Post-COVID-19 Endocrine Abnormalities

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Alpesh Goyal and Nikhil Tandon

8.1 Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as a global health challenge. The SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as the receptor to gain entry into host cells [1]. The disease manifestations, both during the acute and post-acute phase, may extend beyond the respiratory system and involve other systems, including the endocrine system (Table 8.1). The ACE2 receptor is expressed by endocrine organs, including the hypothalamus and pituitary, thyroid, pancreas, adrenals, and testes, and may result in direct gland damage [2]. Furthermore, the immunological cascade triggered by the hyper-inflammatory state of infection may trigger autoimmunity in predisposed individuals [3]. SARS-CoV-2 vaccines, including inactivated whole-virion, viral vector, and mRNA vaccines, have also been reported to cause endocrine adverse events (Table 8.1). In this chapter, we discuss post-acute phase endocrine complications of SARS-CoV-2 infection/vaccines and their mechanisms, emphasizing the need for increased awareness and close clinical surveillance to improve patient outcomes.

A. Goyal · N. Tandon (✉)
Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi, India

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Table 8.1 Endocrine complications reported following SARS-CoV-2 infection and vaccination

Hypothalamus and pituitary
• Hypophysitis (following infection and vaccine, both)
• Isolated central diabetes insipidus
• Isolated central hypocortisolism
• Pituitary apoplexy
Thyroid
• Subacute thyroiditis (following infection and vaccine, both)
• Graves' disease (following infection and vaccine, both)
Pancreas
• New-onset diabetes
Adrenal
• Adrenal hemorrhage and primary adrenal insufficiency (following infection and vaccine, both)
• Autoimmune adrenal insufficiency
Gonads
• Low serum testosterone
• Sertoli cell dysfunction and disruption of spermatogenesis

8.2 Hypothalamus and Pituitary Involvement

Hypothalamus and pituitary cells express ACE2 and are therefore potential targets for SARS-CoV-2. In the previous SARS outbreak, Leow et al. reported SARS-associated pituitary dysfunction in a cohort of 61 participants at 3 months following recovery from infection [4]. The pituitary dysfunction was related to either hypophysitis or direct hypothalamic involvement and involved the hypothalamic-pituitary-adrenal axis (24/61, 39%) more often compared to hypothalamic-pituitary-thyroid axis (3/61, 4.9%). Wheatland proposed that both SARS and influenza viruses use molecular mimicry of adrenocorticotrophic hormone (ACTH) as an immunoevasive strategy to blunt host stress response (through anti-ACTH antibodies) and thus create a state of relative adrenocortical insufficiency [5]. However, molecular mimicry of SARS-CoV-2 and ACTH has not been reported yet.

During the acute phase of SARS-CoV-2 infection, hyperprolactinemia, hyponatremia related to the syndrome of inappropriate antidiuretic hormone (SIADH) secretion, and pituitary apoplexy have been noted [2, 6]. On the other hand, hypophysitis, isolated pituitary hormone deficiency, and apoplexy can occur after recovery from COVID-19 or after SARS-CoV-2 vaccination (Table 8.2). Nonglait et al. reported lymphocytic adenohypophysitis in a 27-year-old male who presented 2 weeks following mild COVID-19 with hyponatremia and multiple anterior pituitary hormone deficits [7]. Although the authors did not perform a pituitary biopsy, the temporality of events and a known relationship between SARS-CoV-2 and pituitary suggest that hypophysitis was related to the viral infection itself. The patient was treated with thyroxine and therapeutic doses of oral steroids for hypophysitis. Similarly, Misgar et al. reported a case of infundibulo-neurohypophysitis in a 60-year-old female who presented with central diabetes insipidus and had a history of mild COVID-19 infection 8 weeks prior [8]. The patient improved

Table 8.2 Hypothalamus and pituitary dysfunction in association with SARS-CoV-2 infection and vaccination

