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PITUITARY FUNCTIONS AFTER RECOVERY FROM COVID-19

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Abstract

Context. Injury and functional disorders in pituitary gland after COVID-19 still need elucidation.

Objective. To investigate pituitary functions, particularly hypothalamic pituitary adrenal (HPA) axis after COVID-19 infection.

Methods. This study was conducted at a university hospital between May and October 2021. Patients who had COVID-19, were enrolled as study group, three months after recovery. Participants who do not have COVID-19 diagnosis, with similar characteristics were included as control group. Blood samples were taken on the morning at 08 AM. Adrenal stimulation test was performed with 1 μg of ACTH (Synacthen).

Results. The study group included 50 patients and control group was 49 cases. One (2%) out of the 50 patients with 8 a.m. serum cortisol below 5 μg/dL. Low serum ACTH levels were detected in 7 (14%) participants in patient group. Stimulation with 1 μg of ACTH (Synacthen) test was performed for 2 (4%) of 50 patients with serum cortisol below 10 μg/dL. Both patients achieved a peak cortisol of over 12.5 μg/dL after stimulation. Standard deviation (SD) score for insulin like growh factor-1 (IGF-1) was lower than –2 SD for age and gender in 7 (14%) patients. TSH levels was mildly increased in five (10%) patients. There was no significant difference in baseline pituitary hormone levels in study and control groups.

Conclusion. Basal pituitary hormone levels and HPA axes were found to be preserved and competently functioning in patients who experienced mild/moderate COVID-19. However, symptoms observed after COVID-19 episode were evident in substantial amount of patients in this study and these symptoms were not associated with changes in pituitary gland function.

Keywords: Adrenal insufficiency, cosyntropin, COVID-19, hypothalamo-pituitary-adrenal axis, thyroid.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the etiological agent of COVID-19. The disease predominantly affects the respiratory system, and the course may be asymptomatic, mild, moderate, or severe. In severe cases, multi-system involvement and particularly respiratory failure is expected (1). This disease has become a pandemic shortly after its beginning in Wuhan, China in December 2019 (2). SARS-CoV-2 infects the host cell using the angiotensin converting enzyme 2 (ACE-2) as receptor. Entry of virus into host cells is facilitated by the viral trans-membrane spike glycoprotein binding the metallo-peptidase ACE-2. Many endocrine glands express the ACE-2 receptor. ACE-2 mRNA expression was reported in pituitary gland and hypothalamus previously (3-6).

SARS-CoV-2 injures endocrine glands through three different mechanisms: direct infection of gland with virus, by the effect of inflammatory mediators on hypothalamic pituitary adrenal (HPA) axis and cellular injury resulting from immune mechanisms (7). Hypophysitis, thyroiditis, and adrenalitis after SARS-CoV-2 infection have been reported previously (8-10). In addition, SARS-CoV-2 was detected in cerebrospinal fluid itself (11).

HPA axis involvement in SARS was firstly reported in 2005 by Leow *et al.* They proposed that hypothalamic-pituitary dysfunction was a consequence of hypophysitis, and direct hypothalamic injury due to viral infection. As observed, HPA dysfunction was resolved within one year in most of the patients (12). The pituitary gland is much vulnerable to ischemic, hypoxic, and hypovolemic changes than other glands. The most frequent pathologies reported in COVID-19

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are euthyroid sick syndrome and thyroiditis (7).

In a study, pituitary glands of patients who died from COVID-19 were inspected in autopsies series and it was found that there were not significant differences between patients who died from COVID-19 and the patients who died from non-COVID-19 causes (13). There are conflicting results in the literature about pituitary functions after COVID-19. Some studies reported that COVID-19 disease may affect pituitary functions (14,15), but one study reported no association between pituitary functions and COVID-19 (16). There are few studies inspecting the impact of COVID-19 on HPA, in the literature. But, entire hormones that are released from anterior hypophysis after COVID-19, were not inspected in previous studies.

The aim of this study is to investigate pituitary functions, particularly hypothalamic pituitary adrenal axis by evaluation of all known hormones released from anterior hypophysis after COVID-19 infection.

PATIENTS AND METHODS

Study setting, duration, design and participants

In this prospective interventional study, participants were the patients who attended to a university hospital between May and October 2021. Patients who had confirmed COVID-19 diagnosis were enrolled as study group, three months after recovery. Participants who attended to hospital for various other reasons, but who did not have COVID-19 history, were enrolled as control group. All participants in study group who had COVID-19 diagnosis were confirmed by real-time polymerase chain reaction (PCR) test with a sample obtained from nasopharyngeal and oropharyngeal swabbing. Informed written consent was obtained from all participants. This study was conducted in concordance with Declaration of Helsinki and good clinical practices directives.

