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Investigation of the neuroendocrine abnormalities in COVID-19 patients

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Running tittle: Neuromodulators abnormalities on COVID-19 patients

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Abstract

At the end of 2019, the first cases of idiopathic lung disease were detected in Wuhan, China. This new pathogen spread throughout Europe and then throughout the world; which was initially named SARS-CoV-2. The recent studies report dysregulation in biosynthesis and release of neurohormones and neurotransmitters influence the incidence and progression of COVID-19 disease. Therefore, the aim of the present paper is to investigate the neurohormones changes in response to the biochemical variations mediated by COVID-19. For this purpose, 60 COVID-19 patients (30 males and 30 female) and 40 control (20 males and 20 female) were selected and the level of biochemical parameters were determined by specific ELISA kits. The obtained results show that, the level of leptin in COVID-19 male and female patients were significantly higher than control group that accompanied with high amount of cholesterol level in blood serum and cytokine storm. The level of oxytocin was significantly lower in male ($P=0.0007$) and female ($P<0.0001$) patients than control subjects while VP increased remarkably. The level of dopamine in female COVID-19 patients was significantly lower than control although, there is no significant difference in dopamine level of male COVID-19 compared to control subjects. Moreover, SARS-CoV-2 infection reduced testosterone and progesterone levels in male and female patients respectively. By considering immunomodulatory function of neurohormones, studied changes could be cause or consequence of harsh inflammatory response mediated by COVID-19. Our results and previous studies showed a positive correlation between neuromodulators dysregulation and severe cases of disease that introduce neuroendocrine system as a possible therapeutic target.

Keywords: *Neurohormones; Iron deficiency; SARS-CoV-2 infection; Vasopressin; Oxytocin; Leptin*

1.Introduction

At the end of 2019, the first cases of idiopathic pulmonary fibrosis (IPF) were detected in China, which was initially named coronavirus disease 2019 (COVID-19) (1). This acute respiratory distress syndrome (ARDS) was caused by 2019-nCoV virus that later renamed SARS-CoV-2 and belongs to the family of Coronaviridae (1, 2). COVID-19 makes changes in

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the host's immunological status, including neutropenia, depletion of dendritic cells and natural killer cells, decreased T (T CD4+ and CD8+) and B lymphocytes, and also increased proinflammatory cytokines (3). More studies in this field have focused on the acute infection and saving lives. These strategies have included preventing infection with vaccines, treating COVID-19 symptoms with medicines or antibodies, and reducing complications in patients (4). While according to some critical studies, COVID-19 causes neurological abnormalities in infected individuals possibly due to immune system malfunction or limited oxygen supply to the brain tissue (5). Most of patients suffer from SARS-CoV-2 infection do have symptoms related to the brain or nervous system including muscle aches, headaches, dizziness, altered taste and smell, and in severe cases a dramatic state of confusion called delirium (5, 6). The rare number of sufferers manifested seizures, major strokes, muscular weakness and nerve injury (6). The pain syndromes also are common in people who require intensive care during infections (7). Recent studies confirmed that the neurological symptoms of COVID-19 are likely a result of the immune response overactivation rather than the virus directly infecting the brain or nervous system (6). According to the previous studies nervous system was affected by some of neurohormones or neurotransmitters which were changed during COVID-19 disease (6, 7). These types of hormones make a coordination between nervous system and peripheral organs function (8) so dysregulation of them is crucial in COVID-19-derived neural symptoms.