Authors	Clinical setting	Presentation	Biochemistry	Radiology	Clinical diagnosis
Nonglait, et al. [7]	27/M Mild COVID-19 2 weeks before	Malaise, anorexia, vomiting, and early morning headache	Hyponatremia Secondary hypocortisolism, hypothyroidism, and hypogonadism Hyperprolactinemia	Diffuse enlarged pituitary, with stalk thickening and homogenous post-contrast enhancement	Lymphocytic hypophysitis
Misgar, et al. [8]	60/F Mild COVID-19 8 weeks before	Acute-onset polyuria, nocturia, and polydipsia	Hypernatremia High serum and low urine osmolality, consistent with DI The rest pituitary hormones normal	Thickened pituitary stalk with post-contrast enhancement, absent posterior pituitary bright spot	Infundibulo-neurohypophysitis
Murvelashvili, et al. [9]	51/M Second dose of SARS-CoV-2 mRNA vaccine (Moderna) 2 days before	Nausea, vomiting, and abdominal pain	Hyponatremia, secondary hypocortisolism, hypothyroidism, and hypogonadism	Homogenous enlargement of pituitary with stalk thickening Empty sella at 1-month follow-up	Acute hypophysitis
Sheikh, et al. [10]	28/M Mild COVID-19 4 weeks before	Admitted with post-viral myocarditis Developed acute-onset polyuria, nocturia, and polydipsia during course of admission	Hypernatremia Low urine osmolality with significant increase after desmopressin challenge	Normal pituitary MRI	Isolated central DI
Chua, et al. [11]	47/M Mild COVID-19 1 week before	New-onset persistent dyspepsia and eosinophilia	Low cortisol and ACTH	Normal pituitary MRI	Delayed-onset central hypocortisolism

(continued)

Table 8.2 (continued)

Authors	Clinical setting	Presentation	Biochemistry	Radiology	Clinical diagnosis
Ghosh, et al. [12]	44/F Concurrent COVID-19	Headache, projectile vomiting, visual blurring, and field defects	Hyponatremia Secondary hypocortisolism Secondary hypothyroidism on follow-up	Pituitary macroadenoma with hemorrhage	Pituitary apoplexy
Chan, et al. [13]	28/F Pregnant Concurrent COVID-19	Headache, blurring of vision, left dilated pupil, left ear pain	Secondary hypothyroidism	Pituitary macroadenoma with hemorrhage	Pituitary apoplexy
LaRoy, et al. [14]	35/M Concurrent COVID-19	Sharp, retro-orbital headache and neck stiffness	Normal hormonal evaluation	Pituitary microadenoma with hemorrhage	Pituitary apoplexy
Liew, et al. [15]	75/M Mild–moderate COVID-19 4 weeks before	Headache, fever, drowsiness, and constipation	Hyponatremia Secondary hypocortisolism, hypothyroidism, and hypogonadism	Pituitary macroadenoma with hemorrhage	Pituitary apoplexy

Abbreviations: *COVID-19* coronavirus disease 2019; *DI* diabetes insipidus; *F* female; *M* male

symptomatically with oral desmopressin. Murvelashvili et al. reported a case of acute hypophysitis in a 51-year-old male who presented with nausea, vomiting, and abdominal pain 2 days following exposure to the second dose of SARS-CoV-2 mRNA vaccine (Moderna mRNA-1273 vaccine) [9]. The patient was treated with thyroxine and high dose oral steroids, to which he responded symptomatically, and a repeat imaging 1 month later revealed partial empty sella.

Isolated pituitary hormone deficiencies, namely, central diabetes insipidus and central hypocortisolism with normal pituitary imaging, have also been reported following SARS-CoV-2 infection [10, 11]. Such cases need ongoing hormone replacement and a close surveillance for any evolving pituitary deficits. Finally, cases of pituitary apoplexy, an acute medical emergency caused by hemorrhage and infarction within a pituitary adenoma, often macroadenoma, have been reported both during active infection and after recovery from acute illness [12–15]. The usual clinical presentation is headaches, vomiting, drowsiness, blurring of vision, visual field defects, cranial nerve palsies, and pituitary hormone deficits. Most patients can be managed conservatively; however, those with deteriorating level of consciousness and visual deficits need urgent neurosurgical intervention [16].

