



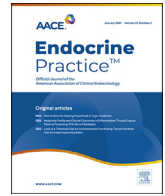
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## Review Article

## Endocrine Follow-up During Post-Acute COVID-19: Practical Recommendations Based on Available Clinical Evidence

Rimesh Pal, DM <sup>1</sup>, Ameya Joshi, DM <sup>2</sup>, Sanjay K. Bhadada, MD, DM <sup>1,\*</sup>, Mainak Banerjee, DM <sup>3</sup>, Suresh Vaikkakara, DM <sup>4</sup>, Satinath Mukhopadhyay, DM <sup>3</sup><sup>1</sup> Department of Endocrinology, Postgraduate Institute of Medical Education and Research, Chandigarh, India<sup>2</sup> Endocrinology Division, Bhaktivedanta Hospital, Thane, India<sup>3</sup> Department of Endocrinology, Institute of Postgraduate Medical Education and Research, Kolkata, India<sup>4</sup> Department of Endocrinology, Sri Venkateswara Institute of Medical Sciences, Tirupati, India

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## ABSTRACT

**Objective:** COVID-19 affects multiple endocrine organ systems during the disease course. However, follow-up data post-COVID-19 is scarce; hitherto available limited data suggest that most of the biochemical endocrine dysfunctions observed during acute phase of COVID-19 tend to improve after recovery. Hence, we aim to provide a rational approach toward endocrine follow-up of patients during post-acute COVID-19.

**Methods:** We performed a literature review across PubMed/MEDLINE database looking into the effects of COVID-19 on endocrine system and subsequent long-term endocrine sequelae. Accordingly, we have presented a practical set of recommendations regarding endocrine follow-up post-acute COVID-19.

**Results:** COVID-19 can lead to new-onset hyperglycemia/diabetes mellitus or worsening of dysglycemia in patients with preexisting diabetes mellitus. Hence, those with preexisting diabetes mellitus should ensure optimum glycemic control in the post-COVID-19 period. New-onset diabetes mellitus has been described post-acute COVID-19; hence, a selected group of patients (aged <70 years and those requiring intensive care unit admission) may be screened for the same at 3 months. Thyroid dysfunction (euthyroid sick syndrome and atypical thyroiditis) and adrenal insufficiency have been described in COVID-19; however, thyroid/adrenal functions usually normalize on follow-up; hence, widespread screening post-acute COVID-19 should not be recommended. Pituitary apoplexy and male hypogonadism have rarely been documented in COVID-19; therefore, appropriate follow-up may be undertaken as per clinical context. Hypocalcemia during COVID-19 is not uncommon; however, routine estimation of serum calcium post-COVID-19 is not warranted.

**Conclusion:** The recommendations herein provide a rational approach that would be expected to guide physicians to better delineate and manage the endocrine sequelae during post-acute COVID-19.

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**Abbreviations:** ACTH, adrenocorticotropic hormone; ADA, American Diabetes Association; AI, adrenal insufficiency; anti-TPO, antithyroid peroxidase; CAM, coronavirus disease 2019-associated mucormycosis; CIRCI, critical illness-related corticosteroid insufficiency; FSH, follicle-stimulating hormone; GIH, glucocorticoid-induced hyperglycemia; HbA1C, glycated hemoglobin; HPA, hypothalamic-pituitary-adrenal; ICU, intensive care unit; LH, luteinizing hormone; mRNA, messenger ribonucleic acid; RECOVERY, Randomised Evaluation of COVID-19 Therapy; SAT, subacute thyroiditis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine.

\* Address correspondence to Sanjay K. Bhadada, MD, Department of Endocrinology, Postgraduate Institute of Medical Education and Research, Nehru Hospital Extension, Room number: 001, Chandigarh, India 160012.

E-mail address: [bhadadask@rediffmail.com](mailto:bhadadask@rediffmail.com) (S.K. Bhadada).

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## Introduction

The novel COVID-19 is now recognized as a multiorgan disease with several clinical manifestations. Like postacute viral syndromes described in survivors of other virulent coronavirus epidemics, there are ever-increasing reports of persistent and long-term effects on human health after acute COVID-19. The sequelae of COVID-19, often referred to as post-acute COVID-19, are defined as persistent symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of symptoms.<sup>1</sup>

The common symptoms observed in postacute COVID-19 include fatigue, poor quality of life, muscle weakness, joint pain,

dyspnea, cough, decreased exercise capacity, and persistent oxygen requirement. In a cohort of individuals with COVID-19 who were followed up for 9 months after illness, approximately 30% reported persistent symptoms. One third of outpatients with mild disease also reported persistent symptoms. Fatigue was the most commonly reported symptom in the cohort.<sup>2</sup> Other long-term sequelae of COVID-19 include neuropsychiatric (headache, dysautonomia, cognitive impairment, anxiety, depression, sleep disturbances, and posttraumatic stress disorder), cardiovascular (palpitations, chest pain, myocardial fibrosis or scarring, arrhythmias), renal (declining renal function), hematologic (thromboembolic events), and dermatologic (hair loss) manifestations.<sup>1</sup>

Like other organ systems, COVID-19 exerts several effects on the human endocrine system.<sup>3</sup> The well-described endocrine manifestations of COVID-19 mainly reported during the acute phase of the disease include dysglycemia, new-onset diabetes mellitus, euthyroid sick syndrome, subacute thyroiditis (SAT), and pituitary apoplexy. However, data on long-term sequelae of COVID-19 on endocrine functions are limited.