Vasopressin (VP) is a neuroactive peptide produced by hypothalamus and transferred by circulation to the goal cells (9). It shown to be had analgesic and nausea effects and also impact the circadian rhythm in CNS (9). VP is also known to regulate blood pressure, osmolality and volume through reabsorption of water from kidney (10). Previous experiments

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reported VP-related disruption in neurological and also kidney disease that manifests its important role in body homeostasis (10). Oxytocin (Oxt) is the other neuropeptide that produced by hypothalamus neurons and mainly affects reproductivity and social behavior while its role in CNS is remarkably unknown (11). Oxt has been implicated in the etiology of autism and previously was approved that individuals with mutation in Oxt receptor gene are at a higher risk for having autism (12). Dopamine (DA) is neuromodulator that its circular content affected by different viral infections and exposure to inflammatory cytokines (13). By considering up-regulation of cytokines in COVID-19 patients that refer to harsh inflammatory condition, its possible COVID-19-derived neural complication is due to alteration in neuromodulators content such as neurohormones and neurotransmitters. Since these hormones have immunomodulatory effects and could trigger cytokines production (14) so they could influence the initiation and progression of COVID-19 disease. Therefore, this study aimed to evaluate the main neuromodulators in circulation of patients suffer from SARS-CoV-2 infection such as VP, Oxt, DA and leptin. This kind of researches could help to clarify some of the ambiguities in COVID-19 symptoms and also elucidate molecular phenomenon take place in viral infections.

2. Material and methods

2.1. experimental design

60 severe COVID-19 patients (30 males and 30 female) and 40 control subjects (20 males and 20 female) were prepared form Imam Reza hospital in Mashhad, Iran from February 2021, to March, 2021. Informed and written consent is obtained from participants. Inclusion criteria for patients are: Age>25 years old, respiratory distress, respiratory rates ≥ 30 breaths/minute,

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oxygen saturation ≤ 90 % at a rest state, arterial oxygen tension (PaO2) over inspiratory oxygen fraction (FIO2) ratio ≤ 300 mmHg (1 mmHg = 133 Pa) and multiple pulmonary lobes showing more than 50% progression of lesion in 24–48 h on imaging. Also, control group has, Age >18 years old, no heart and liver disease, no diabetes (type 1 and type 2), no thyroid disorder, no diabetic nephropathy and using of iron supplement. The diagnosis of SARS-CoV-2 infection is often confused with that of influenza and seasonal upper respiratory tract viral infections. Therefore, SARS-CoV-2 infection was approved by specialist according to physiological symptoms, computerized tomography (CT) scan imaging and real-time reverse transcriptase-polymerase chain reaction (RT-PCR) methods. Then about 7 ml of venous blood were collected in an anti-coagulated tubes containing sodium EDTA and the second plain tube for serum will be taken from all participant and blood serum will be separated by centrifugation at 1500 g for 10 min at 4°C, and separated to small aliquots, and stored at -20 °C until its use for the experimental tests. General characteristics and parameters with diagnostic value in COVID-19 patients and control cases were joined this study are shown in table 1.

2.2. Biochemical parameters evaluation

Human ELISA kits were used for determination of Fe^{2+} content (Abcam, ab211096). Ferritin (Abcam, ab108698), Vitamin D3 (Abcam, ab213966), Human D-Dimer (Abcam, ab260076), Estradiol (ab108667), Testosterone (Abcam, ab108666), Progesterone (Biocompare, UK) also were assessed by using specific kits according to company guideline.

2.2. Neurohormones measurement

In order to neurohormone measurement we used specific ELISA kit due to specificity and accuracy of method. Human Leptin ELISA Kit (Abcam, ab108879), Oxytocin ELISA Kit

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(ab133050) and Arginine vasopressin ELISA Kit (ab205928) were used for measurement of leptin, OXt and VP, respectively by using manufacturer recommendation.

2.3. Statistical analysis

This is a case control study and the results were analyzed by using SPSS 26 statistical software using Chi-square ($\chi 2$), logistic regression, t-test and analysis of variance (ANOVA) methods with a significance level of $P < 0.05$.