8.3 Thyroid Involvement

A variety of thyroid abnormalities have been described in the context of SARS-CoV-2 infection (Table 8.3). Like any other acute illness, low free triiodothyronine (T3), thyroxine (T4) and thyroid-stimulating hormone (TSH) levels, in line with non-thyroidal illness (NTI) syndrome, have been reported in patients admitted with COVID-19 [17, 18]. As expected, these changes resolve spontaneously in disease survivors [18]. In the THYRCOV study, Lania et al. reported a high prevalence of thyrotoxicosis (20.2%) among 287 patients hospitalized for COVID-19 in non-intensive care units [19]. The presence of thyrotoxicosis was significantly associated with higher IL-6 levels. Thyrotoxicosis was mild in most cases and resolved spontaneously during follow-up, which led authors to propose "destructive thyroiditis" as the causative mechanism.

A prospective evaluation of thyroid function at ≥3 months following the index infection was performed in 68 subjects by Clarke et al. [20], and the authors reported normal thyroid function in all study participants. They concluded that (a) thyroid function is preserved in COVID-19 survivors and (b) the symptoms of fatigue commonly seen in the post-acute phase are not explained by thyroid dysfunction. Similarly, in a prospective cohort study (n=240), we reported that predominant mild and asymptomatic infection is not associated with progression of thyroid dysfunction or autoimmunity at a short-term follow-up (<1 year) [21]

There are isolated reports of subacute thyroiditis (SAT) following SARS-CoV-2 infection. SAT, also known as de Quervain thyroiditis, refers to a self-limiting inflammation of the thyroid gland that commonly ensues following a viral upper respiratory tract infection. This condition manifests as acute-onset neck pain, often radiating to the jaw, associated with fever and thyrotoxicosis symptoms. An

Table 8.3 Thyroid dysfunction in association with SARS-CoV-2 infection and vaccination

Authors	Details	Results	Conclusions
Khoo, et al. [18]	Observational cohort study. TFTs performed before, during, and after COVID-19	TSH and free T4 reduced at COVID-19 admission, compared to baseline, but spontaneously recovered on follow-up	TFT picture of non-thyroidal illness is seen in COVID-19. Thyroid function normalizes in survivors
Clarke, et al. [20]	Prospective observational study. 68 patients ≥18 years of age without baseline thyroid disease evaluated at ≥3 months following COVID-19	Normal thyroid function in all patients. Levels of thyroid hormones did not differ in patients with and without fatigue symptoms	Preserved thyroid function in COVID-19 survivors. Post-COVID-19 fatigue symptoms are not explained by thyroid dysfunction
Brancatella, et al. [24] Khatri, et al. [25]	18/F Mild COVID-19 2 weeks before 41/F Mild COVID-19 4 weeks before	Both patients presented with neck pain, fever, and thyrotoxicosis symptoms, had enlarged, tender thyroid gland on examination; diagnosed as subacute thyroiditis and successfully treated with oral steroids (cases 1 and 2) and NSAIDs (case 2)	Like other viral infections, SARS-CoV-2 can trigger subacute thyroiditis
İremli, et al. [27]	Three female healthcare workers (34–37 years) First/second dose of inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac) 4–7 days before	Subacute thyroiditis, successfully managed with oral steroids in two and no treatment in one case	Subacute thyroiditis may occur following SARS-CoV-2 vaccination. Similar cases have been reported following other inactivated whole-virion (Covaxin), viral vector (Covishield), and mRNA (Moderna and Pfizer-BioNTech) vaccines [28–31]
Harris, et al. [32] Montebello, et al. [33]	18/F Mild COVID-19 16 days before 22/F Mild COVID-19 8 weeks before	Clinical and biochemical thyrotoxicosis and elevated TSH-R antibody in both cases. History of previous Graves' disease treatment in case 2	New-onset and recurrent Graves' disease can develop following SARS-CoV-2 infection

Table 8.3 (continued)

Authors	Details	Results	Conclusions
Sriphrapradang, et al. [34]	70/M Second dose of viral vector-based SARS-CoV-2 vaccine (Covishield) 2 days before	Clinical and biochemical thyrotoxicosis and elevated TSH-R antibody	Graves' disease can develop following SARS-CoV-2 vaccination. Similar cases have been reported following other SARS-CoV-2 vaccines [35, 36]