In an attempt to summarize the hitherto available literature on the effects of COVID-19 on the endocrine system and the long-term sequelae of the disease on endocrine functions, we performed a literature search across the PubMed/MEDLINE database from inception to December 20, 2021, using the following keywords interposed with appropriate Boolean operators: “COVID-19” OR “post-acute COVID-19” AND “endocrine function.” Data from relevant articles were collated, and based on the available clinical evidence, we have presented a set of practical recommendations to help guide physicians and endocrinologists to delineate better and manage the endocrine manifestations of post-acute COVID-19.

It should, however, be noted that the interpretation of the literature and the recommendations drawn from it reflect the authors' personal inclinations and medical common sense, rather than collective expert opinions. Moreover, the strength of all recommendations is weak (Grading of Recommendations, Assessment, Development and Evaluations) as they are based on only observational and uncontrolled studies amid the lack of a sufficient number of case-control studies. The recommendations are not meant to be regarded as yardsticks, and other experienced endocrinologists may very well decide to act differently when faced with similar situations.

### COVID-19 and Diabetes Mellitus

Ample data suggest that diabetes mellitus portends a poor prognosis in patients with COVID-19.<sup>4–7</sup> Moreover, COVID-19, directly and/or indirectly, predisposes to hyperglycemia (in patients without preexisting diabetes mellitus) and worsening of dysglycemia (in patients with preexisting diabetes mellitus).<sup>4,8</sup> SARS-CoV-2 has been demonstrated to cause pancreatic  $\beta$ -cell damage *ex vivo* and *in vivo*, resulting in reduced numbers of insulin-secreting granules in  $\beta$ -cells and impaired glucose-stimulated insulin secretion.<sup>9</sup> Furthermore, altered secretome persists in patients even after recovery from COVID-19 and contributes to insulin resistance in the post-COVID-19 period.<sup>10</sup>

In addition, drugs used in managing COVID-19, namely, steroids, remdesivir, and lopinavir-ritonavir, can lead to dysglycemia.<sup>4</sup> The dose of steroids recommended across studies varies remarkably. The landmark Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial showed that oral or intravenous dexamethasone administered at a dose of 6 mg once daily for up to 10 days in patients with COVID-19 receiving either invasive mechanical ventilation or oxygen alone reduced the 28-day mortality by 18% to 32%. In an ambispective cohort study, the treatment of severe COVID-19 pneumonia with high-dose methylprednisolone (250–500 mg/day) for 3 days followed by oral prednisone for 14 days, compared with 6

mg of dexamethasone for 7 to 10 days, statistically significantly decreased the recovery time and the need for transfer to intensive care.<sup>11</sup> A recent Cochrane review showed that systemic corticosteroids probably slightly reduced all-cause mortality in individuals hospitalized because of symptomatic COVID-19. However, the review found no completed studies enabling a comparison of different doses of glucocorticoids for COVID-19.<sup>12</sup>

Of note, the use of steroids in patients with COVID-19, often at an irrationally high dose, has predisposed to the development of in-hospital glucocorticoid-induced hyperglycemia (GIH). Although GIH is suggested to be a transient problem resolving after discontinuing glucocorticoids, data indicate that diabetes can persist, and glucocorticoids may unmask a preexisting disorder of glucose metabolism.<sup>13,14</sup> A meta-analysis summarized studies in which patients without preexisting diabetes who received systemic glucocorticoids and showed a rate of GIH development in 32.3% and in further 18.6% diabetes was sustainable during follow-up.<sup>15</sup>

In a recently published retrospective cohort study from England, 47 780 individuals with COVID-19 who were admitted to the hospital and subsequently discharged by August 31, 2020 were included. Cases were matched to controls for personal and clinical characteristics; controls were recruited from a pool of nearly 50 million individuals retrieved from an electronic health database. After discharge, diabetes was diagnosed in 4.9% of COVID-19 survivors, amounting to a rate of 127 per 1000 person-years. Individuals who needed to be admitted to the intensive care unit (ICU) had higher rates of diabetes (8.8%) after discharge than those who did not require ICU admission (4.6%). The rate ratio was higher for individuals aged <70 years than for those aged  $\geq 70$ .<sup>16</sup>

Apart from diabetes mellitus, metabolic syndrome is also independently associated with poor outcomes in COVID-19. Metabolic syndrome increases the risk of severe disease, complications, hospitalization, and mortality with COVID-19. In a recently published study, 5069 patients hospitalized with COVID-19 had metabolic syndrome (defined as  $\geq 3$  of the following criteria: obesity, prediabetes or diabetes, hypertension, and dyslipidemia). Compared with 23 971 control patients without metabolic syndrome, patients with metabolic syndrome had an increased risk of ICU admission, invasive mechanical ventilation, acute respiratory distress syndrome, mortality, and prolonged hospital length of stay and ICU length of stay. The association with acute respiratory distress syndrome was cumulative for each metabolic syndrome criterion present.<sup>17</sup> Obesity, one of the components of metabolic syndrome, has also been independently associated with poor outcomes in COVID-19. At a body mass index of  $>23$  kg/m<sup>2</sup>, a linear increase in the risk of severe COVID-19 leading to admission to hospital and mortality was observed in a prospective, community-based cohort study.<sup>18</sup>

