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# Managing common endocrine disorders amid COVID-19 pandemic

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# ABSTRACT

*Background and aims:* The novel coronavirus disease (COVID-19) pandemic and the resulting nationwide lockdowns have posed a major challenge to the management of pre-existing and newly diagnosed endocrine disorders. Herein, we have summarized the management approaches of common endocrine disorders amid the ongoing pandemic.

*Methods:* We have performed an extensive literature search for articles in PubMed, EMBASE and Google Scholar databases till 25 May 2020, with the following keywords: "COVID-19", "diabetes mellitus", "thyroid disorders", "primary adrenal insufficiency", "Cushing's syndrome", "pituitary tumors", "vitamin D"", "osteoporosis", "primary hyperparathyroidism", "hypoparathyroidism", "management", "treatment" and "guidelines" with interposition of the Boolean operator "AND".

*Results:* We have summarized the most feasible strategies for the management of diabetes mellitus, thyroid disorders, primary adrenal insufficiency (including congenital adrenal hyperplasia), Cushing's syndrome, pituitary tumors, osteoporosis, primary hyperparathyroidism and hypoparathyroidism amid the constraints laid down by the raging pandemic. In general, medical management should be encouraged and surgical interventions should be deferred whenever possible. Ongoing medications should be continued. Sick-day rules should be sincerely adhered to. Regular contact with physicians can be maintained through teleconsultations and virtual clinics.

*Conclusions:* Considering the burden of endocrine disorders in the general population, their management needs to be prioritized amid the ongoing COVID-19 pandemic.

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# 1. Introduction

The novel coronavirus disease (COVID-19) has been on the rampage ever since its outbreak in December 2019 in Wuhan, China. Till date, the disease has affected over 5.3 million people, inflicting more than 342000 casualties in over 200 nations worldwide [1]. In the absence of any effective vaccine or therapy against SARS-CoV-2, social distancing, hand hygiene and community containment seems to be the most effective means of decelerating the spread of the pandemic. To ensure the same, governments worldwide have imposed nationwide lockdowns. Amid the prevailing scenario, the management of pre-existing medical conditions, including endocrine disorders may take a back seat. With almost 10% of the global population being affected by diabetes mellitus [2], around 5% by hypothyroidism, 0.2–1.3% by hyperthyroidism [3] and over 200 million women having osteoporosis [4],

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the management of endocrine disorders cannot be compromised. Herein, we have summarized the best possible management strategies of common endocrine disorders amid the constraints imposed by the ongoing COVID-19 pandemic.

#### 1.1. Diabetes mellitus

People with diabetes mellitus are at a high risk of severe disease, acute respiratory distress syndrome and increased mortality due to COVID-19 [5,6]. Good glycemic control is expected to strengthen the innate immune system and help ward off these complications [7]. However, limitation of physical activity, altered diet, restricted availability of anti-diabetic medications and lack of in-clinic follow-ups as a result of the ongoing pandemic is expected to adversely affect the glycemic control [8]. Much of the problems can be resolved by appropriate diabetes self-management education (DSME). Physicians, via online media, can impart DSME to home-bound diabetic patients and reiterate the need for a healthy diet and an active lifestyle. Even under lockdown conditions, 30 min/ day of moderate-intensity aerobic physical activity in the form of

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brisk walk in terrace or on treadmill (if available), stationary jogging or stationary cycling could be helpful. This could be supplemented by muscle-strengthening activities (around 15 min/day for 3 days/week) that could include bodyweight exercises (like push-ups, squats, sit-ups, crunches and forward flexes) and resistance exercise (lifting lightweight). In absence of home fitness accessories, readily available household stuffs like buckets half filled with water or bags filled with sand could be used [8]. Although certain anti-diabetic drugs like pioglitazone and liraglutide are associated with upregulation of angiotensin-converting enzyme 2 (ACE2) (and hence carries with it a theoretical risk of increased COVID-19 severity), at present no evidence supports the change of these medications amid the ongoing pandemic. It would be wise to continue the same anti-diabetic medications [7]. Insulin might be good choice for patients with poor glycemic control; however, under the prevailing circumstances it would be difficult to educate patients about insulin injection techniques. Taking help of readily available online educational videos can circumvent the problem. With hydroxychloroquine being used in the management and prophylaxis of COVID-19, it could be a good add-on anti-diabetic drug [7,9]. Although not FDA certified, the drug has been used as an anti-diabetic medication and is approved by the Drug Controller General of India as a third-line drug after metformin and sulfonylureas. The drug acts by raising intracellular pH that inhibits proteolytic degradation of insulin, resulting in recirculation of insulin in its active form. Hydroxychloroquine also reduces proinflammatory cytokines, notably  $TNF\alpha$  and IL6, thereby reducing insulin resistance [10]. Considering its low-cost, moderate efficacy and once daily dosing, hydroxychloroquine might hold a good potential for use as an add-on drug in patients with poor glycemic control amid the ongoing pandemic, especially in countries with a poor socioeconomic background [7].

