; subacute thyroiditis, 0_2 sats; oxygen saturations, pts; patients, NTI; non thyroidal illness, SES; sick euthyroid syndrome

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 3-6 months after COVID-19 infection [34], with no alteration in TSH, fT4 or free triiodothyronine (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 characterised 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 sub-acute 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, 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 8am cortisol ≤138nmol/L, or stimulated cortisol ≤550nmol/L following 250mcg 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 three zones of the adrenal cortex [52]. At autopsy, adrenal haemorrhage, ischaemic 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 one study finding up to 30% of patients with serum sodium values <135mmol/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 (SIADH) and hypovolaemia, if present adrenal insufficiency may also present with hyponatraemia [55].

Acute and Sub-acute Effects

Adrenal insufficiency secondary to acute adrenal infarction [56] and adrenal haemorrhage [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 48hrs 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' (CIRCI), due to 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 (10µg/dL) (threshold used to define CIRCI) in patients with COVID-19 [62]. By contrast, in a study of 28 patients with COVID-19, morning cortisol levels on day 1 and 2 were

observed to be <300nmol/L in 64.3% of patients, but no dynamic function testing was undertaken [64]. Only one patient in this cohort required admission to intensive care and the sample size was small, making it difficult to generalise from these findings. In 84 patients admitted with COVID-19, hypocortisolism (cortisol <414nmol/L) was observed in 38.4% of patients with moderate/severe disease, compared to 6.8% of those with mild disease [50]. However, data from only 13 patients with moderate/severe COVID-19 was 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 48hrs 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 (HPA) 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 post-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 post 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 48hrs 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 (e.g. haemorrhage / thrombosis), corticosteroid 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, utilising 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], one study observed its presence in two patients utilising RT-qPCR, 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 post-mortem, with a near-complete absence of GC in the seminiferous tubules, although strikingly Sertoli cells were spared [69]. Interestingly only one 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 that in some patients with COVID-19 significant morphological changes occur which could impair GC function.

Acute and Sub-acute 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 one study [81] (Table 2). Over 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 post hospitalization, 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 impact 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, reduced total number of sperm per ejaculate and reduced total number of progressive complete motility compared to those with mild disease, and healthy controls [77] (Table 2). Interestingly, men with fever had reduced semen volume and reduced motility compared to 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 [85,75]. When compared to healthy age-matched controls, sperm concentration and total sperm count were reduced in 55 male patients who had recovered from COVID-19, compared to

healthy controls at a median of 80 days post-infection [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 to 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 to age-matched controls, consistent with testicular damage [75] (Table 2). Finally, in a preprint from a study in Germany, men admitted to ITU with COVID-19 had reduced total testosterone compared to 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, it should be noted that 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 that is 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 interleukin-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 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 towards baseline levels by 28 days post-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 (<6.9nmol/L) whilst 18.1% had low inhibin-B, but neither of these correlated with symptoms of 'Post-COVID-syndrome' [92]. Whilst a single testosterone value without pre-infection 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 to other critical illnesses, the evidence to date suggest that any fall in testosterone levels resolves spontaneously after recovery from acute illness.

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 **Study population:** 91 males diagnosed with COVID-19 Aged 18-75yrs Questionnaire to assess for testicular pain, and blood tests (CRP, d-dimer, neutrophil, lymphocyte count)	10 of 91 pts reported testicular pain No difference in blood parameters between groups No difference in age between groups	Limited by recall bias and absence of confirmatory US scan Testicular pain may affect up to 10% of pts with COVID-19.
Chen et al [82]	Retrospective observational study **Study population:** 142 hospitalised male pts 58.3 years (range 24-91 years) Scrotal US scan at 1 week-1month after initial symptoms / admission	n=32 (22.5%) acute orchitis, epididymitis, or epididymo-orchitis on scrotal US imaging Risk of acute scrotal infection increased with age. incidence 53.3% in men >80 years. Risk of epididymo-orchitis increased in severe COVID-19 compared to non-severe COVID-19 (P = 0.04).	Infection with SARS-CoV-2 results in US findings orchitis Increased risk with increasing age and severity of COVID-19
Alkhatabeh et al [83]	Retrospective observational study **Study population:** 253 hospitalised male pts Assessed by Urology team every 2days during admission up until 21days	Mean age 43 yrs No patient had any symptoms or signs of epididymo-orchitis	No association between COVID-19 and symptoms or signs of orchitis Limited assessment undertaken
Holtmann et al	Prospective cohort study	SARS-CoV-2 not detected in semen of either those recovered or	SARS-CoV-2 not detected in semen