Exclusion criteria were: usage of medications affecting the HPA axis or cortisol-binding globulin (either per oral, parenteral, inhalation or intra-articular), previous hypothalamic-pituitary disease or cerebral trauma history, age under 20 and over 65 years. Diseases and conditions affecting cortisol binding globulin, such as pregnancy, malignancy or renal failure, were also exclusion criteria for the study.

All participants were inquired about the presence of fatigue, headache, chest pain, palpitations, forgetfulness, and arthralgia. Body weight and heights were recorded. Body mass indexes (calculated by division of body weight in kilograms to square of body height in meters, BMI), existence of concomitant diseases and smoking status of all participants were inquired and recorded.

Sample collection and study protocol

Blood samples for basal hormone levels were obtained between 08.00 a.m. and 09.00 a.m. from all participants. Samples were reserved in tubes containing EDTA for cortisol, adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), dehydroepiandrosterone sulphate (DHEAS), total testosterone, estradiol, luteinising hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), growth hormone (GH) and insulin-like growth factor-1 (IGF-1).

Subjects with serum cortisol levels between 5 and 10 μg/dL underwent dynamic HPA axis evaluation by low dose 1 μg of ACTH (Novartis Pharma, Synacthen, Lion, France). Test dose of 1 μg of tetracosactide (Synacthen) was prepared by addition of 0.25 mg of ACTH into 250 mL of 0.9% NaCl solution and 1 mL of this solution was injected intravenously in each patient who had lower cortisol levels. Blood samples for cortisol were taken at 30 and 60 minutes after injection. Patients who had serum cortisol below 5 μg/dL at 08.00 a.m. blood sample and/or serum cortisol below 12.5 μg/dL at 30 or 60 min after stimulation test were considered to have adrenal insufficiency.

Biochemical and immunoassay determinations

Serum TSH, FT3, FT4, prolactin, cortisol, DHEAS, ACTH, FSH, LH, estradiol, testosterone, GH, and IGF-1 were analyzed by the electrochemiluminescence immunoassay (ECLIA) technique (Cobas 601; Roche Diagnostics, Mannheim, Germany).

Statistical analysis

SPSS version 22.0 (SPSS Inc., Armonk NY, USA) was used for the statistical analyses. Data distributions were evaluated by Kolmogrov-Smirnov test. Quantitative data were presented as mean±standard deviation for normally distributed variables. Categorical data were presented as frequency and percentage. Student's t-test and chi-square tests were used in appropriate conditions. A p value below 0.05 was considered significant.

Ethical approval

This study was approved by local ethics committee (App. No: 2021/062).

RESULTS

Fifty participants, 21 male (42%), 29 female (58%) were included as patient group and 49 participants, 30 male (61.2%), 19 female (38.8%) were included as control group. Demographic characteristics of the groups were summarized in the Table 1. Gender, BMI, age, and history of chronic medical illness parameters revealed no difference between two groups.

In this study, four (8%) of 50 patients who had COVID-19 had been hospitalized but in none of them, intensive care was necessary.

In follow-up, three months after COVID-19 recovery, mean baseline cortisol was 15.03±4.81 μg/dL and median basal ACTH was 28.30±22.07 pg/mL. Mean cortisol and ACTH levels were similar to the control group (p=0.792, p=0.382 respectively). Mean baseline (all ages and gender specific) IGF-1 was 154.0±56.88 ng/mL and 152.66±58.91 ng/mL, mean basal GH was 1.12±2.02 ng/mL and 1.28±2.79 ng/mL in study and control groups, respectively (p=0.909, p=0.737, Table 2).

Low serum ACTH levels (Table 3) were detected in 7 (14%) participants in patient group and 4 (8.2%) in control group.