Self-monitoring of capillary blood glucose, especially for patients on insulin, should be continued at home and appropriate teleconsultations should be sought during recurrent episodes of hyperglycemia or hypoglycemia [11,12]. Patients with type 1 diabetes mellitus should be kept thoroughly informed about sick-day guidelines and that omission of insulin could be fatal. Often neglected is the psychological wellbeing of patients with DM which is likely to be adversely affected in current times. Meditations, teleconsultations with psychiatrists and avoiding undue stress by intentionally minimizing watching, reading or listening to news about COVID-19 could be helpful [8].

# 1.2. Thyroid disorders

Patients with thyroid disorders are frequently encountered in an endocrinology outpatient clinic. Although there is no evidence that patients with poorly controlled thyroid disease are more likely to contract viral infection in general, it is possible that patients with uncontrolled hyperthyroidism may be at a higher risk of complications (like thyroid storm) precipitated by any infection. In general, patients with underlying hypothyroidism or hyperthyroidism should continue their medications as usual. The usual advice of increasing the dose of levothyroxine during pregnancy should be adhered to. Management of hyperthyroidism usually requires frequent monitoring of thyroid function test. If biochemical monitoring cannot be performed due to prevailing circumstances, a block-and-replace regimen may be followed, especially after teleconsultation with an experienced endocrinologist. Block-andreplace regimen would be most ideal for newly diagnosed patients with hyperthyroidism [13]. The use of anti-thyroid drugs (ATDs) demands a special mention. Use of ATDs is associated with the risk of agranulocytosis, albeit rarely; agranulocytosis in turn may increase the risk of progression of COVID-19 [13]. Symptoms of agranulocytosis (fever, sore throat, oral ulcers) often overlap with those of mild COVID-19 (fever, cough, headache), hence, often making it difficult to clinically differentiate one from the other [13,14]. In the unlikely event that a patient on ATD develops symptoms suggestive of agranulocytosis, the ATD should be immediately stopped and an urgent full blood count should be performed. If a blood count cannot be performed due to severe limitation of healthcare resources, the ATD can be stopped and restarted after 1 week if symptoms resolve [14]. In selected cases of uncontrolled thyrotoxicosis not responding to medical management, urgent surgery or radioactive iodine ablation may be undertaken. In addition, patients with COVID-19 presenting with conjunctivitis may cause diagnostic difficulties in those with newonset or existing thyroid-associated orbitopathy (TAO) [13]. On the other hand, patients with TAO on glucocorticoids and/or mycophenolate mofetil are likely to be immunocompromised and need to take extra precautions against COVID-19. Similarly, patients with metastatic thyroid cancer might be at an increased risk of viral infection or complications if they have lung metastasis and hence need to be more cautious [15].

#### 1.3. Primary adrenal insufficiency (PAI)

Patients with primary adrenal insufficiency including Addison's disease and congenital adrenal hyperplasia are at an increased risk of infections [16,17]. Patients with PAI exhibit an inefficient innate immune response, characterized by decreased cytotoxic natural killer cells, with secondary failure of IgG-mediated activation due to shedding of CD16, its surface receptor [18]. Therefore, PAI can be assumed to increase the risk of infection with COVID-19 [19]. In addition, stress-induced rise in serum cortisol plays an important role in priming the immune system; expectedly, lack of cortisol rise in patients with PAI might predispose them to higher risk of progression to critical stages [20,21]. Besides, COVID-19 can lead to precipitation of acute adrenal crisis in patients with PAI, further increasing the chances of complications and mortality. Hence, patients with PAI, just like patients with diabetes mellitus, need to be extra cautious amid the ongoing pandemic. All patients should be provided with adequate self-management support to enable them to manage their conditions adequately and safely. Self-management support can be facilitated and communicated by mailshot, video, text, email phone call or videoconferencing, as appropriate. All patients (and their caregivers) must be educated in the use of sick day rules, that is, the need to increase their usual glucocorticoid replacement doses during intercurrent illness. In patients with PAI developing an acute COVID-19 infection, stress dose of glucocorticoid with 20 mg hydrocortisone administered orally every six hours can be considered. Such an exercise will prevent precipitation of an adrenal crisis. Patients showing worsening of COVID-19 need parenteral glucocorticoids: a proposed protocol includes a 100 mg hydrocortisone intramuscularly, followed by continuous intravenous infusion of 200 mg hydrocortisone per 24 hours, or until this can be established, administration of 50 mg hydrocortisone boluses every 6 hours.