[77]	**Study population:** 18 males recovered from COVID-19 14 healthy male volunteers n=14 mild COVID-19 n=4 moderate COVID-19 n=14 healthy control Freshly collected semen analysed	healthy controls **Sperm Concentration:** **Mild:** 95.9±50.5 x10^6/ml **Moderate:** 16.2±22.45 x10^6/ml **Control:** 89.5±69.6 x10^6/ml P<0.05 **Total no. of sperm per ejaculate:** **Mild:** 243.7±140.4x10^6 **Moderate:** 11.9±13.4x10^6 **Control:** 233.1±234.4x10^6 P<0.05 **Total no. of immotile** **Mild:** 86.6 ±66.5x10^6 **Moderate:** 7.2±9.4x10^6 **Control:** 109.1±121x10^6 P<0.05 **Sperm Concentration:** **No fever:** 100.9±31.1 x10^6/ml **Fever:** 60.0±66.8 x10^6/ml P<0.05 **Total no. of sperm per ejaculate:** **No fever:** 283.6±124x10^6 **Fever:** 119.0±147.5x10^6 P<0.05 **Total no. of immotile** **No fever:** 98.01 ±67.6x10^6 **Fever:** 45.7±60.6x10^6 P<0.05	Sperm quality reduced in pts with moderate COVID-19 compared to those with mild disease, or healthy controls Sperm quality reduced in pts with COVID-19 who experienced fever, compared to those who did not

Ruan et al [86]	Prospective study **Study population:** N=74 males aged 20-50yrs recovered from COVID-19 Semen, blood tests collected at median of 80 days post COVID-19 confirmation N=55 males with semen for analysis Compared to 145 age-matched healthy controls	No evidence of SARS-CoV-2 mRNA in semen, urine or expressed prostatic secretions **Sperm concentration:** **COVID-19:** 66.41 ±31.82 x10^6/ml **Healthy controls:** 81.31 ±50.60 x10^6/ml P=0.04 **Total sperm count:** **COVID-19:** 197.40 ±123.80 x10^6/ml **Healthy controls:** 261.40 ±189.20 x10^6/ml P=0.02 **Total motility:** **COVID-19:** 48.89 ± 13.72% **Healthy controls:** 56.38 ± 10.83% P=<0.001 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 **Study population:** Males 18-60 yrs n=10 age-matched healthy controls n=10 pts with COVID-19 pre treatment n=10 pts with COVID-19 post treatment (oral hydroxychloroquine and azithromycin)	**Serum LH (IU/L):** **COVID-19 pre-treatment** 2.98±1.65 **COVID-19 post-treatment** 3.22±3.83 **Controls** 4.46±2.06 P=0.04 **Serum FSH (IU/L):** **COVID-19 pre-treatment** 2.04±1.36	Pts with COVID-19 pre-treatment had significantly lower serum LH, FSH and total testosterone compared to controls Pts with COVID-19 post-treatment had similar LH, FSH and total testosterone compared to controls Findings of reduced LH, FSH and total testosterone consistent with stressor effect on HPG axis

		COVID-19 post-treatment 3.15±0.70 **Controls** 3.92±2.35 P=0.01 **Total testosterone (nmol/L):** **COVID-19 pre-treatment** 3.92±4.44 **COVID-19 post-treatment** 7.84±6.45 **Controls** 10.05±6.48	
Ma et al [75]	Prospective observational study **Study population for semen analysis:** n=12 males with confirmed COVID-19 n=1 mild COVID-19 n=11 moderate/severe COVID-19 **Study population for hormonal parameter analysis:** n=119 males with confirmed COVID-19 n=273 age-matched controls	Most pts (n=8) had normal semen parameters **Serum LH (IU/L):** **COVID-19** 6.36 (4.63-8.37) **Healthy controls** 3.38 (2.48-4.52) P<0.0001 **Testosterone:LH ratio** **COVID-19** 0.68 (0.43-0.96) **Healthy controls** 1.24 (0.92-1.84) P<0.0001 **Multiple regression analysis:** Serum T: LH negatively associated with WCC and CRP	Multiple regression analysis showed WCC negatively correlated with total testo:LH, suggesting those with more significant disease had an element of testicular resistance Authors suggest this was immune mediated
Dhindsa et al [91]	Prospective cohort study **Study population:**	**Median T on admission:** **Severe COVID-19:** 1.84 nmol/L **Non-severe COVID-19:** 5.24 nmol/L	Lower total testosterone observed in acute infection in pts with severe COVID-19