In the wake of the COVID-19 pandemic, there has been an upsurge in the number of cases of mucormycosis, an entity being referred to as COVID-19-associated mucormycosis (CAM). Most of the cases of CAM have been reported from India.<sup>19</sup> Uncontrolled hyperglycemia and the use of steroids in the context of COVID-19 have been implicated in the pathogenesis of CAM.<sup>20</sup> Data on other complications of diabetes mellitus post-COVID-19 are yet not available; nevertheless, in a case-control study that had included 145 patients with diabetes and 144 control subjects without diabetes who had recovered from COVID-19, the number of post-COVID-19 symptoms, notably, fatigue, dyspnea on exertion, and pain, was similar between the 2 groups when assessed at 7.2 months after hospital discharge.<sup>21</sup>

### Recommendations Based on Available Evidence

- a. Patients with preexisting diabetes mellitus should be more vigilant about optimum glycemic control in the post-COVID-19 period.

- b. In patients without preexisting diabetes:
- i. Routine evaluation of glycemic status in patients with COVID-19 without documented in-hospital hyperglycemia or new-onset diabetes mellitus is not recommended. Patients with COVID-19 admitted to the ICU and those aged <70 years are at high risk of new-onset diabetes post-COVID-19 and, thus, may be screened for new-onset diabetes at 3 months after discharge with a fasting plasma glucose or 2-hour plasma glucose during oral glucose tolerance test or glycated hemoglobin (HbA1C) as per the American Diabetes Association (ADA) Standards of Medical Care in Diabetes.<sup>22</sup>
  - ii. Patients with COVID-19 with documented in-hospital hyperglycemia (including steroid-induced hyperglycemia) but normoglycemia and off all antidiabetic drugs at the time of discharge should be reevaluated at 3 months after discharge with a fasting plasma glucose or 2-hour plasma glucose during oral glucose tolerance test or HbA1C as per the ADA Standards of Medical Care in Diabetes.<sup>22</sup>
  - iii. Patients with COVID-19 with documented in-hospital hyperglycemia (including glucocorticoid-induced hyperglycemia) and discharged on antidiabetic medications should maintain glycemic control based on the standard of care. The dose and number of antihyperglycemic medications should be adjusted as per the glycemic profile. Antidiabetic medications may need to be stopped based on the blood glucose profile. It may be possible to discontinue antihyperglycemic medications in those with confirmed stress-induced hyperglycemia, that is, an HbA1C level of <6.5% in the presence of hyperglycemia at the time of discharge.
  - c. Patients with COVID-19 with diabetes mellitus/hyperglycemia are at high risk of mucormycosis even after recovery from COVID-19, and the caregivers need to be vigilant about the same.
  - d. Screening for other diabetes-related complications should be undertaken as per routine standard of care.

### COVID-19 and Thyroid Function

There exists ample literature about thyroid function in active COVID-19. The majority of the patients presenting with COVID-19 tend to be biochemically euthyroid.<sup>23,24</sup> The most common thyroid dysfunction observed in patients with active COVID-19 is euthyroid sick syndrome/nonthyroidal illness syndrome, the magnitude of the decrease in thyroid-stimulating hormone (TSH) and triiodothyronine (T3)/thyroxine (T4) levels correlating positively with the severity of the disease.<sup>25,26</sup> While overt hypothyroidism is rare in patients with COVID-19, *thyrotoxicosis without hyperthyroidism*, due to destructive SAT, is more commonly reported. COVID-19-associated SAT is biochemically characterized by low TSH and free T3 levels and normal or elevated free T4 levels. In the context of COVID-19, such an entity is often referred to as atypical thyroiditis<sup>27</sup> and should be considered a differential diagnosis when acutely infected patients present with tachycardia without evidence of progression of COVID-19 illness.<sup>28</sup> Although follow-up data are limited, most of the available data suggest that thyroid function returns to normal without any specific treatment.<sup>23–25</sup>

SAT has also been described after recovery from COVID-19.<sup>29–31</sup> Such patients tend to present with neck pain, fever resurgence, weight loss, and/or palpitations.<sup>32</sup> In addition, occasional cases of Graves' disease have been described following COVID-19.<sup>33–35</sup> In a prospective observational study, 70 patients aged  $\geq 18$  years were included at least 3 months after the diagnosis of COVID-19. Of the 68 patients who were not known to have any thyroid disease, thyroid function (TSH, free T4, and free T3) was all within the normal range. Moreover, there was no difference in the frequency of hypothyroidism or hyperthyroidism in patients complaining of

fatigue compared with those without.<sup>36</sup> In another study where 204 patients with COVID-19 were reassessed at a median of 89 days, most abnormal thyroid function test (TFT) results in acute COVID-19 resolved (81.4%), and incident thyroid dysfunction was rare (1.9%). Nonetheless, the authors observed incident antithyroid peroxidase (anti-TPO) positivity in 5.5% of the patients who were anti-TPO antibody negative at presentation.<sup>37</sup>