Early morning serum cortisol level was below 5 μg/dL in one (2%) participant in the study group while

Table 1. Clinical characteristics of participants

	Study group (n=50)	Control group (n=49)	p value
Age, median	40.14±11.94	39.31±14.45	0.755
Gender (Male/Female)	21/29	30/19	0.071
BMI (kg/m^2)	27.12±6.32	26.22±4.05	0.398
Current smoker	15 (30.0%)	22 (44.9%)	0.149
Chronic medical illness			
Diabetes	9 (18.0%)	8 (16.3%)	0.825
Hypertension	8 (16.0%)	6 (12.2%)	0.774
Cardiovascular disease	5 (10.0%)	5 (10.2%)	0.999
Chronic respiratory disease	1 (2.0%)	2 (4.1%)	0.617
Signs and symptoms			
Fatigue	24 (48.0%)	1 (2.0%)	<0.001
Headache	10 (20.0%)	1 (2.0%)	0.008
Chest pain	6 (12.0%)	0 (0.0%)	0.027
Palpitation	8 (16.0%)	0 (0.0%)	0.006
Forgetfulness	14 (28.0%)	0 (0.0%)	<0.001
Arthralgia	21 (42.0%)	1 (2.0%)	<0.001
Dyspnea	18 (36.0%)	0 (0.0%)	<0.001

Table 2. Basal hormone levels in participants

	Study group (n=50)	Control group (n=49)	p Value	Normal Range
Free T3 (ng/dL)	3.17±0.42	3.22±0.46	0.509	2.30-4.20
Free T4 (ng/dL)	1.26±0.16	1.27±0.17	0.774	0.89-1.76
TSH (mIU/L)	2.63±1.22	2.31±1.40	0.215	0.27-4.20
Anti-TG (IU/mL)	59.43±148.72	23.79±50.03	0.115	0.01-34.00
Anti-TPO (IU/mL)	23.04±83.96	18.13±39.38	0.711	0.01-115.00
ACTH (ng/L)	28.30±22.07	32.90±29.64	0.382	7.2-63.3
Cortisol (μg/dL)	15.03±4.81	15.28±4.74	0.792	10.00-29.00
GH (ng/mL)	1.12±2.02	1.28±2.79	0.737	0.06-6.00
IGF-1 (ng/mL)	154.0±56.88	152.66±58.91	0.909	130-354
LH (IU/L)	11.34±11.96	12.22±13.09	0.727	Various
FSH (IU/L)	13.73±20.29	12.67±19.63	0.791	1.50-12.40
Prolactin (ng/mL)	23.08±24.39	16.63±11.94	0.099	2.1-17.7
Estradiol (pg/mL)	39.13±51.54	30.06±54.92	0.399	Various
Total testosterone (ng/mL)	6.12±7.13	8.47±8.19	0.133	2.49-8.36
DHEAS (μg/dL)	6.06±3.60	6.15±3.13	0.900	65.10-368.00
DHEAS/cortisol ratio	24.85±64.33	17.24±13.16	0.419	

BMI: body mass index, Free T3: triiodothyronine, Free T4: thyroxine, TSH: thyroid-stimulating hormone, ACTH: adrenocorticotropic hormone, GH: growth hormone, IGF-1: insulin-like growth factor 1, LH: luteinising hormone, FSH: follicle stimulating hormone, DHEAS: dehydroepiandrosterone sulphate.

serum cortisol levels in control group were all above 5 µg/dL. ACTH stimulation test was required in 3 patients (6%) of study group and in 7 (14.3%) of the control group who had serum cortisol levels between 5 and 10 µg/dL. Two patients (4%) in study group and five (10.2%) participants in control group accepted to be challenged in the stimulation test. A peak serum cortisol level over 12.5 µg/dL was achieved in both patients of study group and in four of control group after stimulation with ACTH, only in one patient from control group serum cortisol levels were below 12.5 µg/dL (Table 3).

TSH, FT4, and FT3 levels were similar between study and control groups (Table 2). In patient group, 45 (90%) out of the 50 patients had normal serum TSH levels and in 5 (10%) patients' serum TSH levels were elevated.

DISCUSSION

According to the results of this study, basal pituitary hormone levels, HPA and thyroid functions were found to be preserved and competently functioning in patients who experienced COVID-19. In this study group, COVID-19 had no significant impact on functions of adrenal and thyroid glands. It should be taken into consideration that the study group consisted of mild/moderate COVID-19 patients. On the other hand, there is emerging evidence about HPA axis involvement in COVID-19 (17).