Abbreviations: *COVID-19* coronavirus disease 2019; *F* female; *M* male; *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2; *T4* thyroxine; *TFT* thyroid function test; *TSH* thyroid-stimulating hormone; *TSH-R* thyroid-stimulating hormone receptor

enlarged, often asymmetric, and tender thyroid gland may be noted on physical examination. Previously, influenza, mumps, adenovirus, cytomegalovirus (CMV), rubella, and Epstein-Barr virus (EBV) have been linked to SAT [22]. SARS-CoV-2 is a new addition to this list. SAT is associated with HLA-B35, and familial occurrence and recurrent episodes are linked to this high-risk genotype [23]. Thus, SAT occurs through susceptibility to viral infection in genetically predisposed individuals. SAT often runs a triphasic course, characterized by thyrotoxicosis with decreased radioactive iodine uptake, followed by hypothyroidism and, eventually, euthyroidism.

Nearly 90% of patients show complete and spontaneous recovery of thyroid function; the remaining 10% develop permanent hypothyroidism and need long-term replacement. Treatment is mainly symptomatic and comprises beta-blockers for thyrotoxicosis symptoms and nonsteroidal anti-inflammatory drugs (NSAIDs) for neck pain. A trial of oral steroids is indicated for patients with severe neck pain or no response to NSAIDs. A suggested regimen is oral prednisolone 15–25 mg/day for 2 weeks, followed by taper over the next 4–6 weeks. The first case of SAT following SARS-CoV-2 was reported by Brancatella et al. in an 18-year-old female [24]. She presented 2 weeks following the infection with typical symptoms and was successfully treated with a course of oral steroids. Similarly, Khatri et al. reported post-SARS-CoV-2 SAT in a 41-year-old male who was treated successfully with oral NSAIDs [25]. Thyroid function outcomes in patients admitted with SARS-CoV-2-associated thyrotoxicosis, related to subacute thyroiditis, were reported in a study by Pizzocaro et al. [26]. At a median follow-up of 90 days, thyroid function spontaneously normalized in most (28, 97%) patients, and only 1 developed hypothyroidism.

Similar to influenza, H1N1, and hepatitis B vaccines, different SARS-CoV-2 vaccines have been reported to trigger SAT. Cases have been reported following exposure to inactivated whole-virion (e.g., CoronaVac (Sinovac Life Sciences) and Covaxin (BBV152)), viral vector (e.g., Covishield (ChAdOx1 nCoV-19)), and

mRNA (e.g., Moderna mRNA-1273 and Pfizer-BioNTech (BNT162b2)) vaccines [27–31]. In this scenario, SAT reflects postvaccination autoimmune/inflammatory syndrome induced by adjuvants (ASIA) that occurs following exposure to vaccine adjuvants in genetically predisposed individuals [27]. Notably, adjuvants (such as aluminum hydroxide) are used to enhance the immunogenicity of viral antigen and induce a better adaptive immune syndrome. Postvaccination ASIA is a well-described entity, and other endocrinopathies previously reported under this syndrome include type 1 diabetes, premature ovarian failure, autoimmune thyroid disease, and adrenal insufficiency [27].

SARS-CoV-2 infection and vaccination are also known to trigger Graves' disease [32–36], an autoimmune form of hyperthyroidism characterized by the presence of stimulatory antibodies against TSH receptors. Clinically, this condition manifests as goiter, hyperthyroidism, and, in some cases, infiltrative orbitopathy and dermopathy. Graves' disease is postulated to occur following exposure to environmental agents in genetically predisposed individuals. The known environmental triggers include viral infection (e.g., Coxsackie B virus), drugs (e.g., alemtuzumab, ipilimumab), iodine, smoking, and stress. SARS-CoV-2 infection is a new addition to this list of environmental triggers. The proposed mechanisms include (a) triggering of the immunological cascade by the severe pro-inflammatory state of infection, (b) molecular mimicry, and (c) infection-related stress [32]. Subacute thyroiditis is an important differential diagnosis of this condition. Prolonged duration of symptoms, the presence of a prominent goiter, orbitopathy/dermopathy, features of other autoimmune disease such as vitiligo, a high T3/T4 ratio, and diffusely increased thyroidal radioactive iodine uptake all favor the diagnosis of Graves' disease. Notably, the recent use of iodinated contrast agent (within the preceding 3 months) may saturate thyroidal iodine pool and impair radioiodine uptake. A TSH-receptor antibody test may be helpful in such cases, as in pregnancy, where radioactive iodine scan is contraindicated. Management options include antithyroid drugs, radioactive iodine ablation, and thyroidectomy; the reader is directed to an excellent review for more details [37].