	N=90 males with COVID-19 (66 of 90 men had severe COVID-19)	P=0.008 **In males with severe COVID-19:** Total T lower on day 1 vs day 151 (P=0.01) Total T negatively associated with -CRP (P<0.01) -IL-6 (P<0.04) Oestradiol and IGF-1 concentrations not associated with severity of COVID-19	Evidence of recovery with increased time from diagnosis Total testosterone negatively associated with markers of inflammation
Testes - Persistent Effects			
Ruan et al [86]	Prospective study **Study population:** n=74 males aged 20-50yrs recovered from COVID-19 Semen, blood tests collected at median of 80 days post COVID-19 Compared to 145 age-matched healthy controls	Normal endocrine parameters at a median of 77 days post infection	In men recovered from COVID-19, no evidence of persistent reduction in endocrine gonadal function
Moreno-Perez et al [92]	Cross-sectional study **Study population:** n=143 male pts recovered from COVID-19 Median 77 days post symptom onset n=103 severe inpatients n=19 non-severe (outpatient)	**Low serum testosterone:** Defined as total testosterone <6.9nmol/L or calculated free testosterone <0.22nmol/L **Sertoli cell dysfunction:** Inhibin-B <89ng/L **Low serum testosterone:** n=41 (29%) – rates not different in pts according to severity n=25 (18%) – low inhibin-B	Evidence of gonadal function is not uncommon in pts recovered from COVID-19 Prolonged studies required to determine persistent effects in longer-term

		Multivariable analysis: Obesity and hypokalemia associated with low testosterone Age >65yrs independent predictor of Sertoli cell dysfunction No relationship between prevalence hypogonadism/Sertoli cell dysfunction and symptoms of 'post-COVID-syndrome'	

Table 2: The effect of COVID-19 on male gonadal function. Presented are studies investigating the effects of COVID-19 on testicular function. Pts; patients, ITU; intensive care unit, WCC; white cell count, CRP; C-reactive protein, IL-6; interleukin-6

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 post-menopausal 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 ovariectomised mice increased expression of stromal cell ACE2, consistent with progesterone being a regulator of endometrial ACE2 [99].

Acute and Sub-acute Effects

In a prospective study from China, median serum anti-Müllerian hormone (AMH) was lower in patients with COVID-19 compared to controls (P<0.05) (Table 3). Serum LH, total testosterone and prolactin were higher in the follicular-phase of women with COVID-19 compared to 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 insulin-like growth factor (IGF-1) during hospitalisation and no differences with disease severity or with inflammatory markers [91] (Table 3). Importantly, this study included women of all ages diagnosed with COVID-19 and 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 pre-menopausal 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 AMH, LH, FSH, estradiol, progesterone or testosterone compared to age-matched pre-pandemic historic controls [101] (Table 3).

Persistent Effects

Unfortunately, there is scant data on the effects of COVID-19 infection on ovarian function beyond the non-infective 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 post-menopausal bleeding [102].

In summary, both the acute and chronic effects of COVID-19 on the female HPG axis remain unclear. As the prevalence of COVID-19 appears to be equal between genders [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.