### Recommendations Based on Available Evidence

- a. Patients with COVID-19 with biochemically documented euthyroid sick syndrome during the acute phase of the disease may undergo a TFT performed at 6 weeks after discharge.
- b. Patients with COVID-19 with biochemically documented subclinical hypothyroidism during the acute phase of the disease should undergo a TFT 3 months after discharge. An anti-TPO antibody assay should be performed if not found to be positive during the acute phase of COVID-19.
- c. Patients with COVID-19 with biochemically documented overt hypothyroidism during the acute phase of the disease should undergo a TFT performed at 6 weeks after discharge while on levothyroxine supplementation. An anti-TPO antibody assay should be performed if not found to be positive during the acute phase of COVID-19.
- d. Patients with COVID-19 with biochemically documented hyperthyroidism/subclinical hyperthyroidism/SAT during the acute phase of the disease should undergo a TFT performed at 6 weeks after discharge. An anti-TPO antibody assay should be performed if not found to be positive during the acute phase of COVID-19. Even if the thyroid function at 6 weeks is normal, a repeat test should be performed at 12 weeks to rule out the possibility of postthyroiditis hypothyroidism.
- e. Patients with COVID-19 with normal thyroid function assessed during the acute phase of the disease do not need a routine reestimation of thyroid function on follow-up.
- f. Patients with COVID-19 in whom thyroid function was not estimated during the acute phase of the disease do not require a routine assessment of thyroid function on follow-up, even in those complaining of persistent fatigue.
- g. Patients who have recovered from COVID-19 complaining of neck pain, weight loss, resurgence of fever, and/or palpitations should be suspected of having SAT. A TFT should be immediately performed, and if suggestive of thyrotoxicosis, a radionuclide thyroid uptake scan using technetium-99m may be ordered (if facilities are available). A combination of high erythrocyte sedimentation rate (and/or C-reactive protein levels) and poor radionuclide uptake by the thyroid gland is diagnostic of SAT. A thyroid-stimulating immunoglobulin assay may be ordered when Graves' disease is suspected.

### COVID-19 and Adrenal Function

At the inception of the pandemic, there were multiple hypotheses that SARS-CoV-2 may directly damage the adrenocortical cells or induce a state of "molecular mimicry" against adrenocorticotrophic hormone (ACTH).<sup>3,38</sup> However, adrenal insufficiency (AI) in COVID-19 is not as common as hypothesized. In a cohort of 403 patients with COVID-19, the median plasma cortisol level was 619 nmol/L, which was significantly higher than those without COVID-19.<sup>39</sup> Critical illness-related corticosteroid insufficiency (CIRCI) has been reported to be uncommon in the setting of COVID-19; only 18 (4.5%) of 403 patients with COVID-19 had CIRCI.<sup>40</sup> In another similar study, the median cortisol level of COVID-19-positive patients ( $n = 144$ ) was higher than that of COVID-19-negative patients ( $n = 141$ ) (21.84  $\mu\text{g/dL}$  vs. 16.47  $\mu\text{g/dL}$ ;  $P < .001$ ).<sup>41</sup>

However, in another cohort of 235 patients with COVID-19, 34 (14.5%) had AI. Most patients with AI ( $n = 30$ , 88%) had asymptomatic or mild COVID-19. A total of 17 patients (7.2%) had basal cortisol levels of  $<3 \mu\text{g/dL}$ , of whom 11 had a poststimulation cortisol value of  $<18.0 \mu\text{g/dL}$ . CIRCI was present in 18.3% of cases defined by a delta cortisol level of  $<9 \mu\text{g/dL}$ .<sup>42</sup> In another study that had included 28 consecutive patients with COVID-19, 9 (32%) had a biochemical picture consistent with central AI, defined as a plasma cortisol cutoff level of  $<300 \text{ nmol/L}$  in the setting of acute disease with plasma ACTH within the upper limit of the reference range of the assay.<sup>43</sup> In another study with 9 critically ill patients with COVID-19, 6 (66.7%) had random plasma cortisol levels below  $10 \mu\text{g/dL}$ , which met the criteria for the diagnosis of CIRCI.<sup>44</sup> Moreover, a case of delayed-onset central AI has been described during the convalescent phase of COVID-19.<sup>45</sup> Thus, not only the aforementioned data appear conflicting, but also the disparate sample sizes make these studies impossible to compare outside of a systematic review.

With regard to follow-up data on adrenal function post-COVID-19, literature is scarce. In a prospective observational study, 70 patients aged  $\geq 18$  years were included at least 3 months after COVID-19 diagnosis. All participants demonstrated a normal response to Synacthen, achieving a peak cortisol level of  $\geq 450 \text{ nmol/L}$ , irrespective of the severity of COVID-19, antibody status, or dexamethasone use. Neither disease severity nor the absence or presence of persistent fatigue following COVID-19 was found to affect the basal and peak cortisol levels. After the publication of the results of the landmark RECOVERY trial, dexamethasone use became the standard of care for all oxygen-requiring patients with COVID-19. The aforementioned study suggests that dexamethasone administration as per the standard COVID-19 protocol (ie, 6 mg once daily for a maximum of 10 days) does not impair adrenal function in the medium term. This observation is reassuring considering the large number of patients who will have received this regimen as a part of routine COVID-19 treatment.<sup>36</sup>

