Letter to the Editor of Clinical Endocrinology

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It is widely recognised that the effects of COVID-19 extend beyond the respiratory system. Moreover, there are an estimated 1.3 million people living with Long-COVID (symptoms persisting beyond 12 weeks after infection) in the UK alone[1], with one study observing 57% of patients with COVID-19 experienced at least one symptom of long COVID in the 6 months following infection[2]. Current endeavours are therefore now focussed on understanding the pathophysiology of persistent symptoms after acute COVID-19, as well as the development of novel therapeutics.

A recent article by Kanczkowski and colleagues[3] sought to determine whether there was any histological evidence of adrenal damage in patients with COVID-19. This is particularly pertinent given that the presence of both ACE2 receptors and the permissive protein for cellular entry, transmembrane serine protease 2 (TMPRSS2), in adrenal microvasculature and the adrenal cortex itself [4] mean that there is biologic plausibility for SARS-CoV-2 to both gain cellular access and cause adrenocortical dysfunction.

Using autopsy samples from 40 patients who had died from COVID-19, the authors observed small vessel vasculitis within periadrenal fat tissue and adrenal parenchyma, as well as perivascular lymphoplasmacellular infiltration, but did not observe extensive degradation of adrenocortical cells. Additionally, they identified the SARS-CoV-2 spike protein in adrenocortical cells of 45% of adrenal gland tissues and using multiplex RT-qPCR confirmed SARS-CoV-2 expression in 15 out of 30 adrenal gland tissues of patients with COVID-19. These data confirm the presence of SARS-CoV-2 within the adrenal glands and hence raise the question of hypoadrenalism in patients with COVID-19 and, as the authors suggest, whether or not adrenocortical dysfunction contributes to the complications of COVID, particularly long COVID.

We have recently published data from 70 survivors of COVID-19, whereby adrenal function was comprehensively assessed using the gold-standard 'Short Synacthen test' [5]. Briefly, patients aged ≥18yrs with a diagnosis of COVID-19, confirmed using either real-time RT-PCR testing of nasopharyngeal swab, confirmatory imaging (chest radiograph or computed tomography scan) or positive serum SARS-CoV-2 IgG antibody test taken after symptom onset were eligible for inclusion. Participants were invited to attend for a research study visit at ≥ 3 months following initial presentation and underwent clinical assessment, including screening for persistent symptoms and a physical examination. A cannula was subsequently inserted, and serum samples were taken including for cortisol, renin, aldosterone and dihydroepiandrosterone (DHEAS). Following this, 250μg tetracosactide (Synacthen) was administered, and further serum samples were taken at 30 and 60 minutes for measurement of cortisol.

Serum renin, aldosterone and DHEAS were measured using high performance liquid chromatograph mass spectrometry (HPLC-MS/MS). Lower limits of quantification were as

follows: renin 0.6nmol/L, aldosterone 60pmol/L, DHEAS 0.41µmol/L. Interassay coefficients of variation were as follows: renin <10%, aldosterone <15%, DHEAS <10%.

Age- specific reference ranges for DHEAS were as follows: age 20-39years 0.7-11.5µmol/L, 40-59 years 0.8-6.9µmol/L, over 60 years 0.4-4.7µmol/L.

Serum cortisol was measured using Abbott Alinity ci-series analyser, using chemiluminescent mircoparticle immunoassays. The lower limit of detection was 19.3nmol/L, interassay coefficient of variation was ≤5.1%, intra-assay coefficient of variation was ≤4.3%.

Regardless of disease severity or treatment received, all participants had an appropriate response to 250mcg Tetracosactide, consistent with adequate adrenal reserve. Furthermore, although 44 patients (62.8%) had persistent fatigue at ≥ 3 months' post presentation, neither peak cortisol achieved following stimulation, nor baseline cortisol differed between survivors with fatigue compared to those without [5]. Additionally, in unpublished data from this cohort, of the 69 patients with measurement of postural blood pressure, 2 patients (2.9%) had a postural drop of ≥20mmHg, although none were symptomatic with this. These patients had peak cortisol values of 593 nmol/L and 608 nmol/L after administration of Synacthen 250mcg.

