Preserved Adrenal Function in People with Long COVID

0936

Annukka Antar[1], Armaan Jamal[1], Elizabeth Pasetes[1], Zoe Demko[1], Tamilore Adeagbo[1], Selin Akbas[1], Cherie Marvel[1], Andrea Cox[1], Michael Peluso[2], Alan Landay[3], Neal Fedarko[1], Amir Hamrahian[1], Tracy Vannorsdall[1], Alba Azola[1], & Yukari Manabe[1]

[1]Johns Hopkins University, Baltimore, MD, USA, [2]University of California San Francisco, San Francisco, CA, USA, [3]University of Texas Medical Branch at Galveston, Galveston, TX, USA

Background

- The incidence of long COVID after SARS-CoV-2 infection is 10% or greater, even in people who were vaccinated prior to infection.
- Low serum cortisol has been associated with long COVID in two prominent studies.
- However, these studies examined untimed cortisol levels, whereas cortisol is secreted in a diurnal fashion and thus untimed cortisol levels may not adequately assess adrenal function.

Objectives

- Compare total serum cortisol levels in people with long COVID and quick and complete recovery.
- Assess morning cortisol awakening response and diurnal cortisol levels in people with long COVID and quick recovery.
- Assess adrenal function using the high-dose ACTH stimulation test in people with long COVID and quick recovery.

Study 1 Methods & Results

- Serum total cortisol was quantified in samples from two prospective cohort studies.
- Samples were obtained at 1, 3, 6, 12, 18, and 24 months post-infection in one cohort (OutSMART) and at 1 and 4 months post-infection in the other (JHU COVID Recovery Study).
- In a subset of 72 samples, serum aldosterone, plasma ACTH and DHEAS, and urine cortisol to creatinine ratio were assessed.
- Long COVID was defined as reporting at least one symptom in the past week while also reporting not being back to usual (pre-COVID) health or that health was worse currently than before COVID, at any survey 3-12 months post-COVID (both cohorts). In the JHU recovery study, a retrospective self-report of having had long COVID within 1 year of infection counted too.

Table 1. Study 1 participant characteristics

	LC (n = 130)	NC (n = 204)	p - value
Age, median (IQR)	49 (36-59)	48 (34-59)	0.23
Assigned female at birth, % (n)	52% (68)	50% (101)	0.33
Hispanic/Latino ethnicity, % (n)	14% (18)	8.3% (17)	0.38
Black, % (n)	26% (34)	27% (55)	0.90
White, % (n)	55% (72)	64% (131)	0.09
Asian, % (n)	8% (11)	5% (10)	0.58
BMI, median (IQR)	27 (23.1-32.9)	26.5 (23.1-32)	0.27
Hypertension, % (n)	28% (37)	24% (49)	0.43
Diabetes, % (n)	12% (16)	9% (19)	0.32
49 Symptoms Score, median (IQR)	10 (4-25)	3 (0-8)	0.16
Vaccinated before infection, % (n)	69% (90)	79% (161)	0.08

Adrenal dysfunction is not a major mechanism of long COVID.

Cortisol levels are not significantly different in people with and without long COVID.

Future studies should control for timing of cortisol measures and whether participants are taking exogenous glucocorticoids.

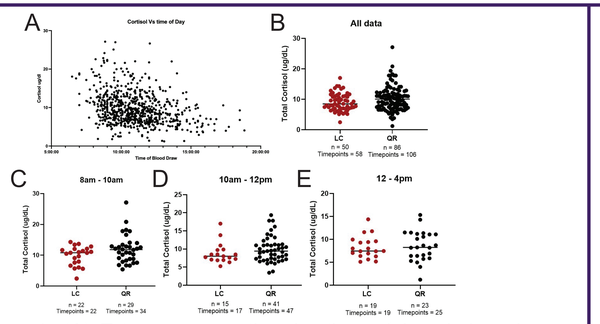


Figure 1. (A) Total serum cortisol by time of blood draw in all participants ages 15+ regardless of COVID status. Cortisol levels are associated with time of day. Total serum cortisol is not different in people with long COVID compared to people without long COVID, whether data is grouped together regardless of time (B) or separated by time of day (C-E).

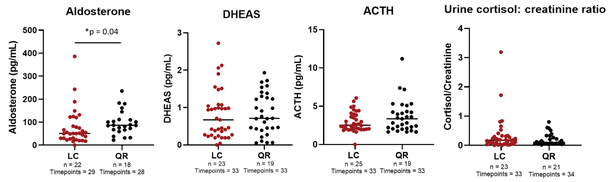


Figure 2. In a subset of participants, serum aldosterone, plasma DHEAS, plasma ACTH, and urine cortisol:creatinine ratios were obtained. Untimed ACTH is lower in people with long COVID than those with quick recovery. However, ACTH, like cortisol, is secreted in a diurnal fashion. No differences were seen in the other comparisons.