In such a scenario, serum potassium should be strictly monitored as hypokalemia has been reported in patients with COVID-19 [5]. Adequate stocks of glucocorticoid and mineralocorticoid should be kept at hand. Patients who usually take modified release hydrocortisone preparations need to keep a sufficient supply of immediate release, regular oral hydrocortisone for emergency use [19]. Hydrocortisone tablets are often difficult to procure at places; in such a scenario an equivalent dose of oral prednisolone can be used. Of note, fludrocortisone acetate (most commonly used mineralocorticoid) tablets are heat labile and should be stored between 2 °C and 8 °C. In addition, all patients should also be in possession of an up-to-

date hydrocortisone emergency self-injection kit and that the patient and a caregiver be confident in self-administration of the injection.

# 1.4. Cushing's syndrome

Patients with active Cushing's syndrome (CS) are immunocompromised and are at a high risk of viral and other infections, although data with regard to COVID-19 is lacking. Hence, patients with active CS should stringently maintain social distancing and ensure proper hand hygiene [22]; moreover, rapid normalization of cortisol secretion is needed to minimize the risk of infection [23]. Cushing's syndrome associated comorbidities like diabetes mellitus and hypertension should be actively managed, as they significant risk factors for adverse outcomes from COVID-19 [24]. Judgment of severity of hypercortisolism and assessment of rapidity of symptoms are needed and can be made by teleconsultations; video consultation may allow assessment of physical features to a certain degree. Investigations of patients having mild clinical features of CS should be deferred for a period of 3-6 months or until COVID-19 prevalence has significantly diminished. Those with moderate and severe clinical disease must be investigated and managed on an urgent basis. Overnight dexamethasone suppression test (ONDST) and 24-hours urinary free cortisol (UFC) are recommended as first line tests. Plasma ACTH should be measured at the initiation of the investigation process to allow rapid stratification into ACTHdependent and independent disease, along with a basal anterior pituitary profile. Measurement of salivary cortisol should be avoided due to the potential risks for viral contamination. Regarding imaging. there are concerns that the confined nature of the magneticresonance imaging (MRI) scanners can lead to increased transmission of SARS-CoV-2, especially in regions having a high prevalence of COVID-19. Thus, in patients with biochemically proven ACTH-dependent CS without any compressive symptoms (visual field defects, severe headache), it is reasonable not to perform a MRI. Hence, some authors believe that once CS is biochemically confirmed, patients should undergo an immediate computed tomography (CT) scan of thorax, abdomen and pelvis to identify sinistrous etiologies like adrenocortical carcinoma (if ACTHindependent) or overt disease causing ectopic ACTH syndrome (if ACTH-dependent) that would require urgent cancer surgery [23]. In a typical patient with ACTH-dependent hypercortisolism without any compressive symptoms and in the absence of any demonstrable pathology on CT scan, the pre-test possibility of Cushing's disease due to an underlying microcorticotropinoma is high. Transsphenoidal surgery (TSS) should be avoided as this procedure results in aerosol formation which conveys a very high risk of viral transmission [25]. However, it remains a viable option in urgent patients, provided the patient tests negative for SARS-CoV-2 and adequate hospital resources are available for safe care. When surgery needs to be contemplated for a macrocorticotropinoma causing compression of the optic chiasma, consideration may also be given to a limited 'eyebrow' craniotomy approach to avoid the formation of aerosol droplets [23]. In most cases of CS where surgery is being deferred, steroidogenesis inhibitors will remain the mainstay of therapy. Country-specific availability will determine which agent can be used. Patients on ketoconazole should have their liver function monitored at least once every month for the first three months at initiation of treatment or following a dose increment [26]. Wherever available, metyrapone may be preferred over ketoconazole considering its faster onset of action and less drug-drug interactions. In the absence of provisions for frequent biochemical monitoring, a 'block-andreplace' may be preferred when using steroidogenesis inhibitors. This approach also reduces the risk of iatrogenic adrenal sufficiency. Patients only on steroidogenesis inhibitors should at least have