3. Results

According to the reports, SARS-CoV-2 infection causes different levels of neurological abnormalities from headache to stoke (15). Here we want to study the possible alterations of neuroactive hormones and metabolites in COVID-19 patients in comparison with age- and sex-match control. Previous results confirmed male is more susceptible rather than female against COVID-19 and mortality rates of male and female reported to be 21.9% and 13.2% respectively (16, 17) therefore we compared patients in sex-based groups. Based on the obtained biochemical results, cholesterol level was significantly higher in male COVID-19 patients compared to control subjects; although there is no significant difference in cholesterol level between female COVID-19 and control subjects (Table 1). Fe and vitamin D3 levels were significantly lower in COVID-19 patients (male and female) compared to control subjects that manifested vitamin D3 plays crucial role in immune system activities. Ferritin and D-Dimer parameters levels were significantly higher in COVID-19 patients compared to the control subjects in both sex ($P<0.05$), these parameters have diagnostic value in SARS-CoV-2 infection (18). Estradiol also showed significant reduction in both of the sex groups, its value was estimated to be 42.90±10.46 and 85.00±12.26 pg/ml in male and female

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COVID-19 patients respectively while estradiol amount is 17.85±2.94 and 56.05±12.13 pg/ml in healthy male and female.

3.1. SARS-CoV-2 infection affects hypothalamic neurohormones

Oxt and VP are neuroactive hormones which are produced in the hypothalamic region of the brain and secreted into the blood by the neurohypophysis (part of the pituitary gland) and both of them play crucial role in coordinated function of brain and peripheral tissues (19). The level of Oxt was significantly lower in male ($P=0.0007$) and female ($P<0.0001$) patients than control subjects. Fig 1A confirmed circular Oxt content in female is less than male remarkably in both of the healthy and COVID-19 groups.

VP also showed harsh increase in COVID-19 patients in comparison with control. This raise estimated to be more than 5-fold. The mean of circular hormone concentration is 26.00 and 3.90 pg/ml in male COVID-19 patients and male healthy control respectively. We can see a similar difference in female groups also. While the content of this hormone in blood sample of female is more than male (Fig 1B).

3.2. Dopamine circular concentration could not be affected by COVID-19

Our results don’t show significant changes between male COVID-19 patients in comparison with sex-match control group. Of course, the concentration of dopamine in blood serum of COVID-19 patients increased slightly but this difference is not significant according to statistical analysis (Fig 2A). While, the level of dopamine in female COVID-19 patients was significantly lower than control subjects ($P<0.05$).

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3.3. Leptin level decreased as a result of SARS-CoV-2 infection

Leptin is a peptide hormone released from adipose tissue and regulate appetite, neuroendocrine function, and energy homeostasis in body while it seems to influence immune response also (20). It could control both innate and adaptive responses through regulation of immune cells survival, proliferation and activity (21). According to Fig 2B, the level of leptin in male and female patients with severe COVID-19 were significantly higher than control group ($P<0.0001$). The range of variation in leptin level of patients is more than control.

3.4. Effect of COVID-19 infection on circular sex hormone levels

By considering the harsh changes in endocrine system were mediated by COVID-19, disruption of circular concentration of sex hormones is predictable also. Previous studies revealed that females are more resistant to SARS-CoV-2 infections than men possibly due to sex hormones differences and high expression of coronavirus receptors (ACE 2) in men (16, 17). Therefore, we aimed to evaluate estradiol, testosterone and progesterone content in blood serum of COVID-19 patients and compare with sex-match control. Circular concentration of testosterone was evaluated to be 266.53±57.25 ng/dL in male COVID-19 patients that is significantly more than control group (403.15±63.48 ng/dL) (Fig 3). Female COVID-19 patients also manifested reduced amount of progesterone in comparison with control female. Progesterone level was evaluated to be 25.35±8.21 ng/ml in female control that reduced to 19.73±7.84 ng/ml in female patients that difference is significant according to statistical analysis ($P<0.0001$).

