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ORIGINAL ARTICLE

A SHORT-TERM FOLLOW-UP STUDY ON HORMONAL CHANGES AFTER THREE TO SIX MONTHS OF SARS-COV-2 INFECTION

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Abstract

Background: *Long-COVID symptoms may develop following coronavirus disease 2019 (COVID-19) and mimic various endocrine dysfunctions. Hormonal assessment during and after COVID may be necessary to distinguish between these conditions. This study evaluated hormone status during active infection and after three to six months post-COVID-19 infection.* ***Methods:*** *This prospective study initially included ninety-one noncritically ill hospitalized patients with COVID-19 infection (18-65 years, m/f: 37/54). The participants were reassessed three to six months after their hospitalization.Eight patients died during their hospital stay, and we were able to collect follow-up data for only fifteen [age (years): 47.3±13.3, m/f: 6/9] out of eighty-three survived patients. Thyroid (TSH, FT4, and FT3), adrenal (basal cortisol and ACTH), and sex-steroid (total testosterone and dehydroepiandrosterone sulfate) axes were evaluated and compared with laboratory cut-offs at diagnosis and three to six months later. All the hormones were measured by chemiluminescent microparticle immunoassay.* ***Results:*** *At baseline, six participants (40.0%) had normal values for all the studied hormones, five (33.3%) exhibited one abnormality, and four (26.7%) displayed two abnormalities. After three months of COVID-19 infection, four had normal values (26.7%), six (40.0%) had one abnormality, three (20.0%) had two, and two (13.3%) had three abnormalities in the studied hormone status.* ***Conclusion:*** *Endocrine dysfunctions are not uncommon during short-term follow-up after COVID-19, and hormonal evaluations may be necessary, particularly for symptomatic patients.*

Keywords: *Coronavirus disease 2019, Post-COVID, Hormone, Thyroid, Adrenal, Testosterone, Dehydroepiandrosterone sulfate*

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Introduction:

The devastating pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) still exists, but in a milder form.[1] So, the importance has shifted from acute infection to prolonged and persistent long COVID syndrome. The long-term effects of post-COVID syndrome comprise several overlapping features of endocrine dysfunctions including fatigue, reduced libido, menstrual irregularity, palpitations, etc.[2] Endocrine glands are vulnerable to destructions and dysfunctions by COVID-19 due to the expression of both angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) which

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are located on the cell membrane and facilitate viral entry. Androgens are known to regulate the TMPRSS2 receptors.[3] Despite these, the effects of COVID-19 on endocrine glands are mostly acute and usually not related to direct damage; instead, they are affected by inflammatory cytokines and hypercoagulable states, depending on the severity of the illness.[4,5] Furthermore, the use of steroids during an acute illness might impair different hormonal axes, making it challenging to assess hormonal levels.[6] Follow-up hormone evaluation data are unavailable among Bangladeshi patients in the literature.

Regardless of steroid treatment during their acute phase of infection, we sought to evaluate the adrenal, thyroid, and sex hormone levels in non-critically sick individuals threeto six months following COVID-19 infection.

Methods:

The study was carried out in compliance with the Helsinki Declaration. Before being included in the study, all individuals gave written informed consent. The Institutional Review Board of Bangladesh Medical University gave ethical permission for this study (No. BSMMU/2021/557).

This prospective study recruited participants from a cohort of patients admitted to two tertiary hospitals in Dhaka city. These patients had been RT-PCR positive for COVID-19 between three and six months before enrolment in the study. All patients between 18 and 65 with a nasopharyngeal swab real-time RT-PCR test confirming their COVID-19 diagnosis were eligible for inclusion. The study excluded patients who were on other medications known to impact cortisol-binding globulin, such as oral estrogens, or who had taken steroids (oral, inhaled, topical, or intra-articular) after recovering from COVID-19. Similarly, those patients with known chronic diseases or states known to influence cortisol-binding globulin (e.g., pregnancy, end-stage renal failure, or underlying malignancy) were also excluded.

Two fasting blood samples (eight ml on each occasion), at diagnosis and three to six months of diagnosis were taken from participants for assaying of cortisol, thyroid-stimulating hormone (TSH), free thyroxine (FT4), free tri-iodothyronine (FT3), total testosterone (TT), dehydroepiandrosterone sulfate (DHEA-S), and adrenocorticotropic hormone (ACTH, the sample was collected within icepack and centrifuged in 2-8 degree centigrade) by chemiluminescent immunoassay method. All the samples were analyzed on the same day atthe Department of Microbiology and Immunology of BMU. The inter- and intra-assay coefficient of variation was ≤10% for all the measured hormones. The reference values of all the hormones were taken as per the cut-offs provided by the laboratory. The presence of comorbidities was recorded by taking history and laboratory investigations as part of a routine check on admission. Thediagnosis and classification of COVID-19 (mild, moderate, and severe) were done according to the World Health Organization's interim guidance.[7]

Data were expressed in mean ±SD or median (inter-quartile range, IQR) for numerical data and frequency (percent, %) for qualitative data. Statistical analysis and comparison of variables between baselines and three to six months after infection were done by paired t-test and Wilcoxon signed-rank test. A p-value below 0.05 was considered statistically significant.