8.4 Endocrine Pancreatic Abnormalities

It is well known that diabetes is associated with poor COVID-19 outcomes [38]. Recent data also suggest increased susceptibility to SARS-CoV-2 infection among persons with diabetes [39, 40]. Furthermore, SARS-CoV-2 may itself induce metabolic dysfunction and new-onset diabetes (Table 8.4) [41–43]. In this regard, a global registry of COVID-19-related diabetes has been established [44]. This registry defines new-onset diabetes following COVID-19 as follows: (a) confirmed SARS-CoV-2 infection, (b) no past history of diabetes, and (c) a previously normal glycated hemoglobin (HbA1c) level. The precise mechanisms are unknown, but multiple factors may contribute, including pre-existing undiagnosed diabetes, stress-related hyperglycemia, steroid-induced hyperglycemia, and the direct/indirect effects of SARS-CoV-2 on the pancreatic beta cell [41].

Table 8.4 New-onset diabetes (NOD) in association with SARS-CoV-2 infection

Authors	Details	Results	Conclusions
Huang, et al. [42]	Ambidirectional cohort study 1733 patients admitted for COVID-19 evaluated at a median follow-up of 6 months	New-onset diabetes in 3.3% of patients	Extrapulmonary manifestations, including diabetes may appear as a part of post-COVID-19 syndrome
Ayoubkhani, et al. [43]	Retrospective cohort study 47,780 patients admitted for COVID-19 evaluated at a mean follow-up of 140 days	New-onset diabetes in 4.9% of patients	Same as above
Ghosh, et al. [48]	Retrospective cohort study 282 patients with NOD before COVID-19 pandemic (September 2019–February 2020) compared with 273 patients with NOD during the pandemic (April–October 2020)	Patients with NOD during the pandemic had higher fasting and postprandial blood glucose and glycated hemoglobin, compared to those diagnosed before the pandemic No difference in C-peptide or glycemic parameters in patients with NOD during the pandemic who tested positive or negative for COVID-19 antibody	Individuals with NOD during the pandemic had more severe glycemic parameters at diagnosis; however, they did not differ in symptomatology and phenotype
Goyal, et al. [56]	Prospective cohort study 352 participants, without baseline diabetes, evaluated at two time points: pre-COVID-19 (2016–2019) and peri-COVID-19 (2020–2021). SARS-CoV-2 antibody test at the second visit to determine infection Glycemic progression between visits defined as conversion from normoglycemia to prediabetes/diabetes and from prediabetes to diabetes	159 (45.2%) participants in the cohort had SARS-CoV-2 infection. Of these, 122 (76.7%) had mild/asymptomatic infection Progression in glycemic category not significantly different between the infected and noninfected groups. Similarly, the two groups were not different in terms of progression of insulin indices (HOMA-IR, oDI, Matsuda index)	Predominant mild/asymptomatic SARS-CoV-2 infection was not associated with glycemic progression or worsening of beta cell function and insulin resistance

Abbreviations: *COVID-19* coronavirus disease 2019; *HOMA-IR* homeostasis model assessment of insulin resistance; *NOD* new-onset diabetes; *oDI* oral disposition index; *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2