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4. Discussion

SARS-CoV-2 infection causes immunomodulation process resulted to excessive amounts of interleukins and cytokines (22). Changes in the immune system have been observed in cerebrospinal fluid, blood and other fluids of the body (23). These kinds of alterations include the presence of antibodies, interleukins and cytokines that may also react with the nervous system and other organs of the body (24). Therefore, the most of symptoms in COVID-19 patients are related to the immune response overactivation rather than the virus infection (6). According to the previous study, neuroendocrine system could be affected by SARS-CoV-2 infection and some of the patients were manifested secondary symptoms related to endocrine system dysregulation (25). By considering the widespread abnormalities in COVID-19 patients, this study aimed to assess the possible alterations in neurohormones circular content. Our results revealed cytokine storm as a result of COVID-19 causes decreased amounts of Oxt and VP in circulation. Previous studies reported high blood viscosity in COVID-19 patients that possibly caused by dysregulated amounts VP that involves in the control of blood osmotic system, reabsorption of water from the kidney, blood pressure and plasma volume (9, 10). The mechanism of VP activation is related to the fact that acute inflammatory response with a higher concentration of pro-inflammatory cytokines mainly interleukin (IL)-6 leads to significant stimulation of hypothalamic VP with progression of hyponatremia (26). Oxt is a peptide of nine amino acids and a well-known anti-inflammatory, anti-oxidant, and immune-modulator that could motivate the adaptive immune system, improve curative mechanisms and cause rapid recovery of COVID-19 patients (27). It also has protective effects against ARDS, nephrotoxicity, sepsis, and ischemia-reperfusion medical condition (27). Therefore, reduced amount of Oxt in COVID-19 causes more severe pathophysiological signs in

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hospitalized patients. Our results also confirmed reduced Fe content and ferritin level as a result of cytokine storm. The functional iron deficiency in turn is a major determinant of the anemia of inflammation, and can alter either oxygen sensing and lymphocyte function (28). Hypoferremia has been consistently reported in severe COVID-19, and might play a substantial role as contributing factor to a worsening clinical course (29). Also, hypoferremia is associated to the marked increase of pro-inflammatory cytokines, including IL-6 which is a major stimulator of hepcidin production by the liver (29-31). Moreira et al., in 2021 evaluated iron metabolism and immune response in COVID-19 patients. Their results show that iron levels negatively correlated with IL-6 and higher levels of this cytokine were associated with worse prognosis (29). Moreover, serum ferritin levels at diagnosis were higher in COVID-19-positive than in COVID-19-negative patients. Therefore, COVID-19 is a systemic disturbance which could be recognized by two independent biomarker, reduced ferritin and raised D-Dimer (18).

In this research, the level of sex hormones was determined in COVID-19 patients (male and female groups) which are known to play a role in immunity and infections (32). Estrogen, testosterone and progesterone are endogenous reproductive steroids and play as an important physiological role by modulating inflammatory processes and behavior (33). Estradiol and progesterone exert peripheral and neuronal functions mediated by genomic influencing nuclear hormone receptors, are anti-inflammatory and stimulate antibody production (34). Based on the results obtained in this study, testosterone and progesterone level were significantly lower in male ($P<0.0001$) and female ($P=0.0013$) COVID-19 patients compared to control subjects, respectively as presented in Fig. Progesterone exerts its neuromodulatory effects through motivation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid

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receptors (AMPARs) so could control convulsive status (35). It seems, the protective and anti-inflammatory properties of progesterone cause less incidence of COVID-19 between women and men with COVID-19 are more at risk for worse outcomes and death (16, 17). Alloprognolon as a secondary metabolite of progesterone also play anxiolytic and sedative role through binding to the γ-aminobutyric acid receptors (GABARs) (36).