There are few studies about central adrenal insufficiency after COVID-19 in the literature (18, 19). A study inspecting 43 patients who recovered from COVID-19 reported that basal pituitary hormone levels, GH and HPA were examined by glucagon stimulation test (GST) and low-dose ACTH stimulation tests and GH levels were found to be lower (14). In this mentioned study, low-dose ACTH stimulation test revealed insufficiency in cortisol response in 16.2% of patients and insufficiency in GH response to GST in 46.5% of the patients. According to these results, COVID-19 might provoke pituitary dysfunction. But when comprehending the results of mentioned study, low participant numbers in control group must be considered.

In a study, the impact of SARS-CoV-2 on the HPA axis was searched; early morning plasma cortisol, ACTH, and DHEAS levels were inspected in 28 patients with COVID-19 on hospital admission and the morning plasma cortisol levels were found to be low (<100 nmol/L) in eight patients (28.6%). Four patients (16.7%) had low DHEAS levels (14). In another study investigating relation between adrenocortical system hormones and COVID-19, it was reported that serum levels of ACTH were significantly lower, and serum cortisol levels were higher in non-critically ill COVID-19 patients compared to healthy individuals (20). Clarke and colleagues inspected patients with COVID-19; patients who had respiratory distress and were treated with dexamethasone were in one group and patients who did not get dexamethasone medication constituted the control group. These patients were re-evaluated three months after recovery from COVID-19 with ACTH stimulation test. There were no differences between the groups (16). In our study, 2% of the COVID-19 patients had serum cortisol level below 5 µg/dL and 14% of patients had low serum ACTH levels but the mean cortisol and ACTH levels were similar with those of the control group. Serum FT3, FT4, and TSH levels were similar between study and control groups. In addition, our study inspected entire anterior pituitary hormones in patients after COVID-19, and dynamic tests were only performed when necessary.

When symptoms that resulted in patient attendance to hospital after COVID-19 recovery were analyzed: fatigue, dyspnea, smell and taste dysfunctions, cough, headache, myalgia, chest and joint pains, mental and cognitive impairments, gastrointestinal and cardiac symptoms such as palpitations and tachycardia, many studies concluded that these symptoms could persist for months after COVID-19 resolution and the condition was defined as 'long COVID' (21, 22). Sudre *et al.* (22)

Table 3. Changes in hormone levels

	Study group (n=50)	Control group (n=49)	p value	Normal range
Low IGF-1 levels	7 (14.0%)	3 (6.1%)	0.318	Age and gender specific in all cases
Basal serum cortisol level (lower than 5 µg/dL)	1 (2.0%)	0 (0.0%)	0.999	
Insufficient peak cortisol in low dose (1 µg) short Synacthen (ACTH-1-24) test	0 (0.0%)	1 (2.0%)		Peak value <12.5 µg/dL
Lower ACTH levels	7 (14.0%)	4 (8.2%)	0.349	7.2–63.3 pg/mL
High TSH levels	5 (10.0%)	5 (10.2%)	0.999	0.27–4.20 µIU/mL
Normal DHEAS levels	50 (100.0%)	49 (100.0%)		Age and gender specific in all cases

IGF-1: insulin-like growth factor 1, ACTH: adrenocorticotropic hormone, TSH: thyroid-stimulating hormone, DHEAS: dehydroepiandrosterone sulphate.

defined 'long COVID' as the persistence of the symptoms more than four weeks; in their study, 13.3% of total participants had persistent symptoms which lasted over one month, 4.5% over two months and 2.3% over three months. It was reported that especially in patients with advanced age, increased BMI and female gender, long COVID-19 was more likely to develop (22). Despite the fact that in our study, COVID-19 patients presented mild and moderate forms of illness, they presented long COVID symptoms (Table 1) in a significant percentage *versus* the control group.

There are some limitations of this study. The study has not been designed to compare COVID-19 effects on HPA axis between patients' groups categorized as asymptomatic, mild, moderate, severe and critical. Second is absence of the pituitary magnetic resonance imaging (MRI) evaluation. Due to overloading of radiology unit in the pandemic, limited patients could be evaluated by MRI. Another is, number patients enrolled into study group may be relatively low. With a larger number of patient group, more precise data could have been obtained.

In conclusion, according to the results of this study, in the patients who experienced COVID-19 episode at least three months before enrolment, basal pituitary hormone levels and HPA axes were found to be preserved and competently functioning. However, symptoms observed after COVID-19 episode were evident in substantial amount of patients in this study and these symptoms were not associated with changes in pituitary gland function. Prospective studies inspecting pituitary function and HPA axis involvement for prolonged durations are necessary to elucidate the condition thoroughly.

Conflict of interest

The authors declare that they have no conflict of interest.

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