Results:

Among ninety-one noncritically ill hospitalized patients with COVID-19, eight (8.8%) died during their hospital stay, and eighty-two survived. Among the surviving patients, we collected follow-up data in only fifteen patients (Figure-1). Onlythreewere above 60 years old; six were males, and nine were females. Diabetes mellitus was the most common (60.0%) comorbidity. None of them had severe COVID-19 during admission (Table I). All the baseline characteristics are available elsewhere.[8-10]

The frequency of all the COVID-related symptoms improved after three months of admission. While the median pulse rate values were reduced, blood pressure increased. Body mass index remained almost similar.

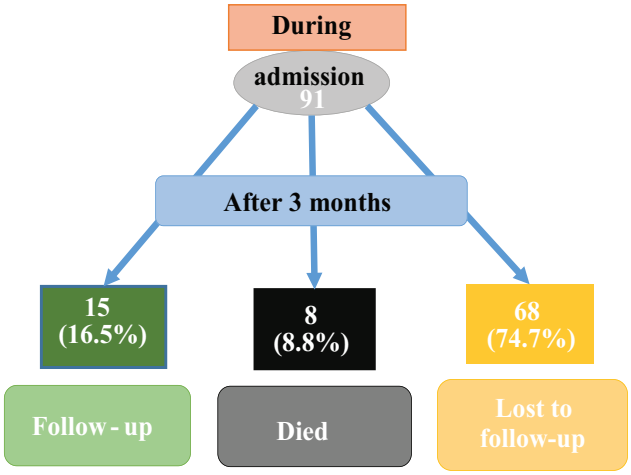

Fig.-1: *The study flow chart*

Table-I

Baseline characteristics of the study participants (n=15)

Variables	Values
Age, years	47.3±13.3
Agee"60 years	3 (20.0)
Age <60 years	12 (80.0)
Sex	
Male	6 (40.0)
Female	9 (60.0)
Comorbidities	
Hypertension	6 (40.0)
Diabetes mellitus	9 (60.0)
Obstructive lung disease	2 (13.3)
Severity of illness	
Mild	10 (66.7)
Moderate	5 (33.3)
Investigations	
Hemoglobin, g/dL	11.7±1.7
Total leukocytes, $\times10^3$ /µL	8.5 (6.5-8.5)
Total platelet count, $\times10^3$ /µL	242.4(200.0-250.0)
Neutrophils/lymphocytes ratio	1.9 (1.9-3.0)
Platelets/lymphocytes ratio	90.5(86.9-108.8)
S. Na^+, mmol/L	132.4±2.7
S. K^+, mmol/L	4.0±0.5
S. ALT, U/L	45.6 (40.0-50.0)
S. creatinine, mg/dL	0.9±0.2
C-reactive protein, mg/L	33.6 (12.0-60.5)
D-dimer, mg/L	0.5 (0.1-1.5)
S. ferritin, ng/dL	609.0 (461.0-630.0)

Out of the fifteen individuals, only one had adrenal insufficiency at admission (serum basal cortisol <276 nmol/L) and continued to be such. However, among the rest, six patients developed new adrenal insufficiency three-sixto six months after hospital admission. They all had normal plasma ACTH levels (>46 pg/mL), indicating central adrenal insufficiency. So, during follow-up, we found seven (46.7%) patients with adrenal insufficiency (Table-II).

Eight patients (53.3%) had normal thyroid function tests (TFTs) during admission and remained euthyroid after three to six months of admission. One patient with subclinical thyrotoxicosis returned back to euthyroid status. Another three out of five patients from isolated hyperthyroxinemia also became euthyroid. One patient with isolated hyperthyroxinemia developed the biochemical feature of the nonthyroidal illness. Two patients became hypothyroid- one from isolated hyperthyroxinemia and one from subclinical hypothyroidism. Three of seven patients with abnormal TFTs remained abnormal (Table-II).

All six males had normal TT levels, but one developed low TT status after three months. On the other hand, two females with higher TT levels remained high during the follow-up. Another two out of seven females with normal TT levels also became high after three to six months of admission (Table-II). One male had low, and the other five had normal DHEAS during admission.