Leptin as a neurohormone is one of the pro-inflammatory adipokines which influenced both adaptive and innate immune responses by stimulating the production of many cytokines like tumor necrosis factor α (TNF-α**)**, interferon- **γ** and IL-2 and inhibits the production of many anti-inflammatory cytokines including IL-4 and IL-5 (37). Larsson et al., in 2022 reported that the plasma leptin is increased in intensive care patients with COVID-19 (38). Our results show that leptin levels were significantly higher in patients with COVID-19 in comparison with healthy controls. By considering important role of the leptin in metabolism control, its possible increased level of this neuroactive hormone is an adaptive reaction to high energy demand in infectious disease. It seems increased cholesterol content of blood serum is a results of leptin function in COVID-19 patients.

4. Conclusion

According to the previous reports, COVID-19 patients may experience short- and long-term mental health problem could be caused by neurohormonal dysregulation that mediated by cytokines storm (3, 5, 6). Of course, some of the neurohormones could regulate immune response by trigger inflammatory condition. Oxt is a neuromodulator, effective for stress, anxiety, social behavior, and depression, which may be helpful for better outcomes in patients with COVID-19. Neuromodulators play hemostatic and regulatory role in central nervous

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system and also immune system and could be implicated in the course of disease caused by SARS-CoV-2. Therefore, it's not clear neurohormonal dysregulation is cause or consequence of the inflammation in COVID-19 patients. Reduced amounts of Fe and ferritin are closely associated with pathophysiological signs of COVID-19 that suggest iron supplement could improve hospitalized patients. Finally, it could be concluded that neuroendocrine abnormalities enhance the incidence of hospitalization and may be considered as a potential therapeutic target.

Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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Table 1. Biochemical parameters in control and patient groups

Parameter	**Male COVID-19**	**Female COVID-19**	**Male Control**	**Female Control**	**P-value**
Age (years)	49.0±10.6	53.0±6.5	39.0±8.5	38.5±5.6	<0.0001 (1) <0.0001 (2)
Cholesterol (mg /dl)	216.2 ±24.68	210.57±23.62	200.30±13.68	201.70±12.14	0.0371 (1) 0.0885 (2)
Fe (µg/l)	718.03±172.83	659.87±175.25	860.25±206.85	830.05±152.12	0.011 (1) 0.0009 (2)
Ferritin (µg/l)	313.85±80.24	259.60±71.67	59.05±12.14	77.55±11.21	<0.0001 (1) <0.0001 (2)
Vitamin D3 (ng/ml)	27.67±5.73	29.13±7.31	38.40±7.78	37.40±10.07	<0.0001 (1) 0.0015 (2)
D Dimer (mg/l)	4.50±1.27	3.35±0.61	0.41± 0.10	0.44± 0.12	<0.0001 (1) <0.0001 (2)
Estradiol (pg/ml)	42.90±10.46	85.00±12.26	17.85±2.94	56.05±12.13	<0.0001 (1) <0.0001 (2)

(1) P-value for Male COVID-19 and male control.
(2) P-value for Female COVID-19 and female control.

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Figure Legends

Fig 1. Comparison of the circular concentration of oxytocin and vasopressin in male and female COVID-19 patients and healthy control. (A) Oxt hormone reduced as a result of SARS-CoV-2 infection in male and female. (B) VP measurement showed harsh increase in synthesis and release of VP in COVID-19 patients rather than heathy control. All data were expressed as mean ± SD. Significant differences indicated by star symbol (****, P=0.0001 and *, P=0.05).

Fig 2. The count of leptin and dopamine in blood serum of COVID-19 patients and healthy individuals. (A) Multiple comparison of results by using ANOVA analysis showed there is no significant differences in dopamine concentration in male patients rather than control. While in female groups significant reduction was detected. (B) Leptin level reduced in male and female COVID-19 patients. All data were manifested as mean ± SD. Significant differences indicated by star symbol (**** P=0.0001; * P=0.05; ns: non-significant).

Fig 3. The effects of SARS-CoV-2 infection on sex hormones of male and female. (A) results revealed significant reductio of testosterone hormone in blood serum of male patients in comparison with sex-match control. (B) Progesterone hormone also reduced in female patients who suffer from severe COVID-19 disease. Data were represented as mean ± SD and number above the columns manifested P-value in comparison of patients with control groups.

