

## Endocrine vigilance in COVID-19

Fritz-Line Velayoudom,<sup>1</sup> Piyumi Sachindra Alwis Wijewickrama,<sup>2</sup> H Ishara Ranathunga,<sup>3</sup> Noel Somasundaram<sup>4</sup>

### Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus responsible for a pandemic that emerged in December 2019. Heterogeneous clinical forms are described from asymptomatic to severe hypoxaemic acute respiratory syndrome with multisystem organ failure. The impact of this coronavirus disease 2019 on the endocrine glands remains unknown. However, the results of previous studies on viruses from the same family allow us to write proposals for patients followed for chronic endocrine diseases. Currently, if these subjects are infected with SARS-CoV-2, they must not stop their treatment. In some cases, hormone replacement doses have to be increased. In case of worsening clinical signs, hormonal biological monitoring must be done. This article will be helpful for improving the management of chronic endocrine diseases that could affect thyroid, adrenals, gonads and pituitary gland functions. Proposals could be applied in COVID-19 infected subjects or in those who have been in contact with COVID-19 infected people.

**Keywords:** COVID-19, SARS-CoV-2, Endocrine glands, Endocrine vigilance.

**DOI:** <https://doi.org/10.5455/JPMA.16>

### Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that belongs to the Coronaviridae family with main tropism for the respiratory tract cells, responsible for coronavirus disease 2019 (COVID-19) pneumonia.<sup>1</sup> Except for diabetes mellitus, there is no data on the impact of this new virus on the endocrine glands. This article provides a summary to help physicians to improve the management of patients with chronic endocrine diseases.

<sup>1</sup>Diabetes and Endocrine Unit, University Hospital of Guadeloupe, Les Abymes, Guadeloupe, and LAMIA EA4540, University of the French West Indies, Guadeloupe, <sup>2-4</sup>Diabetes and Endocrine Unit, National Hospital of Sri Lanka, Colombo, Sri Lanka.

**Correspondence:** Fritz-Line Velayoudom.  
Email: [Fritz-line.Velayoudom@univ-antilles.fr](mailto:Fritz-line.Velayoudom@univ-antilles.fr)

### Endocrine Vigilance for Thyroid Diseases

As SARS-CoV-2 is a recently emerged virus, there is no information as yet on its effect on individuals with thyroid diseases. However, as thyroid hormones regulate both normal metabolic and neural activity, it is important to control thyroid levels particularly in patients with chronic thyroid illness.

Viral infection is one of the most frequently considered environmental factors involved in autoimmunity, promoting the production of inflammatory mediators leading to the recruitment of lymphocytes.<sup>2</sup> Extrapolation can be made from SARS CoV-1 data.<sup>3-5</sup> Indeed, in previous studies, SARS-CoV-1 was responsible for follicular cell dysfunction linked to destruction of the follicular epithelium, exfoliation of epithelial cells into the follicle and extension of fibrosis after acute phase. The damage from SARS CoV-2 is likely to be similar to that of SARS CoV-1 even if some contradictions persisted<sup>5,6</sup>. During an acute illness, changes in thyroid hormone binding, cellular uptake and low thyroxine (T4) to triiodothyronine (T3) conversion are linked to the decreased activity of the deiodinase 1 enzyme. An increased T3 catabolism due to the increased activity of iodothyronine D3 in peripheral tissues is also described.<sup>6</sup> Currently, it could be necessary to increase the dosage of levothyroxine and to monitor thyroid hormones levels in patients with chronic hypothyroidism who are suspected, infected or recently cured of COVID-19. Scientific societies have published their proposal for managing subjects with hypothyroidism and also hyperthyroidism.<sup>7</sup>

Infected COVID-19 subjects with hyperthyroidism have to continue antithyroid drugs (ATDs) unless neutropenia (neutrophil count of  $<1.0 \times 10^9/L$ ) is present. Measurement of white cell count is necessary in case of symptoms such as fever or suggestive of neutropenia under ATDs. Lymphopenia does not justify stopping ATDs. Patients treated with steroid therapy at immunosuppressive dosage or immunosuppressive agents for thyroid eye disease are extremely vulnerable with an increased risk of severe form of COVID-19. They must respect the barrier measures but not stop their treatment. As regular biochemical monitoring of thyrotoxicosis could be

difficult, management proposed by the Society for Endocrinology of "block and replace regimen" has to be considered.<sup>7</sup>