#### Recommendations Based on Available Evidence

- We do not recommend the routine estimation of serum cortisol/ACTH in post-COVID-19 patients.
- Since patients with COVID-19 treated with dexamethasone as per the RECOVERY trial (6 mg once a day for a maximum of 10 days) do not have impaired adrenal function, they do not require a routine evaluation of adrenal function in the post-COVID-19 setting.
- Patients with COVID-19 who have received steroids during the acute phase of the disease for  $<3$  weeks are unlikely to have clinically significant hypothalamic-pituitary-adrenal (HPA) axis suppression and, hence, do not require the evaluation of their HPA function.
- Suppression of the HPA axis is inevitable in patients taking the equivalent of 15 mg/day or more of prednisolone for  $\geq 3$  weeks. Hence, the evaluation of the HPA axis may be performed after tapering and stopping glucocorticoids.
- Morning serum cortisol/ACTH levels may, however, be estimated in post-COVID-19 patients with surrogate evidence of AI, that is, recent onset anorexia, involuntary weight loss, diarrhea, hyponatremia and/or hyperkalemia, and/or eosinophilia.
- Patients with COVID-19 with biochemically documented AI during the acute phase of the disease should undergo a morning serum cortisol/ACTH test estimated with/without Synacthen stimulation test at 12 weeks after discharge, withholding hydrocortisone 24 hours prior to the test.
- Any documentation of central AI (in the absence of a prior history of glucocorticoid intake) should prompt the evaluation for other anterior pituitary hormone deficiencies.

#### COVID-19 and Pituitary Function

Occasional cases of pituitary apoplexy in relation to COVID-19 have been reported in the literature.<sup>46</sup> While most cases have been described in association with active COVID-19, some have been reported following recovery from COVID-19 as well. The typical presenting features are headache and visual disturbance, associated with anterior pituitary hormone deficiencies. Whereas most patients were successfully managed with emergent transphenoidal surgery, postoperative follow-up data are limited.<sup>46</sup> Cases of post-COVID-19 infundibulo-neurohypophysitis have also been occasionally reported.<sup>47</sup>

#### Recommendations Based on Available Evidence

- Patients with COVID-19 complaining of new-onset headache and visual disturbance after recovery should be suspected of having pituitary apoplexy, and a noncontrast computed tomography of the head should be performed at the earliest. The possibility of pituitary apoplexy should be kept higher on the cards, especially in those already known to have an underlying pituitary adenoma, pregnant women, and those on antiplatelet medications.
- Patients with COVID-19 diagnosed with pituitary apoplexy in the acute phase of the disease and not found to have any anterior pituitary hormone deficiency should be reevaluated at 6 weeks for incident hormone deficiencies.
- Patients with COVID-19 diagnosed with pituitary apoplexy in the acute phase of the disease and found to have 1 or more anterior pituitary hormone deficiencies and supplemented with the respective hormones should be reevaluated at 6 weeks for other incident hormone deficiencies.

#### COVID-19 and Gonadal System

Hitherto literature suggests that hypogonadism is not uncommon in men affected with COVID-19. In a prospective cohort study involving 221 hospitalized male patients (aged  $>18$  years) with laboratory-confirmed SARS-CoV-2 who had been hospitalized due to COVID-19, 113 (51.1%) had hypogonadism (defined as a serum total testosterone level of  $<300 \text{ ng/dL}$ ).<sup>48</sup> Men with severe disease tended to have lower testosterone levels.<sup>48–50</sup> The probable mechanisms involve cytokine-driven gonadotropin suppression<sup>50</sup>; nevertheless, elevated luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels have been reported in conjunction with low testosterone levels, pointing toward the possibility of a primary gonadal failure.<sup>48,51</sup> In fact, testicular samples from autopsies of deceased patients with COVID-19 have shown histopathologic evidence of orchitis.<sup>52</sup> Moreover, SARS-CoV-2 has been detected in the testes of patients with severe disease.<sup>53</sup>

The risk of impaired spermatogenesis has also been observed in patients with moderate infection and convalescents.<sup>51,54</sup> In an observational study that had involved 43 sexually active men who had recovered from COVID-19, oligo-crypto-azoospermia was observed in 25.6% of the patients. The severity of COVID-19 was related to the occurrence of azoospermia. Azoospermia was observed in 80%, 11.5%, and 8.3% of patients admitted to the ICUs and medicine department and those nonhospitalized, respectively. However, gonadal hormones were not estimated in the study. Multivariate analysis revealed that hospitalization (not recovered vs. hospitalized vs. ICU) was the primary determinant of crypto-azoospermia.<sup>55</sup> Nevertheless, there are no robust follow-up data on the effect of COVID-19 on male gonadal function and subsequent fertility.

Although it may be inappropriate to the context of the manuscript, it needs to be emphasized that there exist no data to suggest that COVID-19 vaccines cause male infertility.<sup>56,57</sup>

With regard to the female gonadal system, robust clinical data are scarce. Among 177 women of childbearing age with confirmed COVID-19, almost one fifth of patients exhibited a decrease in menstrual volume or cycle prolongation. As part of the same study, the sex hormone and anti-Mullerian hormone levels were estimated in the early follicular phase in 91 patients with COVID-19 and an equal number of controls. There was no significant difference in the FSH, LH, estradiol, progesterone, testosterone, and anti-Mullerian hormone levels between patients with COVID-19 and controls. The authors, thus, concluded that menstrual changes in women with COVID-19 may result from transient sex hormone changes caused by suppression of ovarian function that quickly resume after recovery.<sup>58</sup> In another cohort study, 32 consecutive women undergoing in vitro fertilization were included. They were divided into 3 study groups: recovering from confirmed COVID-19 (n = 9), vaccinated with the BNT162b2 messenger ribonucleic acid (mRNA) COVID-19 vaccine (n = 9), and uninfected/nonvaccinated controls (n = 14). Overall, there was no difference in the surrogate parameters for ovarian follicle quality between the 3 groups.<sup>59</sup>