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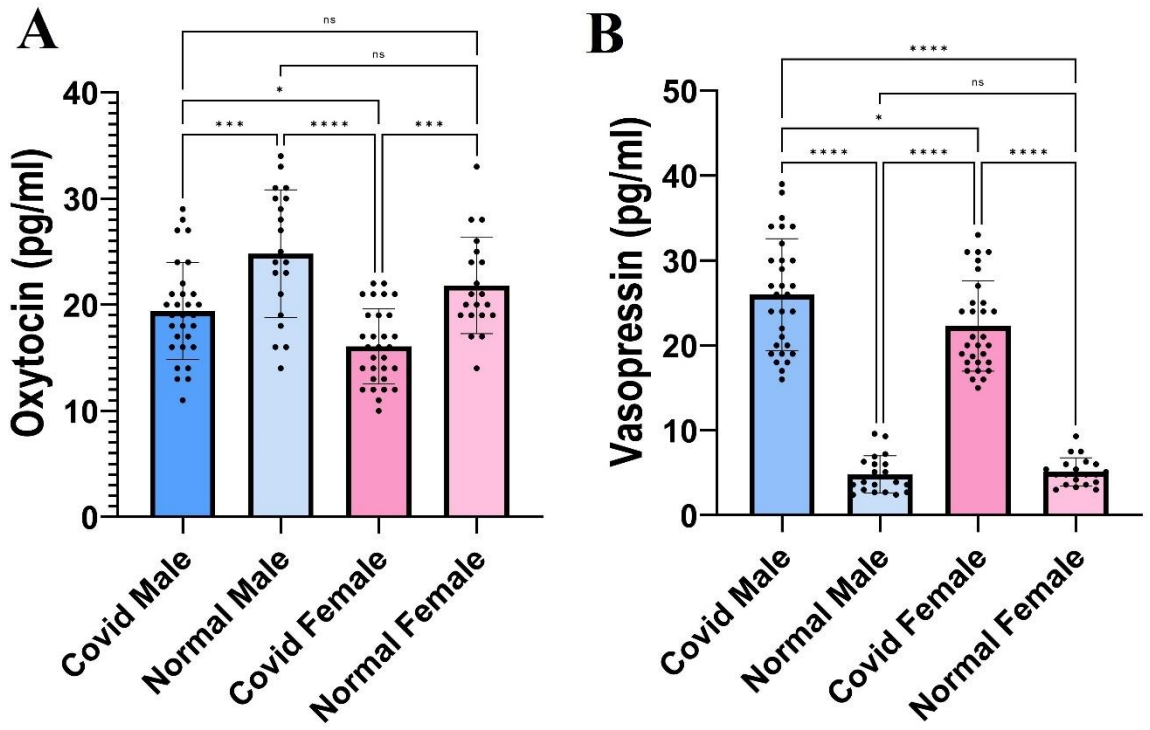