Patients who require radioiodine treatment (for hyperthyroidism or thyroid cancer) must postpone their procedure during the COVID-19 pandemic. There is no evidence that deferred treatment can worsen the prognosis from thyroid cancer; high-risk patients should have well-restrained and clinically tolerated thyroid stimulating hormone (TSH).<sup>8</sup>

### Endocrine Vigilance for Parathyroid Diseases

Calcium seems to be required for previous SARS-CoV-2 mediated fusion.<sup>9</sup> Therefore, monitoring of patients followed for parathyroid disorders is important. Endocrine societies confirm that there is no increased risk to contract COVID-19 in subjects with hypoparathyroidism.<sup>7</sup> However, as unstable calcium levels can cause a weaker immune system and as calcium levels may be affected by SARS-CoV-2, they propose performing regular blood tests to control calcium levels. It is suggested to keep the calcium levels slightly higher than usual to avoid the risk of an emergency hypocalcaemia.

On the other hand, there is no evidence that having primary hyperparathyroidism alone increases the risk to contract the coronavirus.

In the same way, phosphate, magnesium and vitamin D levels should also be controlled as they can affect calcium levels.

In all cases, calcium levels should be monitored in acute phase and recovered subjects of COVID-19 due to kidney damage from COVID-19, and the unknown impact on parafollicular thyroid cells and calcitonin levels. The recrudescence of the clinical signs of hypocalcaemia such as tingling, spasms, and cramps, and those of hypercalcaemia such as polyuria and polydipsia syndrome, headaches, tiredness and lethargy should be sought.

### Endocrine Vigilance for Adrenals

Severe adrenal insufficiency symptoms or adrenal crisis can be observed in infected subjects with history of primary or secondary adrenal insufficiency.<sup>10,11</sup> Clinical signs of severe primary adrenal insufficiency involve vomiting, abdominal pain, weight loss, and orthostatic hypotension due to dehydration. Laboratory features include hyponatraemia, hyperkalaemia, hypoglycaemia and changes in blood count such as anemia, eosinophilia, lymphocytosis. Parenteral hydrocortisone treatment at

100mg immediate dose has to be started (50 mg/m<sup>2</sup> for children) followed by appropriate fluid resuscitation and 200 mg of hydrocortisone/24 hours (50-100 mg/m<sup>2</sup> for children). Additional treatment with fludrocortisone will not be necessary in this setting as hydrocortisone doses above 50 mg daily would have sufficient action on mineralocorticoid receptors. However, it should be started as soon as total daily hydrocortisone dose decreases below 50mg/24h.<sup>12</sup>

### Critical Illness-Related Corticosteroid Insufficiency in COVID-19

Acute stress during critical illness activates the hypothalamic-pituitary-adrenal (HPA) axis, increasing the secretion of cortisol. However, this pathway seems impaired in critically ill patients and leads to critical illness related corticosteroid insufficiency (CIRCI) that can occur with SARS-CoV-2 infection. This impairs the acute stress response similar to "Koala Stress Syndrome" seen in koalas with vestigial adrenal glands.<sup>13</sup> CIRCI is associated with increased inflammatory markers, abnormal coagulation, increased morbidity and prolonged intensive care unit stay. Patients classically have impaired mentation, hypotension refractory to fluid resuscitation and vasopressor therapy, and persistent electrolyte imbalances including hyperkalaemia, hyponatraemia, as well as normal anion gap metabolic acidosis and hypoglycaemia.<sup>13</sup> Diagnosis is performed with measurement of a random plasma cortisol level below 10µg/dl (275 nmol/l) or the lack of cortisol response after cosyntropin injection. Treatment with low dose of IV hydrocortisone (<400 mg/day) for 3 days or longer according to the clinical response, is proposed.<sup>13</sup> In other situations and based on experiences with previous SARS epidemics where steroid treatment resulted in adverse outcomes, current WHO guidelines recommend against corticosteroids when COVID-19 is suspected (released January 28, 2020). Indeed, patients who were given corticosteroids were more likely to require mechanical ventilation, vasopressors and renal replacement therapy.<sup>14</sup>