#### Recommendations Based on Available Evidence

- a. Men with COVID-19 with biochemically documented hypogonadism (either primary or secondary) during the acute phase of the disease should undergo serum total testosterone, LH, and FSH tests performed at 3 months after discharge.
- b. Men with COVID-19 with normal gonadal function documented during the acute phase of the disease do not require a routine reevaluation of gonadal hormones on follow-up.
- c. Men with COVID-19 in whom the gonadal function was not estimated during the acute phase of the disease do not require a routine assessment of gonadal hormones on follow-up.
- d. Men who have recovered from COVID-19 and complaining of new-onset erectile dysfunction and/or low/loss of libido should undergo serum total testosterone, LH, and FSH tests performed irrespective of the gonadal status during the acute phase of the disease. A psychiatry opinion should be sought to exclude psychogenic erectile dysfunction in such men with normal gonadal function.
- e. On follow-up, men found to have hypogonadism (low serum total testosterone level) with low/normal LH/FSH levels after recovery should be evaluated for other anterior pituitary hormone deficiencies. In addition, the serum prolactin level should also be estimated.
- f. On follow-up, in men found to have hypogonadism (low serum total testosterone level) with elevated LH/FSH levels after recovery, a possibility of a primary testicular failure should be kept in mind.
- g. In either scenario, a semen analysis may be performed for men of reproductive age if they wish to father children.
- h. Routine semen analysis in men of the reproductive age group desirous of a future child is not recommended.
- i. Hitherto, there is no robust evidence to recommend a routine evaluation of gonadal function in women of childbearing age who have recovered from COVID-19.

#### COVID-19 and Bone and Mineral Metabolism

Hypocalcemia has been commonly reported in patients with COVID-19. Of 531 patients with COVID-19 admitted to the emergency department, 462 (82%) had hypocalcemia. In univariate and multivariate analyses, hypocalcemia emerged as an independent risk factor predicting hospitalization.<sup>60</sup> In another observational cohort study, 445 patients admitted with COVID-19 were included. Hypocalcemia was observed in 68.8% of the patients. Patients with hypocalcemia needed a significantly longer duration of

hospitalization and required more high-dependency unit/ICU admissions than those without hypocalcemia.<sup>61</sup> Nevertheless, a high frequency of asymptomatic hypocalcemia (and hypophosphatemia) has also been reported in patients with nonsevere COVID-19, the clinical relevance of which remains uncertain.<sup>62</sup>

Hypovitaminosis D has been linked to an increased risk of COVID-19 infection, disease severity, and poor outcomes.<sup>63,64</sup> In fact, hypocalcemia in the context of COVID-19 is associated with hypovitaminosis D, along with an inadequate compensatory parathyroid hormone response.<sup>65</sup> Vitamin D supplementation, in the form of either cholecalciferol or calcifediol, has also been shown to improve clinical outcomes in COVID-19, although robust and consistent data are lacking.<sup>66</sup>

With regard to long-term changes in calcium and vitamin D post-COVID-19, data are scarce. In a case-control study, 120 COVID-19 survivors were compared with an equal number of age- and sex-matched healthy controls at least 3 months after recovery. Although the serum calcium levels did not differ between the 2 groups, healthy controls had significantly higher 25-hydroxyvitamin D levels (40.32 ± 11.76 ng/mL) than COVID-19 survivors (23.22 ± 8.45 ng/mL).<sup>67</sup>

#### Recommendations Based on Available Evidence

- a. We do not recommend the routine estimation of serum calcium in post-COVID-19 patients.
- b. Patients with COVID-19 with symptomatic hypocalcemia during the acute stage of the disease should undergo a repeat estimation of serum calcium at 2 weeks after discharge.
- c. The 25-hydroxyvitamin D levels may be estimated in post-COVID-19 patients, and vitamin D may be supplemented accordingly.

#### COVID-19 Vaccination and Endocrine Systems

The European Society of Endocrinology statement has supported the recommendation that “COVID-19 vaccination should not be handled differently in patients with stable endocrine diseases such as autoimmune thyroiditis, Graves’ disease, Addison’s disease, pituitary adenomas, diabetes type 1 and 2 and obesity as compared to the general population.”<sup>68</sup> In fact, COVID-19 vaccination should be prioritized in individuals with diabetes mellitus.<sup>69</sup>

The reciprocal effect of COVID-19 vaccination on the endocrine system has not been explored in details. Nevertheless, blood glucose monitoring is required more often than usual for several days after vaccination in individuals with diabetes, and glucocorticoid doses may need to be temporarily hiked up in individuals with AI.<sup>70</sup>

Emerging data suggest that COVID-19 vaccines are associated with thyroid dysfunction. Multiple cases of thyrotoxicosis have been reported following vector-based or mRNA-based SARS-CoV-2 vaccines with a spectrum ranging from SAT and silent thyroiditis to Graves’ disease.<sup>71–75</sup> Thyroid dysfunction could be explained by various mechanisms such as autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome), molecular mimicry between human and viral proteins, mRNA “self-adjuvant” effect, and immune disruption from external stimuli.

#### Recommendations Based on Available Evidence

- a. Subjects complaining of involuntary weight loss, palpitations, tremors, and/or neck pain after vaccination with vector-based or mRNA-based SARS-CoV-2 vaccines should be suspected of having thyrotoxicosis, and a TFT should be performed.

The herein proposed recommendations have been summarized in [Table 1](#).