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 **Study population:** n=237 women aged 18-45 yrs with confirmed COVID-19 Of these: n=177 complete menstrual history n=91 serum bloods in early follicular phase n=91 age-matched controls	**Menstrual cycle:** n=50 (28%) menstrual cycle disturbance (inc change in cycle length) **Serum AMH:** Not significantly different between healthy controls and those with COVID-19 Not significantly different between those with severe and non-severe COVID-19 **Serum E2 and Prog:** Not significantly different between healthy controls and those with COVID-19	Transient changes in menstrual function No significant differences in endocrine parameters
Dhindsa et al [91]	Prospective cohort study **Study population:** n=62 women mean age 63yrs with COVID-19 Of whom: 60% severe disease 40% non-severe disease Serum T, E2, IGF-1 taken on admission, day 3,7,14 and 28 of admission	**Serum T, E2, IGF1:** Not different between severe vs non-severe COVID-19 **Serum T, 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 Endocrine parameters did not alter with inflammatory response

Ding et al [104]	Observational single-centre study **Study population:** n=78 women aged 43.5yrs diagnosed with COVID-19 n=17 diagnosed as severe COVID-19 n=39 had bloods taken in the follicular phase Compared to: 151 healthy controls	**Menstrual cycle:** n=51 (75%) normal menstrual cycle **Serum AMH (ng/ml):** **COVID-19:** 0.28 **Healthy controls:** 1.12 P=0.03 **Serum FSH (IU/L):** **COVID-19:** 6.35 **Healthy controls:** 7.81 P = 0.02 **Serum Testosterone (ng/ml)** **COVID-19:** 0.39 **Healthy controls:** 0.22 P<0.001 **Serum PRL (ng/ml)** **COVID-19:** 24.1 **Healthy controls:** 12.12 P<0.001	Menstrual cycle disturbed for 25% of pts with COVID-19 Serum AMH reduced in pts with COVID-19 Serum T and prolactin increased in pts with COVID-19
Ovaries – persistent effects			
Davis et al [102]	Retrospective study International survey distributed via social media	n=6472 (36.1%) reported menstrual disturbance 26.1% had abnormally irregular cycles 19.7% had abnormally heavy cycles	Whilst no direct measure of ovarian function, disordered menstrual bleeding observed

	Study population: N=17929 women aged ≥18yrs with menstrual cycle COVID-19 or suspected COVID-19 Symptoms for >28days	Of 1123 women > 49yrs: 4.5% post-menopausal bleeding/spotting.	

Table 3: The effect of COVID-19 on female gonadal function. Presented are select studies investigating the effects of COVID-19 on ovarian function. T; testosterone, LH; luteinising hormone, FSH; follicle stimulating hormone, PRL; prolactin, E2; oestradiol, IGF-1; insulin-like growth factor, CRP; C-reactive protein, IL-6; interleukin-6

The endocrine pancreas

Background and Pathophysiology

Whilst a full discussion regarding the hyperglycaemic effects of COVID-19 is beyond the scope of this mini-review, and has been skilfully covered by others [105,106], this section will focus on the potential for islet cell destruction and subsequent impairment of glycaemic control.

During the SARS pandemic, hyperglycaemia in patients not previously known to be diabetic was reported, with 51.3% of 39 non-diabetic 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 hyperglycaemia and new diagnoses of diabetes [109,110], and patients with type 1 or type 2 diabetes had 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 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 Sub-acute Effects

Ketoacidosis can occur in the context of insufficient pancreatic insulin secretion to meet the glycaemic needs, and is typically observed in T1 diabetes, secondary to autoimmune

destruction of beta cells. However, ketoacidosis has also been reported in patients with T2 diabetes with COVID-19. Indeed, one 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 could also be 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 non-white 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 beta 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 to 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 hyperglycaemia remain to be fully elucidated, one study found that by 6 months post-admission, 63% of those diagnosed with hyperglycaemia during their admission had recovered euglycaemia [125]. Nevertheless, more than one third still had persistent hyperglycaemia (blood glucose 100-199mg/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 summarise, SARS-CoV-2 is associated with hyperglycaemia 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 (characterised by increased cortisol and glucagon, resulting in a relative insulin deficiency) direct damage to β cell structure and function is possible. Thus, further characterisation 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 impact on health and quality of life. The endocrine system is particularly vulnerable to perturbation due to COVID-19 infection, with thyroid dysfunction and hyperglycaemia being widely reported. However, much remains to be investigated regarding the impact of COVID-19 on the endocrine system. Specifically, the trajectory of hyperglycaemia 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 under-researched 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 healthcare 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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Figure Legends

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

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.