Table-II

Individual hormone status of the study participants (n= 15)

Age (years)	Sex	Adrenal reserve		Thyroid status		TT status		DHEAS status		No. of gland involvement	
		During	F/U	During	F/U	During	F/U	During	F/U	During	F/U
19	M	A	A	N	N	N	N	N	N	0	0
31	M	A	A	IH	N	N	N	L	L	2	1
45	M	A	A	N	N	N	L	N	N	0	1
51	M	A	**I**	IH	N	N	N	N	L	1	2
64	M	A	A	N	N	N	N	N	N	0	0
65	M	A	A	ST	N	N	N	N	N	1	0
28	F	A	**I**	IH	ESS	N	N	N	N	1	2
38	F	A	A	N	N	N	N	N	N	0	0
47	F	A	A	SH	PH	N	N	N	N	1	1
47	F	A	**I**	IH	N	N	N	L	N	2	1
51	F	A	**I**	N	N	H	H	H	H	2	3
53	F	**I**	**I**	IH	PH	N	H	N	N	2	3
54	F	A	**I**	N	N	N	N	N	N	0	1
57	F	A	A	N	N	H	H	N	N	1	1
60	F	A	**I**	N	N	N	H	N	N	0	2
Total abnormality		01	07	07	03	02	05	03	03	13	18

Table-III

Hormones in COVID-19 during and 3-6 months after infection (n= 15)

Hormones	During infection	3-6months after inf.	p
TSH, mIU/mL	1.2 (0.8 – 2.8)	2.4 (1.9 – 5.4)	**0.001**
FT4, ng/dL	1.4 (1.3 – 3.0)	1.1 (1.0 – 1.3)	**0.002**
FT3, pg/mL	2.9 (2.5 – 3.2)	3.1 (2.6 – 3.2)	0.798
Cortisol, nmol/L	495.0 (327.0-615.0)	280.0 (218.2 – 448.7)	**0.017**
ACTH, pg/mL	21.2 (17.5 – 27.1)	26.0 (23.5 – 29.6)	0.156
Total testosterone, ng/dL			
Male (n=6)	329.5 (283.3 – 483.8)	343.5 (270.0 – 452.8)	0.917
Female (n=9)	32.0 (21.4 – 44.9)	40.5 (31.3 – 53.0)	0.343
DHEAS, ìg/dL			
Male (n=6)	84.6 (45.9-194.0)	73.0 (49.6 – 126.3)	0.225
Female (n=9)	41.0 (28.5 – 74.5)	98.4 (62.5 – 109.0)	**0.021**

Data were expressed in median (IQR)
Wilcoxon-signed rank test was done

During follow-up, the male with low DHEAS maintained the same status, and another male developed low DHEAS from a normal DHEAS status. One female with low and another seven with normal DHEAS at admission had a normal DHEAS status during follow-up. One female with high DHEAS remained the same during the follow-up (Table II).

Overall, six(40.0%) had normal values for all the studied hormones, five(33.3%) had one abnormality, and four(26.7%) had two abnormalities at baseline. After 3 months of admission, four had normal (26.7%), six(40.0%) had one, three(20.0%) had two, and two(13.3%) had three abnormalities of the studied hormone status (Table-II).

Elaborations: M (male), F (female), A (adequate), I (insufficiency), N (normal), IH (isolated hyper-thyroxinemia), ST (subclinical thyrotoxicosis), SH (subclinical hypothyroidism), ESS (euthyroid sick syndrome), PH (primary hypothyroidism), L (low), H (high)

Reference levels: *Cortisol* cut-off 10 ìg/dL, *ACTH*: 0 – 46 pg/mL; *TSH*: 0.35 – 5.5 ìIU/mL, *FT4*: 0.8 – 1.8 ng/dL, *FT3*: 1.4 – 4.2 pg/mL; *total testosterone*: Male (Age, years: 18-49: 2.7 – 17.3, ≥50: 2.1 – 7.6, ng/mL), Female (Age, years: 18-49: 0.1 – 0.5, ≥50: 0.1 – 0.4, ng/mL); *DHEAS*: Male (Age, years: 18-20: 24.0 – 537.0, 31-40: 106.0 – 464.0, 41-50: 70.0 – 495.0, 51-60: 38.0 – 313.0, 61-70: 24.0 – 244.0, µg/dL), Female (Age, years: 18-20: 51.0 – 321.0, 21-30: 18.0 – 391.0, 31-40: 23.0 – 266.0, 41-50: 19.0 – 231.0, 51-60: 8.0 – 188.0, 61-70: 12.0 – 133.0, µg/dL)

The TSH levels significantly increased, the FT4 levels decreased, and the FT3 levels remained unchanged. While the cortisol levels significantly reduced, plasma ACTH levels were statistically similar. Except for the significant increase in DHEAS levels in females, TT and DHEAS levels remained statistically identical in both sexes (Table-III).