**Table 1**  
Summarizing the Herein Proposed Recommendations on the Endocrine Follow-up of post-COVID Patients

Endocrine systems/disorders	Proposed recommendations
Diabetes mellitus	<ul style="list-style-type: none"> <li>a. Patients with preexisting diabetes mellitus should be more vigilant about optimum glycemic control in the post-COVID period.</li> <li>b. In patients without preexisting diabetes:                             <ul style="list-style-type: none"> <li>i. Routine evaluation of glycemic status in patients with COVID-19 without documented in-hospital hyperglycemia or new-onset diabetes mellitus is not recommended. Patients with COVID-19 admitted to the ICU and those aged &lt;70 years are at high risk of new-onset diabetes post-COVID and, hence may be screened for new-onset diabetes at 3 months after discharge with a fasting plasma glucose or 2-hour plasma glucose during oral glucose tolerance test or HbA1C as per the ADA Standards of Medical Care in Diabetes.<sup>22</sup></li> <li>ii. Patients with COVID-19 with documented in-hospital hyperglycemia (including steroid-induced hyperglycemia) but normoglycemia and off all antidiabetic drugs at the time of discharge should be reevaluated at 3 months after discharge with a fasting plasma glucose or 2-hour plasma glucose during oral glucose tolerance test or HbA1C as per the ADA Standards of Medical Care in Diabetes.<sup>22</sup></li> <li>iii. Patients with COVID-19 with documented in-hospital hyperglycemia (including steroid-induced hyperglycemia) and discharged on antidiabetic medications should maintain glycemic control based on the standard of care. The dose and number of antihyperglycemic medications should be adjusted as per the glycemic profile. Antidiabetic medications may need to be stopped based on the blood glucose profile. It may be possible to discontinue antihyperglycemic medications in those with confirmed stress-induced hyperglycemia, that is, an HbA1C level of &lt;6.5% in the presence of hyperglycemia at the time of discharge.</li> </ul> </li> <li>c. Patients with COVID-19 with diabetes mellitus/hyperglycemia are at high risk of mucormycosis even after recovery from COVID-19, and the caregivers need to be vigilant about the same.</li> <li>d. Screening for other diabetes-related complications should be undertaken as per standard of care.</li> </ul>
Thyroid	<ul style="list-style-type: none"> <li>a. Patients with COVID-19 with biochemically documented euthyroid sick syndrome during the acute phase of the disease may undergo a thyroid function test performed at 6 weeks after discharge.</li> <li>b. Patients with COVID-19 with biochemically documented subclinical hypothyroidism during the acute phase of the disease should undergo a thyroid function test 3 months after discharge. An anti-TPO antibody assay should be performed if not found to be positive during the acute phase of COVID-19.</li> <li>c. Patients with COVID-19 with biochemically documented overt hypothyroidism during the acute phase of the disease should undergo a thyroid function test performed at 6 weeks after discharge while on levothyroxine supplementation. An anti-TPO antibody assay should be performed if not found to be positive during the acute phase of COVID-19.</li> <li>d. Patients with COVID-19 with biochemically documented hyperthyroidism/subclinical hyperthyroidism/subacute thyroiditis during the acute phase of the disease should undergo a thyroid function test performed at 6 weeks after discharge. An anti-TPO antibody assay should be performed if not found to be positive during the acute phase of COVID-19. Even if the thyroid function at 6 weeks is normal, a repeat test should be performed at 12 weeks to rule out the possibility of postthyroiditis hypothyroidism.</li> <li>e. Patients with COVID-19 with normal thyroid function assessed during the acute phase of the disease do not need a routine reestimation of thyroid function on follow-up.</li> <li>f. Patients with COVID-19 in whom thyroid function was not estimated during the acute phase of the disease do not require a routine assessment of thyroid function on follow-up, even in those complaining of persistent fatigue.</li> <li>g. Patients who have recovered from COVID-19 complaining of neck pain, weight loss, resurgence of fever, and/or palpitations should be suspected of having subacute thyroiditis. A thyroid function test should be immediately performed, and if suggestive of thyrotoxicosis, a radionuclide thyroid uptake scan using technetium-99 m may be ordered (if facilities are available). A combination of high erythrocyte sedimentation rate (and/or C-reactive protein levels) and poor radionuclide uptake by the thyroid gland is diagnostic of subacute thyroiditis. A thyroid-stimulating immunoglobulin assay may be ordered when Graves disease is suspected.</li> </ul>
Adrenals	<ul style="list-style-type: none"> <li>a. We do not recommend the routine estimation of serum cortisol/ACTH in post-COVID patients.</li> <li>b. Since patients with COVID-19 treated with dexamethasone as per the RECOVERY trial (6 mg once a day for a maximum of 10 days) do not have impaired adrenal function, they do not require a routine evaluation of adrenal function in the post-COVID setting.</li> <li>c. Patients with COVID-19 who have received steroids during the acute phase of the disease for &lt;3 weeks are unlikely to have clinically significant HPA axis suppression and, hence, do not require the evaluation of their HPA function.</li> <li>d. Suppression of the HPA axis is inevitable in patients taking the equivalent of 15 mg/day or more of prednisolone for ≥3 weeks. Hence, the evaluation of the HPA axis may be performed after tapering and stopping glucocorticoids.</li> <li>e. Morning serum cortisol/ACTH levels may, however, be estimated in post-COVID patients with surrogate evidence of AI, that is, recent onset anorexia, involuntary weight loss, diarrhea, hyponatremia and/or hyperkalemia, and/or eosinophilia.</li> <li>f. Patients with COVID-19 with biochemically documented AI during the acute phase of the disease should undergo a morning serum cortisol/ACTH test estimated with/without Synacthen stimulation test at 12 weeks after discharge, withholding hydrocortisone 24 h prior to the test.</li> <li>g. Any documentation of central AI (in the absence of a prior history of glucocorticoid intake) should prompt the evaluation for other anterior pituitary hormone deficiencies.</li> </ul>
Pituitary	<ul style="list-style-type: none"> <li>a. Patients with COVID-19 complaining of new-onset headache and visual disturbance post-recovery should be suspected of having pituitary apoplexy, and a noncontrast computed tomography of the head should be performed at the earliest. The possibility of pituitary apoplexy should be kept higher on the cards, especially in those already known to have an underlying pituitary adenoma, pregnant women, and those on antiplatelet medications.</li> <li>b. Patients with COVID-19 diagnosed with pituitary apoplexy in the acute phase of the disease and not found to have any anterior pituitary hormone deficiency should be reevaluated at 6 weeks for incident hormone deficiencies.</li> <li>c. Patients with COVID-19 diagnosed with pituitary apoplexy in the acute phase of the disease and found to have 1 or more anterior pituitary hormone deficiencies and supplemented with the respective hormones should be reevaluated at 6 weeks for other incident hormone deficiencies.</li> </ul>
Gonads	<ul style="list-style-type: none"> <li>a. Men with COVID-19 with biochemically documented hypogonadism (either primary or secondary) during the acute phase of the disease should undergo serum total testosterone, LH, and FSH tests performed at 3 months after discharge.</li> <li>b. Men with COVID-19 with normal gonadal function documented during the acute phase of the disease do not require a routine reevaluation of gonadal hormones on follow-up.</li> <li>c. Men with COVID-19 in whom the gonadal function was not estimated during the acute phase of the disease do not require a routine assessment of gonadal hormones on follow-up.</li> <li>d. Men who have recovered from COVID-19 and complaining of new-onset erectile dysfunction and/or low/loss of libido should undergo serum total testosterone, LH, and FSH tests performed irrespective of the gonadal status during the acute phase of the disease. A psychiatry opinion should be sought to exclude psychogenic erectile dysfunction in such men with normal gonadal function.</li> </ul>