Table Legends:

Table 1: The effect of COVID-19 on thyroid gland function. Presented are studies investigating the effects of COVID-19 on thyroid function test parameters.

Table 2: The effect of COVID-19 on male gonadal function. Presented are studies investigating the effects of COVID-19 on testicular function.

Table 3: The effect of COVID-19 on female gonadal function. Presented are select studies investigating the effects of COVID-19 on ovarian function.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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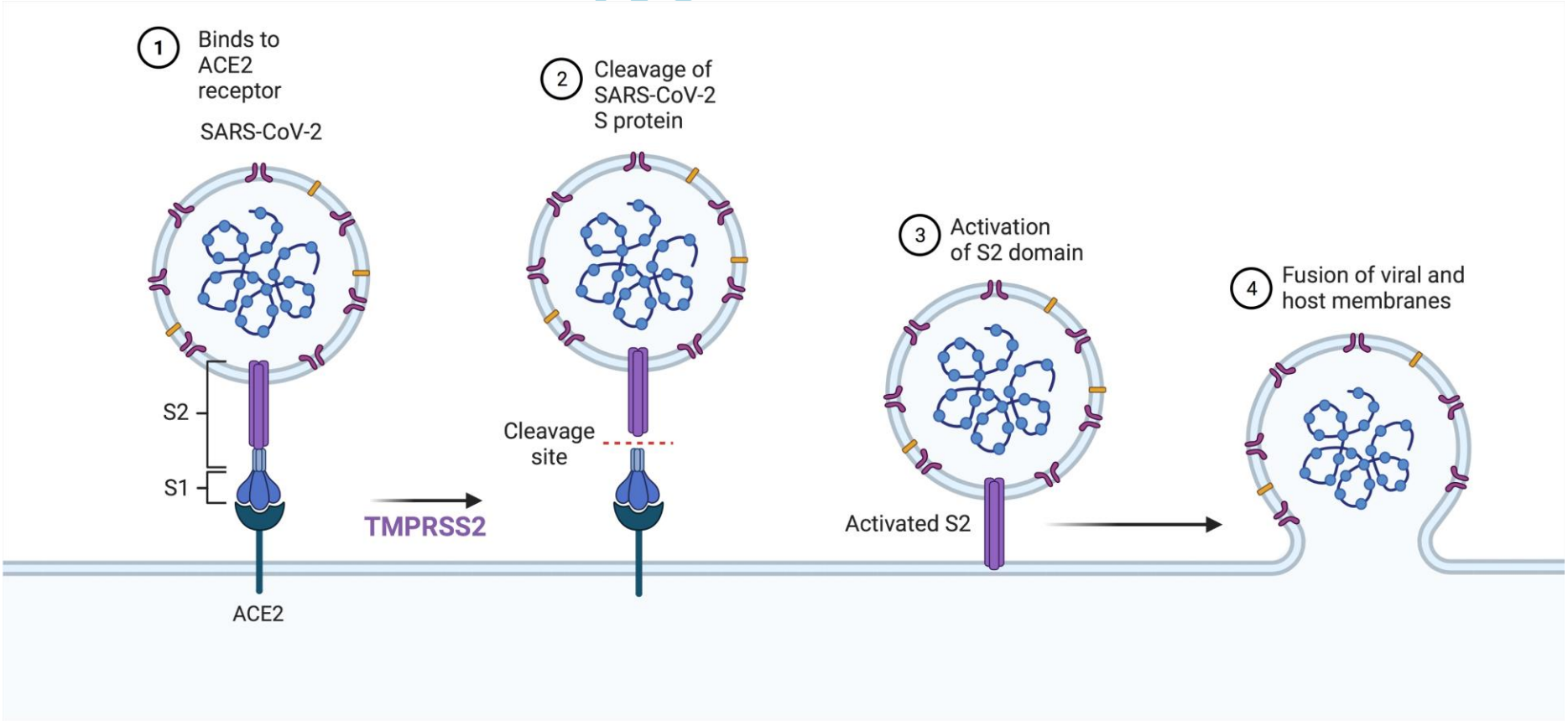
Figure 1


1
Binds to
ACE2
receptor
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Cleavage of
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3
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of S2 domain
Activated S2
4
Fusion of viral and
host membranes

Figure 2