

Letter To the Editor: [Our Response to COVID-19 as Endocrinologists and Diabetologists]

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We read with interest the article by Kaiser et al. highlighting some relevant aspects about the management of patients with endocrine conditions who are simultaneously infected with the 2019 novel coronavirus (SARS-CoV-2).¹

As far as we are concerned, understanding the evidence of the role played by corticosteroids in SARS-CoV-2 infection is of immediate clinical importance. The existing literature does not currently provide conclusive evidence regarding their administration for the treatment of COVID-19.² There have been a number of reports stating generally positive outcomes upon corticosteroids use especially in the early acute phase of infection, as they are capable of reducing immune-mediated damage³. In this regard, Fu Y et al. suggest to adopt steroids in combination with the use of intravenous immunoglobulin to block Fc receptors (FcR) activation in order to prevent severe lung injury. However, such treatment remains to be clinically tested for effectiveness.⁴

On the other hand, patients taking supra-physiologic doses of glucocorticoids may have increased susceptibility to COVID-19 because of the immunosuppressive effects of steroids, which can be ultimately responsible for severe lymphocytopenia, thus promoting a viral rebound. Moreover, steroids have also been associated with higher risk of acute respiratory distress syndrome (ARDS)⁵ and may therefore determine exaggerated pro-inflammatory responses and even worsen the clinical condition of the patients.

However, in the event of COVID-19, patients on long-term steroids, or suffering from adrenal insufficiency and uncontrolled Cushing syndrome may be unable to develop a normal stress response, thus requiring a rescue dose of glucocorticoids.¹

In our opinion, this evidence by Kaiser and colleagues should be extended to those patients with chronic pain on therapy with opioids. Long-term use of opioids has been associated with suppression of the hypothalamic-pituitary-adrenal (HPA) axis through the inhibition of corticotrophin-releasing hormone (CRH) and antidiuretic hormone (ADH) secretion, resulting in decreased adrenocorticotrophic hormone (ACTH) release⁶ and central

hypocortisolism (defined as stimulated cortisol concentration of $<18 \mu\text{g/dL}$ [500 nmol/L] in an insulin tolerance test [ITT]).^{7,8}

Further investigations on the balanced use of corticosteroids therapy in COVID-19 patients with alteration of the HPA axis due to long-term opioids or steroid treatment are necessary, since these subjects represent a frail population at major risk.

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References

1. Kaiser, U. B., Mirmira, R. G. & Stewart, P. M. Our Response to COVID-19 as Endocrinologists and Diabetologists. *J. Clin. Endocrinol. Metab.* **105**, 1–3 (2020).
2. Russell, B., Moss, C., Rigg, A. & Hemelrijck, M. Van. COVID-19 and treatment with NSAIDs and corticosteroids : should we be limiting their use in the clinical setting ? *Ecancer* 1–3 (2020).
3. Russell, B. *et al.* Associations between immune-suppressive and stimulating drugs and novel COVID-19—a systematic review of current evidence. *Ecancermedicalscience* **14**, (2020).
4. Fu, Y., Cheng, Y. & Wu, Y. Understanding SARS-CoV-2-Mediated Inflammatory Responses: From Mechanisms to Potential Therapeutic Tools. *Viol. Sin.* **12250**, (2020).
5. Russell, C. D., Millar, J. E. & Baillie, J. K. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* **395**, 473–475 (2020).
6. Fountas, A., Van Uum, S. & Karavitaki, N. Opioid-induced endocrinopathies. *Lancet Diabetes Endocrinol.* **8**, 68–80 (2020).
7. Abs, R. *et al.* Endocrine consequences of long-term intrathecal administration of opioids. *J. Clin. Endocrinol. Metab.* **85**, 2215–2222 (2000).
8. Valverde-Filho, J., Cunha Neto, M. B. C. da, Fonoff, E. T., Meirelles, E. de S. & Teixeira, M. J. Chronic Spinal and Oral Morphine-Induced Neuroendocrine and Metabolic Changes in Noncancer Pain Patients. *Pain Med. (United States)* **16**, 715–725 (2015).