In a multicenter study from London, Unsworth et al. reported an 80% increase in new-onset type 1 diabetes during the pandemic, compared with previous years [45]. To the contrary, a study by Tittel et al., which pooled data from 216 pediatric centers in Germany, reported no such increase [46]. Notably, both the cohorts demonstrated an increased severity of diabetes at presentation, with significant increases in the proportion of diabetic ketoacidosis (DKA) and severe DKA at the time of diagnosis [45, 47]. The reasons could be multiple and include (a) delayed presentation due to fear of contracting virus and reduced medical care for non-COVID-19 illnesses, (b) complex psychosocial factors, and (c) SARS-CoV-2-related insulinopenia and rise in pro-inflammatory cytokines. Similarly, a retrospective study by Ghosh et al. found that patients with new-onset diabetes diagnosed during the pandemic had higher fasting and postprandial blood glucose and glycated hemoglobin levels than those diagnosed before the pandemic [48]. However, there was no difference in C-peptide levels or glycemic parameters between seropositive and seronegative patients diagnosed during the pandemic. Recently, there have been reports of hyperglycemic emergencies [DKA and hyperglycemic hyperosmolar state (HHS)] following COVID-19 vaccination in patients with poorly controlled type 1 and type 2 diabetes [49–53]. These events occurred within 1–6 weeks following the exposure to various SARS-CoV-2 vaccines, including inactivated whole-virion (Covaxin (BBV152)), viral vector (Covishield (ChAdOx1 nCoV-19)), and mRNA (e.g., Moderna mRNA-1273 and Pfizer-BioNTech (BNT162b2)) vaccines. It is therefore advisable that patients with diabetes, especially those with suboptimal glycemic control, be closely monitored for hyperglycemia and ketosis in the initial few weeks following the vaccination [49].

Various autopsy studies have confirmed that SARS-CoV-2 infects beta cells and leads to beta cell apoptosis, loss of insulin secretion, and transdifferentiation into glucagon-producing alpha cells [54, 55]. However, most data on new-onset diabetes have been derived from hospitalized patients, who often suffer from more severe disease than those in the community. To address this lacuna, we performed a longitudinal study, wherein 352 healthy participants from an established cohort were evaluated in pre-COVID-19 (2016–2019) and peri-COVID-19 (2020–2021) periods for progression of glycemic and cardiometabolic variables [56]. The study was performed before the onset of the national vaccination program, and therefore, seropositivity (for SARS-CoV-2 IgG) was a surrogate for viral infection. A total of 159 (45.2%) participants had SARS-CoV-2 infection, of whom 122 (76.7%) had mild/asymptomatic infection, representative of the real-world scenario. The progression of glycemic categories, i.e., from normal glucose tolerance to prediabetes or diabetes and from prediabetes to diabetes, was not significantly different between infected (20.8%) and noninfected (19.7%) groups. Thus, we concluded that predominant mild/asymptomatic infection is not associated with worsening of glycemic parameters and excessive development of new-onset diabetes, at least on a short-term follow-up. More prospective studies are needed globally, involving different patient populations and at a longer duration following the index infection to delineate the burden and pathophysiology of SARS-CoV-2-induced new-onset diabetes. Such data should also clarify whether new-onset diabetes is a permanent condition or not.

Until such time, clinicians should watch for metabolic dysfunction in patients with a history of SARS-CoV-2 infection.

8.5 Adrenal Involvement

Glucocorticoids have been widely used in COVID-19 for their anti-inflammatory properties, especially in patients with the moderate-severe disease. In the post-acute phase, there is always a risk for secondary adrenal insufficiency following abrupt withdrawal or even exogenous Cushing's syndrome following unsupervised prolonged use of glucocorticoids [57, 58]. The risk increases with the use of more potent and long-acting formulations (e.g., dexamethasone, methylprednisolone, and prednisolone in that order), a higher dose (e.g., prednisolone 40 mg/day equivalent or more), a longer treatment duration (e.g., more than 7–14 days), and administration at a nonphysiological time of the day (e.g., evening-night, compared to morning-afternoon hours) [57]. Primary adrenal dysfunction has been reported less often in the context of COVID-19 (Table 8.5). In a prospective evaluation of the

Table 8.5 Adrenal dysfunction in association with SARS-CoV-2 infection and vaccination