Fig. 1

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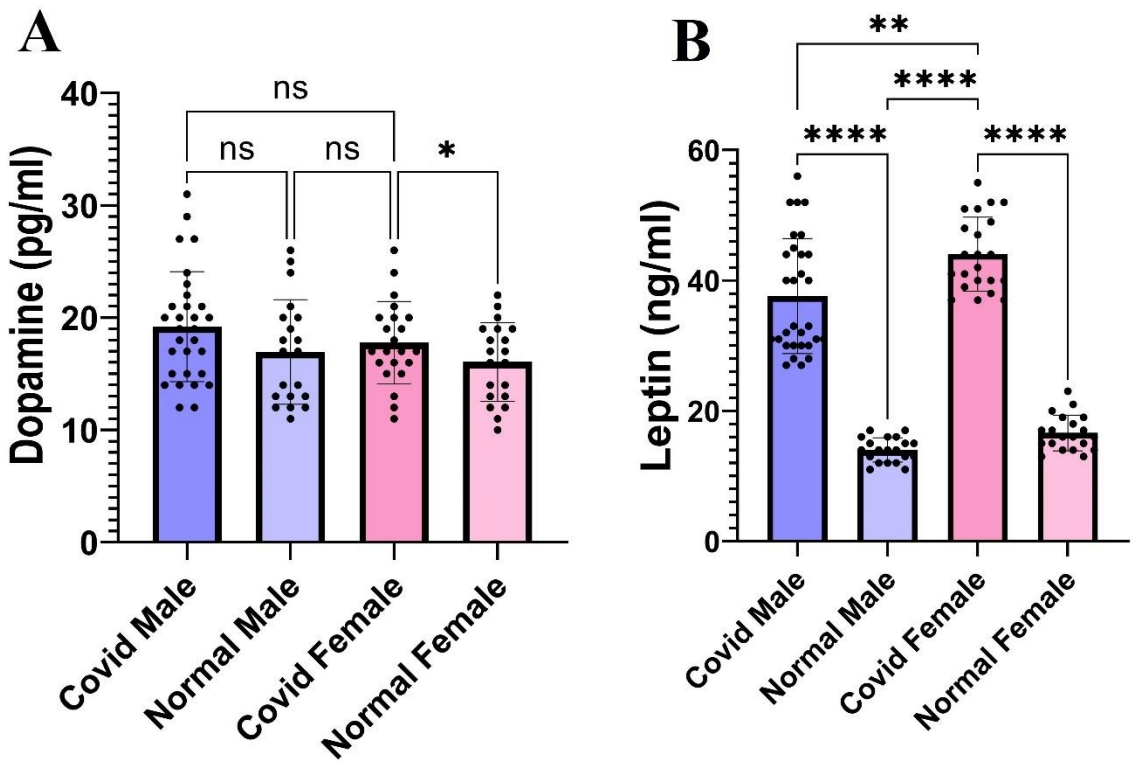

Fig. 2

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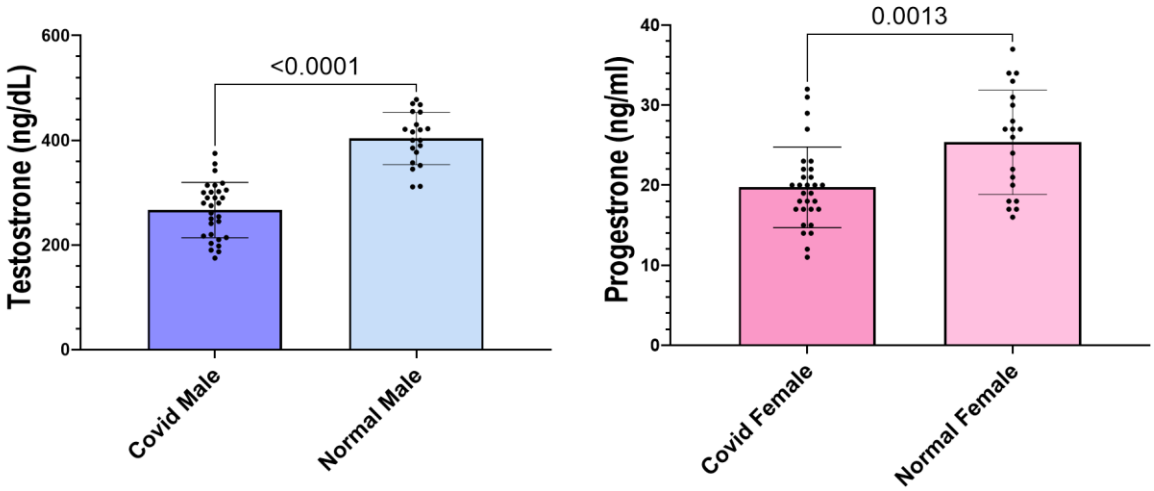

Fig. 3

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