access to stress doses of glucocorticoid tablets, and preferably an emergency injection kit for intra-muscular injection of 100 mg hydrocortisone in case of intercurrent infection or trauma [23]. If possible, monitoring of medical treatment can be best done by measuring 24 hours UFC. The process entails collection of urine that can be handed to a laboratory by a family member or a relative without the patient having to leave the safe confines of home. thereby minimizing the risk of inadvertent exposure to COVID-19. In addition, patients with serum cortisol levels above 1200 nmol/l need prophylaxis against Pneumocystis carinii with co-trimoxazole. In patients with CS developing cough, fever and respiratory distress, differentiation needs to be made between COVID-19 and other pulmonary infections such as Pneumocystis carinii that may share similar radiological features in the early stages, to ensure appropriate treatment. Similarly, patients having moderate-to-severe CS, prophylaxis with low molecular weight heparin may be considered till definite surgery can be undertaken [27].

#### 1.5. Pituitary tumors

Hitherto, there currently exists no proven concern that pituitary tumors per se affect the immune system, apart from corticotropinomas causing Cushing's disease. Nevertheless, a number of patients with pituitary tumors have co-morbidities that can portend a poor prognosis in COVID-19 (e.g. diabetes mellitus, hypertension, obesity, cardiovascular diseases). Thus, co-morbidities need to adequately managed. Patients with pituitary tumors often have underlying secondary thyroid and adrenal insufficiencies that need to be dealt with appropriate thyroid hormone and glucocorticoid supplementations. Even patients with secondary adrenal insufficiency are at a high risk of infections and hence need to take extra precautions amid COVID-19 pandemic [28]. Sick-day rules need to be followed as in patients with primary adrenal insufficiency. Patients with underlying diabetes insipidus need to be more cautious regarding the development of hypernatremia, which is likely in the context of increased insensible fluid loss associated with fever and tachypnea as well impaired ability for fluid intake during periods of severe acute illness [29]. Regarding treatment, all types of pituitary tumors causing visual compromise (except macroprolactinomas) need to be operated upon. However, as has already been discussed, transsphenoidal surgery (TSS) in otherwise undiagnosed COVID-19 patients is a high-risk procedure. Testing for SARS-CoV-2 is strongly recommended 48 hours prior to TSS. If results are positive, surgery is best deferred until infection has cleared. If this is not possible considering the urgency of the clinical condition, appropriate personal protective equipment (PPE) for each and everyone in the operating theatre is a must. Besides, given the possibility of false negative results of real time-polymerase chain reaction (RT-PCR), the surgical theatre team should still wear full PPE even in COVID-19 negative cases [25].

Patients with acromegaly having no compressive symptoms can be managed with medical therapy in the interim period with longacting somatostatin-receptor ligands (SRLs), pegvisomant and/or dopamine agonists. Long-acting SRLs are better administered at a high-dose to reduce the frequency of injections (and thus contact with health care professionals). Patients and caregivers can be trained regarding administration of injections at home via teleconsultations and/or via readily available online videos. Dose titration during COVID-19 pandemic can de done through virtual clinics relying mainly on the clinical status, IGF-I measurement (when it can be safely arranged) and adverse effects as reported by the patients. Macroprolactinomas causing visual compromise should be initially treated with dopamine agonists, preferably cabergoline; dose titration and monitoring of treatment should depend on tolerability of these agents (manifestations of impulse control disorders should be specifically enquired upon) and improvement of visual dysfunction (subjective improvement reported by the patient in case of virtual visits or by formal visual field assessment 2–3 weeks after initiating treatment) [30]. TSS has to be contemplated if no improvement in visual symptoms occurs inspite of maximum tolerable doses of dopamine agonist therapy. In the unfortunate event of pituitary apoplexy, patients with significant neurovisual compromise need urgent surgical decompression. However, in patients with mild visual dysfunction, a conservative approach with high-dose glucocorticoids, exploiting their anti-inflammatory properties, can be considered with close monitoring of visual function [31].