Authors	Details	Results	Conclusions
Clarke, et al. [20]	Prospective observational study. 70 patients ≥18 years of age evaluated at ≥3 months following COVID-19	All patients had peak cortisol ≥450 nmol/L after Synacthen stimulation. Levels of basal and peak cortisol did not differ in patients with and without fatigue symptoms	Preserved adrenal function in COVID-19 survivors. Post-COVID-19 fatigue symptoms are not explained by adrenal dysfunction
Frankel, et al. [59]	66/F Concurrent COVID-19 Known case of APLA syndrome	Primary adrenal insufficiency due to bilateral adrenal hemorrhage. Persistent glucocorticoid and mineralocorticoid requirement 4 weeks after recovery from infection	Like other infections, SARS-CoV-2 can precipitate adrenal hemorrhage and result in primary adrenal insufficiency
Taylor, et al. [60]	38/M First dose of adenoviral vector SARS-CoV-2 vaccine (Covishield) 8 days before	Bilateral adrenal hemorrhage and primary adrenal insufficiency. Diagnosed as VITT and managed accordingly	VITT is a rare complication of adenoviral vector-based vaccines that may manifest as adrenal hemorrhage
Sanchez, et al. [61]	64/F Mild COVID-19 5 months before	Clinical and biochemical features of primary adrenal insufficiency. Positive anti-21 hydroxylase antibodies	SARS-CoV-2 can promote the development or progression of autoimmune adrenal insufficiency

Abbreviations: *COVID-19* coronavirus disease 2019; *F* female; *M* male; *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2; *VITT* vaccine-induced thrombosis and thrombocytopenia

adrenal function at ≥3 months following the index infection, Clarke et al. reported a peak post-Synacthen (ACTH 1–24) cortisol level ≥ 450 nmol/L (18 μg/dL) in all study participants (n = 70), suggestive of preserved adrenal function [20]. Moreover, baseline or peak cortisol levels were not different in patients with and without fatigue, confirming that adrenal dysfunction does not explain post-COVID-19 fatigue symptoms.

Isolated case reports indicate that SARS-CoV-2 may lead to the progression or development of primary adrenal insufficiency through adrenal hemorrhage or by inducing autoimmunity. Adrenal hemorrhage presents with nonspecific signs and symptoms, including abdominal pain and tenderness, nausea, vomiting, fatigue, fever, and hypotension. Pathogenesis involves increased arterial inflow during a stressful event coupled with reduced venous drainage, resulting in vascular congestion and hemorrhage. Frankel et al. reported a case of acute COVID-19 associated with primary adrenal insufficiency and bilateral adrenal hemorrhage in a 66-year-old female with a background history of APLA syndrome [59]. The patient recovered completely from acute illness but had persistent glucocorticoid and mineralocorticoid requirements at 4 weeks. Similarly, Taylor et al. reported a case of bilateral adrenal hemorrhage and adrenal insufficiency in a 38-year-old male, 8 days after receiving the first dose of adenoviral vector-based SARS-CoV-2 vaccine (Covishield (ChAdOx1 nCoV-19)) [60]. This adverse event represented a manifestation of vaccine-induced thrombosis and thrombocytopenia (VITT), a prothrombotic syndrome with thrombocytopenia rarely reported in subjects receiving adenoviral vector-based vaccines. Finally, Sanchez et al. reported autoimmune adrenal insufficiency in a 64-year-old female, possibly related to mild COVID-19 she had 5 months prior [61]. Thus, although rare, clinicians should consider primary adrenal insufficiency as a differential diagnosis in patients who present with suggestive symptoms during or after the acute illness.

8.6 Gonadal Involvement

SARS-CoV-2 entry receptor, ACE2, is highly expressed in human testicular tissue, including spermatogonia, Leydig cells, and Sertoli cells [62]. Orchitis and germ cell damage were reported in the previous SARS outbreak [63]. In hospitalized patients with COVID-19, a pattern of elevated luteinizing hormone (LH) and maintained testosterone have been reported, suggestive of an early testicular dysfunction [64]. Postmortem examination of 12 patients who died of COVID-19 revealed a significant seminiferous tubular injury, reduced Leydig cells, and interstitial inflammation [65]. However, the SARS-CoV-2 was not detected in the testis by polymerase chain reaction (PCR) in a majority (90%) of subjects. The mechanisms for testicular dysfunction include direct damage by the virus and inflammatory/immunological orchitis [66].