Table 1 (continued)

Endocrine systems/disorders	Proposed recommendations
	<p>e. On follow-up, men found to have hypogonadism (low serum total testosterone level) with low/normal LH/FSH levels after recovery should be evaluated for other anterior pituitary hormone deficiencies. In addition, the serum prolactin level should also be estimated.</p> <p>f. On follow-up, in men found to have hypogonadism (low serum total testosterone level) with elevated LH/FSH levels after recovery, a possibility of a primary testicular failure should be kept in mind.</p> <p>g. In either scenario, a semen analysis may be performed for men of reproductive age if they wish to father children.</p> <p>h. Routine semen analysis in men of the reproductive age group desirous of a future child is not recommended.</p> <p>i. Hitherto, there is no robust evidence to recommend a routine evaluation of gonadal function in women of childbearing age who have recovered from COVID-19.</p>
Bone and mineral metabolism	<p>a. We do not recommend the routine estimation of serum calcium in post-COVID patients.</p> <p>b. Patients with COVID-19 with symptomatic hypocalcemia during the acute stage of the disease should undergo a repeat estimation of serum calcium at 2 weeks after discharge.</p> <p>c. The 25-hydroxyvitamin D levels may be estimated in post-COVID patients, and vitamin D be supplemented accordingly.</p>
COVID-19 vaccination and endocrine systems	<p>a. Subjects complaining of involuntary weight loss, palpitations, tremors, and/or neck pain after vaccination with vector-based or mRNA-based SARS-CoV-2 vaccines should be suspected of having thyrotoxicosis, and a thyroid function test should be performed.</p>

Abbreviations: ADA = American Diabetes Association; AI = adrenal insufficiency; anti-TPO = antithyroid peroxidase; COVID-19 = coronavirus disease 2019; FSH = follicle-stimulating hormone; HbA1C = glycated hemoglobin; HPA = hypothalamic-pituitary-adrenal; ICU = intensive care unit; LH = luteinizing hormone; mRNA = messenger ribonucleic acid; RECOVERY = Randomised Evaluation of COVID-19 Therapy; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## Conclusions

The majority of the available data indicate that biochemical endocrine dysfunctions observed during the acute phase of COVID-19 tend to improve after recovery. However, robust data in this regard are still lacking. Conduction of case-control studies to bridge the knowledge gap in this area, including studies aimed to investigate the effects of vaccination on possible endocrine outcomes, is the need of the hour. Meanwhile, a rational approach should be adopted, and management and follow-up of subjects with COVID-19 should be carried out as per recommendations laid down by various professional bodies such as the Endocrine Society, American Association of Clinical Endocrinology, European Society of Endocrinology, and ADA.

## Author Contributions

R.P. wrote the original draft. R.P., A.J., M.B., S.V., and S.M. performed the data curation. R.P. and S.K.B. performed the study conceptualization. A.J., S.K.B., M.B., S.V., and S.M. reviewed and edited the manuscript.

## Disclosure

The authors have no multiplicity of interest to disclose.

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