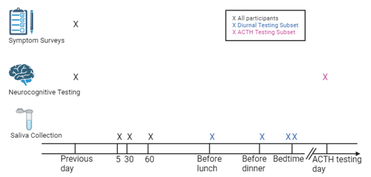


Figure 3. Study 2 schematic.

Study 2 Methods & Results

- We prospectively enrolled 92 adults: 44 with moderate-to-severe long COVID and 48 with rapid and complete recovery after SARS-CoV-2 infection, matched on age, sex, BMI, years of education, and months since acute COVID-19.
- We excluded people with recent use of any corticosteroid - oral, inhaled, topical, or injectable.
- Cortisol awakening response was assessed in saliva (total cortisol in saliva, Salimetrics) at 5, 30, and 60 minutes after awakening in all participants.
- In half, we assessed diurnal salivary cortisol before lunch, before dinner, and before bedtime.
- The high-dose ACTH stimulation test with blood sampling before, 30- and 60-minutes post-injection assessed adrenal function in 16 LC and 16 controls.

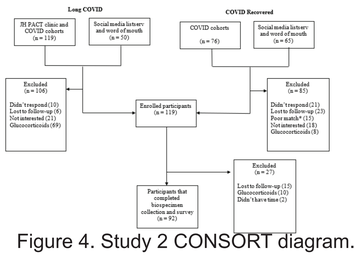


Figure 4. Study 2 CONSORT diagram.

Table 2. Study 2 participant characteristics.

	LC (n =44)	QR (n =48)	p - value
Age, median (IQR)	42 (36-55)	45 (23.5-60)	0.75
Assigned female at birth, % (n)	68% (30)	67% (32)	0.88
Hispanic/Latino ethnicity, % (n)	0	2% (1)	0.87
Black, % (n)	7% (3)	6% (3)	0.91
White, % (n)	89% (39)	71% (34)	0.16
Asian, % (n)	2% (1)	29% (14)	0.0005*
BMI, median (IQR)	26.9 (22.9-32.8)	25 (21.8-28.3)	0.1
Hypertension, % (n)	27% (12)	21% (10)	0.47
Diabetes, % (n)	7% (3)	8% (4)	0.78
49 Symptoms Score, median (IQR)	49 (31-71)	3 (1-11.5)	<.00001*
Vaccinated before infection, % (n)	39% (17)	60% (29)	0.04*

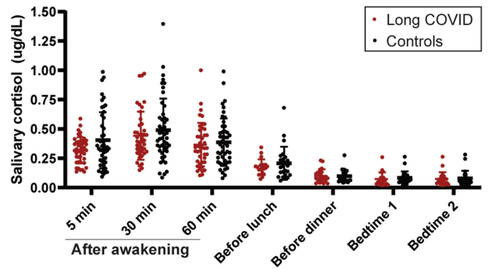


Figure 5. Salivary cortisol in people with long COVID and matched controls. Peak (highest) morning cortisol level trended lower in people with LC (p=0.11).

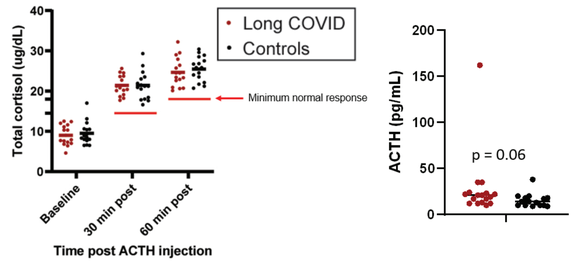


Figure 6. (Left) High-dose ACTH stimulation testing is normal in people with and without long COVID. No differences were observed between the groups at any time point. (Right) Pre-stimulation (untimed) ACTH levels trended higher in LC even after excluding the outlier.

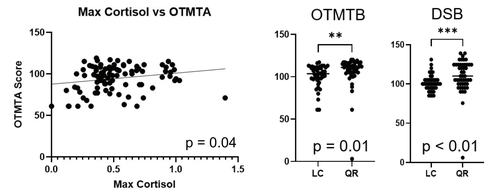


Figure 7. (Left) Peak morning cortisol levels associate with standardized Oral Trail Making Test (OTMT) A score, which tests mental processing. (Right) People with long COVID had lower standardized scores in tests of executive functioning and cognitive flexibility.

Funding and Acknowledgements

- We thank all study participants and study team members from each cohort study.
- Funding provided by the Henry M. Jackson Foundation, the Sherrilyn and Ken Fisher Center at Johns Hopkins, the Foundation for AIDS Research, the Johns Hopkins University Center for AIDS Research (P30AI094189), & NIAID (K08AI143391).