#### 1.6. Osteoporosis

Patients with osteoporosis (post-menopausal osteoporosis) should continue calcium and vitamin D supplements. A growing body of circumstantial evidence also links outcomes of COVID-19 with vitamin D status. COVID-19 emerged and had spread in the Northern hemisphere at the end of 2019 (winter), when the level of 25-hydroxyvitamin D is usually at its nadir. Also, the nations in the Northern Hemisphere have borne much of the disease burden and mortality. In a cross-sectional analysis, mortality due to COVID-19 was significantly associated with vitamin D status. Additionally, black people, who are more likely to have vitamin D deficiency because of darker skin. seem to be worse affected by COVID-19 than white people. Black people in England and Wales are more than four times more likely to die from COVID-19 than are white people. The role of vitamin D in the response to COVID-19 infection is believed to be twofold. First, vitamin D promotes production of antimicrobial peptides by the respiratory epithelial cells, thus making infection with the virus and development of COVID-19 symptoms less likely. Second, vitamin D might help to reduce the inflammatory response induced by SARS-CoV-2 and thereby avert an impeding cytokine storm. In addition, vitamin D upregulates host ACE2 which is downregulated following intrusion of SARS-CoV-2 [32,33]. Pulmonary ACE2/angiotensin (1-7) system plays a vital anti-oxidant and anti-inflammatory role in the lungs, protecting them against inflammation-induced lung injury [34]. Whether supraphysiological doses of vitamin D would offer extra protection against COVID-19 is a matter of speculation, however, supplemental doses of vitamin D at 800-1000 IU/day should be continued in patients with post-menopausal osteoporosis. Patients with osteoporosis should be advised to engage in regular weightbearing exercise to improve their strength, balance, posture and reduce the risk of falls [35]. Only home-based exercise programs would be feasible amid the circumstances and such programs have been shown to improve the quality of life and muscle mass in older individuals [36]. Preventing falls and remaining fracture free are critical. A temporary delay in some anti-osteoporotic medications can be allowed. Patients on intravenous bisphosphonates can afford a delay of 6–9 months. Flu-like reactions are very common after intravenous bisphosphonates that can mimic the symptoms produced by COVID-19. Hence, patients receiving intravenous bisphosphonates amid the ongoing pandemic need to be thoroughly explained about the chances of a flu-like reaction [37]. Patients on denosumab need to be injected with the next dose within a maximum of 4 weeks so as to avoid the risk of rebound fractures [38]. Pre-injection blood tests prior to denosumab therapy can be waived off and empirically treated with 25,000-50,000 IU of vitamin D around the time of each injection [39]. Patients and caregivers can be trained about the technique of denosumab selfadministration at home through virtual clinics. Even pauses in teriparatide and/or abaloparatide therapy for a few weeks are unlikely to blunt the long-term beneficial effects on fracture-risk reduction; similarly patients about to complete 2 years of teriparatide therapy can extend the treatment for a few more weeks till anti-resorptive therapy can be initiated.

#### 1.7. Primary hyperparathyroidism

Patients with diagnosed primary hyperparathyroidism (PHPT) can be managed conservatively and surgery can be deferred unless the patient is severely symptomatic and/or serum calcium > 3.25 mmol/l. Patients should be educated about maintaining good a hydration status at home. Patients with PHPT developing COVID-19 need to be cautious about insensible fluid loss (fever, tachypnea) and accordingly increase fluid intake. Severe hypercalcemia may necessitate hospital admission; initial treatment would involveuse of parenteral fluids. However, overzealous fluid administration should be avoided as it can increase the chances of acute respiratory distress syndrome in those with underlying COVID-19. Pharmacological modalities like calcitonin, zoledronic acid and denosumab can be safely used [39].

# 1.8. Hypoparathyroidism

Patients with hypoparathyroidism should continue calcium/ active vitamin D supplements. In addition, they should be made conversant with the sick-day guidelines, specially the need to double the dose of calcium/vitamin D during periods of stressful situations. The relevance lies in the fact that any acute illness and even anxiety (as is prevalent amid the ongoing pandemic) can lead to hyperventilation, respiratory alkalosis and subsequently reduce serum ionized calcium [40].

## 2. Conclusions

The COVID-19 pandemic and consequent need for community containment of the virus poses a challenge to the management of common endocrine disorders. At the same time, certain endocrine maladies like DM and CS need to be optimally managed in order to avoid being infected with SARS-CoV-2 and avert the gruesome complications of COVID-19. Continuing prescribed medications and keeping in regular touch with physicians via telecommunication is the need of the hour. In addition, physicians and endocrinologists worldwide should educate patients about sick-day guidelines using virtual clinics and various social platforms and thereby minimize unnecessary hospital visits amid the ongoing pandemic.

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## **Declaration of competing interest**

None

#### **CRediT** authorship contribution statement

**Rimesh Pal:** Writing - original draft, Data curation. **Sanjay K. Bhadada:** Conceptualization, Supervision, Writing - review & editing.

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