Discussion:

COVID-19 is a multi-organ infectious disease, and complications may occur even after recovery. Limited studies are available in our country to evaluate short-term follow-up endocrine function in individuals following COVID-19 infection. In a recent investigation by us, 19%-40% of patients were found to have adrenal insufficiency in an acute setting (depending on various cut-offs).[8] We intended to see if individuals who recovered from COVID-19 had any symptoms of hormone imbalances at a later time. Unfortunately, only fifteen treated cases came to us for follow-up, eight cases died during the hospital course, and the rest didn't come back for a follow-up. Seven of the fifteen individuals still lacked sufficient adrenal reserves.All received standard doses of steroids during their hospital course. Those who developed new insufficiencies after COVID-19 remission may have a contributory factor that leads to post-COVID fatigue. Among the seven persons who had inadequate adrenal reserve, at least one person is likely to have definite adrenal insufficiency, as his serum DHEAS was also low.[11] In contrast to our study, Clarke SA, et al. (2021) found that all the participants had a normal adrenal

function, which was confirmed after the synacthen test.[12] However, we couldn't do the standard synacthen test to confirm adrenal insufficiency, which is a significant drawback of our study and might have diluted the impact of observed cortisol level at follow-up, and our sample size was also low. In agreement with our study, Sunada N, et al. (2022) found that symptomatic long-term COVID patients had lower serum cortisol levels without altering plasma ACTH.[13]Almost all of the symptoms in the study participants improved after three months; however, four people still had fatigability, and five people had postural dizziness, both of which are signs of adrenal insufficiency.

The clinical impact of thyroid dysfunction in the context of COVID-19 is still unknown, and it has been observed in a remarkable number of people with SARS-CoV-2 infection from the early months of the COVID-19 outbreak.[14]Subclinical thyrotoxicosis was routinely described in COVID-19 hospitalized patients.[15] A prospective study demonstrated that 96% of thyrotoxicosis patients became euthyroid after 30-120 days.[16] We also looked for thyroid dysfunction and found five out of fifteen had isolated hyper-thyroxinaemia, and another two had subclinical hypothyroidism during their admission to the hospital. After three months, among the five patients with thyroid dysfunction, three became normal, one of them became frank hypothyroid, and another had biochemical features of euthyroid sick syndrome. Most of our cases turned to euthyroid state, which was in agreement with other previous studies.[12,17] Only one had subclinical thyrotoxicosis during the acute infective phase, which became normal during the follow-up.

A growing number of studies have suggested that the viral infection may lower the production of testosterone and is associated with more severe clinical outcomes.[18] In a seven-month follow-up study, over fifty percent of men who recovered from COVID-19 infection still had low circulating testosterone levels, indicating hypogonadism.[19]Meanwhile, a systematic review and meta-analysis showed that testosterone levels fall immediately after infection and rebound duringrecovery.[20] However, the findings were inconsistent and inconclusive. Over half of the trials examined reported no significant change in testosterone levels in the recovery period, even those comparing severe vs. moderate COVID-19.In the current study, among six men who recovered from COVID-19, only one (16.6%) developed hypogonadism after 3-6 months, and others became normal,which was compatible with the findings of several other prospective studies.[20] Of the nine female participants, two had baseline high levels of testosterone; however, during a follow-up period, the levels of serum testosterone rose in two more individuals, two of whom had chronically elevated levels. The majority of the afflicted females were menopausal, and we were unable to measure their gonadotropin or estradiol levels, making it impossible to determine their sex hormone status accurately.

This study has several limitations, including a small number of participants, a short follow-up period, and inadequate etiological evaluation for persistent hormone abnormalities.

Conclusion:

Endocrine dysfunction as a result of SARS-CoV-2 infection is prevalent. In the current prospective study, almost one-third of infected people had signs of involvement of more than two endocrine glands; thus, endocrine function may be examined during the post-COVID state in symptomatic patients.

Declarations

Ethical approval: IRB, BMU (No. BSMMU/2021/557)

Conflict of interest: None

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Authors' contributions:

HB, MSM, NS, HAH, SMA (Conceptualization, Methodology, Software); MAH (validation); HB, MSM (Investigation, Data curation); HB, MSM, NS (Formal analysis, Writing- Original draft preparation, Visualization); MAH, SMA (Supervision, Writing- review & editing, Project administration, Funding acquisition). All authors read and approved the final manuscript.

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