### Endocrine Vigilance for Cushing Syndrome

Patients with Cushing syndrome (CS) may face delays in diagnostic and surgical management. Disruptions of medications in medically managed patients should be avoided. Although data regarding CS and COVID-19 is scarce up to now, these patients may have a poor prognosis due to multiple reasons. Indeed, the associated diabetes and hypertension are identified as risk factors for poor prognosis in COVID-19, increasing mortality independently of age. Moreover,

glucocorticoid excess is known to increase prothrombotic states that contribute to poor prognosis in such patients. It also increases susceptibility to infections by alteration of white blood cell count and function, reduced lymphocytes with CD4 to CD8 ratio and reduced action of natural killer cells.<sup>15</sup> Therefore, patients with CS, should be given strict advice to adhere to standard infection prevention measures. COVID-19 infected subjects with CS need regular self-monitoring of arterial pressure and glucose.

### Endocrine Vigilance for Gonads

The SARS-CoV-1 was described to affect the reproductive system with destruction of germ cells, impairment of spermatozoa in the seminiferous tubules and infiltration of testes by mainly lymphocytes and macrophages.<sup>5</sup> A guidance on androgen replacement during COVID-19 crisis has been published by the Society of Endocrinology.<sup>7</sup> According to their recommendations, men with androgen deficiency on androgen replacement injections have to continue the treatment without interruptions. Those who are on intramuscular testosterone preparations could be temporarily commenced on a testosterone-based gel at an empirical dose. The testosterone gel should be commenced as from the date the next injection would have been due. The intramuscular preparation could be recommenced once non-urgent services resume.

It would be interesting after the acute crisis to assess the gonadal functions of affected and cured men and women.

### Endocrine Vigilance for Pituitary Diseases

Hypopituitarism includes all clinical conditions that result in partial or complete failure of the pituitary gland's ability to secrete hormones. The usual aim of the management is to replace the target hormone of HPA axis. SARS-CoV-1 was described to cause central hypothyroidism or secondary adrenal insufficiency by inducing hypophysitis or directly affecting the hypothalamus.<sup>16</sup> Therefore, we cannot rule out an impact of SARS-Cov-2 on the HPA axis. Moreover, the cases of anosmia and ageusia described in subjects with COVID-19 seem to be linked to a central cause for which the role of the hypothalamus cannot be dismissed. In this situation, fluid and electrolytes need to be monitored carefully in order to prevent hyponatraemia or hypernatraemia. An alteration of the dopamine synthetic pathways could also be involved in the pathophysiology of COVID-19.<sup>17</sup>

Patients with pituitary disease are on replacement doses of multiple deficient hormones. Patients who are already on regular treatment for pituitary insufficiency require

special attention.

For COVID-19 infected patients, secondary hypothyroidism as well as primary hypothyroidism should be advised to continue the same dose or higher doses of levothyroxine depending on the clinical context.<sup>7</sup> In the same way, patients with secondary adrenal insufficiency should be thoroughly advised regarding intake of higher doses (double the usual dose) of usual hydrocortisone dose at slightest suspicion of COVID-19 such as development of high fever, fatigue, cough, shortness of breath, nausea and diarrhea.<sup>7</sup> If clinical condition deteriorates, they should urgently seek emergency medical care and admission. Management will be the same as that mentioned above in the subjects with primary adrenal insufficiency.<sup>12</sup>

### Electrolyte Imbalance and DDAVP Replacement

Minority of patients have cranial diabetes insipidus which require treatment with desmopressin (DDAVP). In case of an altered level of consciousness, intranasal DDAVP can be converted into IV or IM form to allow a tighter titration.<sup>18</sup> In the event of COVID-19, electrolyte imbalances can occur due to insensible losses caused by high fever and tachypnoea, gastrointestinal losses such as vomiting and diarrhea, as well as due to inability to take adequate fluids due to impaired level of consciousness. The dysregulation of the renin-angiotensin system after degradation of Angiotensin-converting enzyme 2 by the SARS-CoV-2 induces an increased renal loss of potassium, and explains the hypokalaemia observed in infected COVID-19 subjects.<sup>17</sup>

### Conclusion

Novel SARS-CoV2 infection can affect the endocrine system in multitude of ways and the scientific data is under evaluation. The vigilance is pivotal to manage underlying diseases as well newly originating entities.