A recent study by Moreno-Perez et al. evaluated Leydig and Sertoli cell dysfunction in a cohort of 143 males with a median age of 59 years, enrolled at 8–12 weeks

Table 8.6 Gonadal dysfunction in association with SARS-CoV-2 infection

Authors	Details	Results	Conclusions
Moreno-Perez, et al. [67]	Cross-sectional study 144 patients evaluated 8–12 weeks after recovery from COVID-19. Of these, 72% had severe pneumonia Low testosterone defined as total testosterone level < 2 ng/ml or level 2–4 ng/ml with free testosterone <6.34 ng/dl. Sertoli cell dysfunction defined as inhibin B < 89 pg/ml	Low testosterone in 41 (28.7%) and Sertoli cell dysfunction in 25 (18.1%) participants. Obesity and hypokalemia were predictors of low testosterone, while age > 65 years predicted Sertoli cell dysfunction	High prevalence of low testosterone and Sertoli cell dysfunction in severe COVID-19 survivors

Abbreviations: *COVID-19* coronavirus disease 2019

following recovery from COVID-19 (Table 8.6) [67]. A majority of participants (72%) had a history of severe pneumonia. "Low testosterone," defined as total testosterone <200 ng/dL or calculated free testosterone <6.36 ng/dL in those with total testosterone of 200–400 ng/dL, was found in 41 (28.7%) participants. Among these, 22% had high LH levels, suggestive of primary testicular dysfunction, while 78% had low or inappropriately normal LH, suggestive of impairment of hypothalamic-pituitary-gonadal axis. Sertoli cell dysfunction, defined as serum inhibin <89 pg/ml, was found in 25 (18.1%) participants. The presence of obesity and hypokalemia predicted "low testosterone," while age >65 years was predictive of Sertoli cell dysfunction. This study highlights a relatively high prevalence of male hypogonadism in COVID-19 survivors. However, the study was limited by (a) short follow-up duration, and therefore, it remains to be seen whether these changes are transient or permanent, (b) inclusion of a relatively older population with higher disease severity at baseline, (c) pre-existing hypogonadism that was not excluded since pre-COVID-19 hormonal levels were not available, (d) semen analysis that was not performed, and (e) testosterone measurement that was not repeated and performed using a non-mass spectrometric method. While prospective studies that address these limitations are needed in the future, clinicians should maintain a close vigil and consider COVID-19-induced testicular dysfunction in an appropriate clinical scenario.

Data on SARS-CoV-2 infection and female gonadal and reproductive function are limited. In their experiments, Goad et al. demonstrated that SARS-CoV-2 receptors, ACE2, and TMPRSS2 are not expressed at significant levels in the female reproductive tract [68]. Accordingly, it is expected that the viral infection does not have a major impact on this organ system [69]. In a retrospective study, Li et al. described transient menstrual changes, mainly decreased flow and increased intermenstrual interval, in 177 COVID-19 patients of childbearing age [70]. Notably, menstrual cycles returned to normal within 1–2 months following discharge in 99%

of cases. Furthermore, the mean sex hormone and AMH concentrations in such patients were similar to those of age-matched controls.

8.7 Take-Home Message

- Endocrine abnormalities reported following COVID-19 include hypophysitis, isolated pituitary hormone deficiency and apoplexy (hypothalamus and pituitary), subacute thyroiditis and Graves' disease (thyroid), new-onset diabetes (pancreas), adrenal hemorrhage and primary adrenal insufficiency (adrenals), and male hypogonadism (testis).
- Post-COVID-19 endocrinopathies often manifest within 3–6 months following the index infection and result either from direct damage by the virus or indirect inflammatory/immunological damage.
- Endocrine adverse events have also been reported following different SARS-CoV-2 vaccines, including inactivated whole-virion, viral vector-based, and mRNA vaccines.
- Vaccine-induced endocrinopathies are extremely rare and should not discourage the general public from being vaccinated since the benefits of vaccination far outweigh the small potential risks.
- Clinicians caring for patients with COVID-19 should suspect endocrine complications in appropriate clinical scenarios and report any new and previously unknown manifestations.

Conflicts of Interest None

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