For those who had DHEAS measured (n=68), 4.4% (n=3) had values below the age-specific reference range. All of these patients had a satisfactory cortisol response to Synacthen, and had baseline cortisol of 94.0, 288.0 and 304.0nmol/L and peak cortisol of 507, 572 and 608 nmol/L. Peak cortisol response following Synacthen was not significantly different in those with DHEAS values within the age- and sex-specific reference range and those with DHEAS values below the age- and sex-specific reference range (P=0.12). Additionally, peak cortisol level was not related to basal DHEAS values (P=0.79) (see Figure 1A). DHEAS was not significantly different between those patients who were fully recovered, and those with persistent fatigue (n=26, P=0.25) (see Figure 1B). In our cohort, of those who had aldosterone measured (n=60), 13 (21.7%) had aldosterone below the lower limit of the reference range, although none had elevated renin values.

Our findings are similar to those from other groups. In data recently presented at the British Endocrine Society meeting, Eltayeb and colleagues observed that in patients who received dexamethasone treatment for acute COVID-19, although 30% (18/60) had evidence of adrenal insufficiency after initially stopping dexamethasone, the majority of patients had recovered by 4 weeks, suggesting that any early adrenal insufficiency observed was likely related to steroid treatment, rather than COVID-19 per se[6].

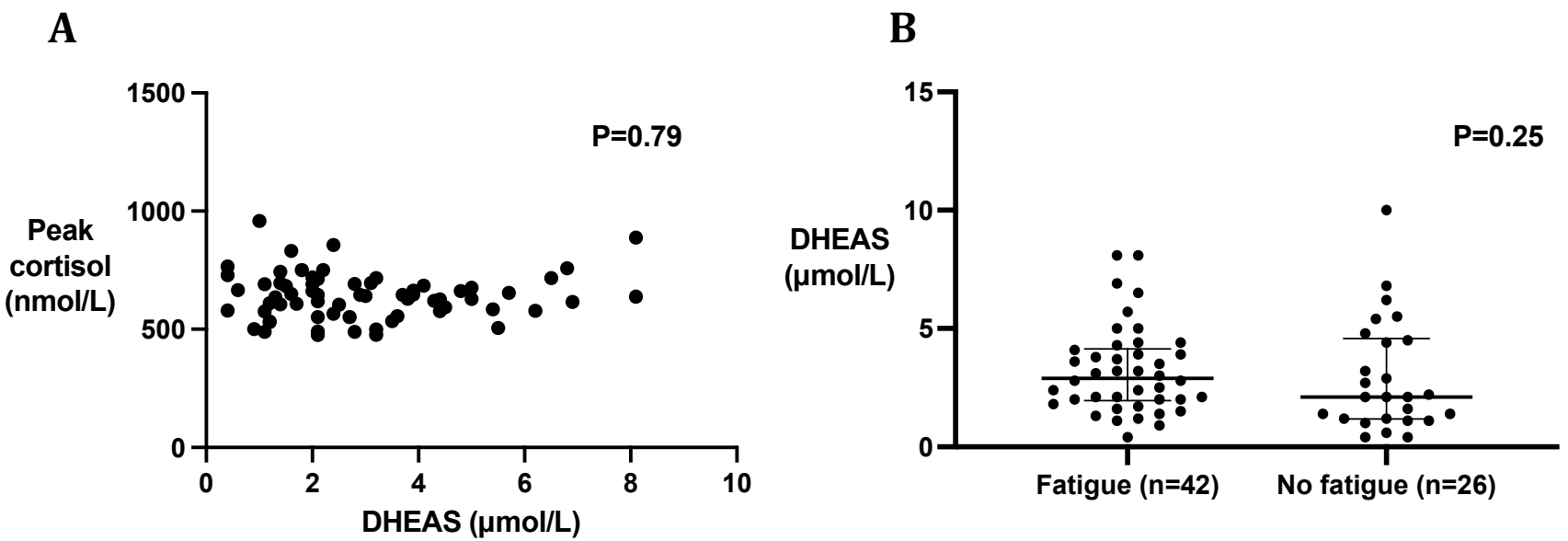
In summary, despite recent histopathological evidence of the presence of SARS-CoV-2 within the adrenal glands, there is no evidence to date that, in patients who survive COVID-19, adrenocortical or mineralocorticoid function is persistently affected, even in those patients with ongoing fatigue at ≥3 months after presentation.

Figure 1 Dihydroepiandrosterone (DHEAS) and peak cortisol levels following administration of Synacthen (Tetracosactide) 250µg in survivors of COVID-19 ≥3 months after initial presentation.

Figure 1A: Individual peak cortisol (nmol/L) levels and baseline DHEAS values (µmol/L) following administration of Synacthen (tetracosactide) 250µg are presented for patients for whom data is available (n=68).

Figure 1B: Individual DHEAS values are presented for those patients with persistent fatigue ≥3 months after initial presentation with COVID-19 (n=42) and those without persistent fatigue (n=26).

Figure 1



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