### References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;20:382:727-733.
2. Perlman S, Dandekar AA. Immunopathogenesis of coronavirus infections: implications for SARS. *Nat Rev Immunol* 2005;5:917-27.
3. Guo Y, Korteweg C, McNutt MA, Gu J. Pathogenetic mechanisms of severe acute respiratory syndrome. *Virus Res* 2008;133:4-12. doi: 10.1016/j.virusres.2007.01.022.
4. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507-13.
5. Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. *J Exp Med* 2005;202:415-24. doi: 10.1084/jem.20050828.

6. Wei L, Sun S, Xu CH, Zhang J, Xu Y, Zhu H, Peh SC, Korteweg C, McNutt MA, Gu J. Pathology of the thyroid in severe acute respiratory syndrome. *Hum Pathol* 2007;38:95-102. doi: 10.1016/j.humpath.2006.06.011
  7. COVID-19 resources for managing endocrine conditions [Internet] Society for Endocrinology [cited 2020 Apr 10]. Available from: <https://www.endocrinology.org/clinical-practice/covid-19-resources-for-managing-endocrine-conditions>
  8. Thyroid Cancer Forum UK, Society for Endocrinology, British Thyroid Association. Thyroid cancer and coronavirus (COVID-19) [Internet]. British Thyroid Foundation. [cited 2020 Apr 10]. Available from: <https://www.btf-thyroid.org/thyroid-cancer-and-coronavirus>
  9. Lai AL, Millet JK, Daniel S, Freed JH, Whittaker GR. The SARS-CoV fusion peptide forms an extended bipartite fusion platform that perturbs membrane order in a calcium-dependent manner. *J Mol Biol* 2017;429:3875-92. doi: 10.1016/j.jmb.2017.10.017
  10. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2016;101:364-89. doi: 10.1210/jc.2015-1710.
  11. Alexandraki KI, Grossman A. Management of hypopituitarism. *J Clin Med* 2019;8:2153. doi: 10.3390/jcm8122153.
  12. Arlt W; Society for Endocrinology Clinical Committee. Society For Endocrinology Endocrine Emergency Guidance: emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients. *Endocr Connect* 2016;5:G1-G3. doi: 10.1530/EC-16-0054
  13. Marik PE, Levitov A. The "koala stress syndrome" and adrenal responsiveness in the critically ill. *Intensive Care Med* 2010;36:1805-6. doi: 10.1007/s00134-010-1974-6
  14. Annane D, Pastores SM, Rochweg B, Arlt W, Balk RA, Beishuizen A, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Intensive Care Med* 2017;43:1751-63. doi: 10.1007/s00134-017-4919-5.
  15. Aranda G, Lopez C, Fernandez-Ruiz R, Esteban Y, Garcia-Eguren G, Mora M, et al. Circulatory immune cells in Cushing syndrome: bystanders or active contributors to atherometabolic injury? A study of adhesion and activation of cell surface markers. *Int J Endocrinol* 2017;2017:2912763. doi: 10.1155/2017/2912763.
  16. Chrousos GP, Kaltsas G. Post-SARS sickness syndrome manifestations and endocrinopathy: how, why, and so what? *Clin Endocrinol (Oxf)* 2005;63:363-5. doi: 10.1111/j.1365-2265.2005.02361.x
  17. Nataf S. An alteration of the dopamine synthetic pathway is possibly involved in the pathophysiology of COVID-19. *J Med Virol* 2020;1-2. doi: 10.1002/jmv.25826
  18. Baldeweg SE, Ball S, Brooke A, Gleeson HK, Levy MJ, Prentice M, et al. Society for Endocrinology clinical guidance: inpatient management of cranial diabetes insipidus. *Endocr Connect* 2018;7:G8-G11. doi: 10.1530/EC-18-0154.
-