

## **Impact of COVID-19 Infection on the Endocrine System**

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An acute respiratory disease, caused by a novel coronavirus (SARS-CoV-2) named officially as COVID-19 started in China in December 2019 and has spread throughout the world(1). On 30 January 2020, the World Health Organization (WHO) officially declared the COVID-19 epidemic as a public health emergency of international concern(2). Worldwide, as of 31 March, 2020, almost 800,000 people have been infected with an overall mortality of about 2-3%. The major impact of this disease is on the respiratory system where the severity ranges from asymptomatic patient detected on laboratory testing to flu-like symptoms to pneumonia, ARDS, multiorgan failure and death(3,4). The vast majority of patients have mild to moderate symptoms, However, about 10-15% have severe symptoms that need an intensive care unit and mechanical ventilation(3,4).

Although the impact of COVID-19 is mainly on the respiratory system, many organs are affected, especially in patients with severe pneumonia and ARDS(3,4). These include gastrointestinal system, liver, kidneys, cardiovascular system, central nervous system and musculoskeletal systems(5-7). The endocrine organs are likely to be involved, especially in patients with severe disease. However, this has not been assessed in COVID-19 infection. In this proposal, we plan to study the impact of COVID-19 infection on a number of endocrine organs including the hypothalamic pituitary adrenal axis, thyroid gland, pituitary function and islet cell function.

Acute illness has major impact on endocrine system(8-12). Changes in thyroid function tests are common in patients with acute illnesses, especially inflammatory illnesses. The syndrome of sick euthyroid syndrome is well known(10,12). It is usually characterized by low T3, low T4 and low TSH level. Adrenal dysfunction/insufficiency is another well-known phenomenon, especially in an ICU setting(8,11). Other endocrine dysfunction has been described including hypogonadism, parathyroid dysfunction and development of hyperglycemia(8).

Aims of the study:

1. To study the hormonal changes that occur in patients with COVID19 infection. This has not been studied and may reveal important information on the metabolic and hormonal derangements that occur in this new infection. Some derangements can have major impact on the patient's illness e.g. adrenal insufficiency
2. To study the changes in the metabolic parameters and hormonal level with respect to the severity of the illness, age, sex and inflammatory markers (correlation studies)

**Methods:**

**Inclusion criteria:**

1. **Pts  $\geq$  18 years**
2. **Admitted with a positive test for COVID19**

#### **Exclusion criteria**

1. **Patients on hemodialysis**
2. **Pregnant ladies**
3. **Children < 18 years**
4. **Patients taking drugs affecting endocrine function**

We have two arms for this study:

#### **A. Patients admitted in the general floor:**

The following tests will be done on two consecutive days after admission then every other day for 2 weeks or until the patient get discharged or transferred to ICU whichever comes first:

1. TSH, FT4, T3, Cortisol, ACTH, DHEAS, RENIN, ALDOSTERONE, RENAL PROFILE, PROLACTIN, LH, FSH, Testosterone (in males), Estradiol (In females), fasting blood glucose, C-peptide, fasting insulin (If not diabetic or on insulin), Total Cholesterol, Bone profile, PTH, Growth hormone,
2. The following tests will be done at the time of admission and then every 5 days: IGF-1, Hba1c, lipid profile, 25- OH Vitamin D for 2 weeks or until patient get discharged or transferred to ICU whichever comes first

#### **B. Patients in the ICU:**

The same tests listed in # 1 will be done daily for 1 week then every other day for 1 week then every 3 days for 1 week and the tests listed in # 2 every 3 days for 2 weeks then once 5 days for 2weeks or until the patient is transferred to the floor or dies

Changes in hormone levels over time will be analyzed and will also be correlated with clinical severity of the disease.

Target patients: 30 patients in the general floor and 30 patients in the ICU

It is possible that patients with severe illness/ARDS develop acute adrenal insufficiency. This has not been assessed in COVID-19 but was observed in other types of severe sepsis (11). Therefore, this study could also be of major clinical benefits in case patients develop unrecognized adrenal insufficiency, for that reason, if serum cortisol is < 150 nmol/l, a short cosyntropin test will be performed and if abnormal, patients will be started on hydrocortisone stress doses (25-50 mg PO/iv TID).

#### ***Ethical issues:***

The work in this proposal does not involve any patient direct contact and will be simply based on laboratory measurement of a number of hormones. So, we would like to ask for a waiver of consent. If that is not possible, we will do consent by phone and document it in the medical record (ICIS) to minimize risk of spread of infection. All patients' identity will be kept confidential and limited to the research team.

**Amendment:**

We have undertaken the above project in about 40 patients and submitted a manuscript on adrenocortical function in COVID-19 which showed very interesting findings suggesting impaired response and adrenal insufficiency in about 30% of cases. We have submitted this manuscript to three international journals and all had good comments on it but pointed out a major deficiency of not doing the gold standard test for adrenal insufficiency "short synacthen test". We didn't include that in our original proposal as we didn't expect these findings. Therefore, we would like to request an amendment to the proposal by allowing us to do short synacthen test in 30 patients with COVID-19 moderate to severe illness (grade C and D). This will answer the question of whether adrenal insufficiency is a feature of COVID-19 or not. On the new 30 patients, we will only do synacthen test once and also thyroid function test once (to increase the number of patients with thyroid function test as we have another manuscript on thyroid dysfunction in COVID-19). So the protocol will be as follows:

1. Patients admitted with positive COVID-19 test and stage C or D disease will be considered for recruitment after excluding any condition that may affect adrenal function. These include:
  - a) Patients with known adrenal or pituitary disease
  - b) Patients on chronic glucocorticoid therapy
  - c) Patients with advanced liver or kidney disease
  - d) Patients on drugs that may interfere with adrenal function or measurement of cortisol and ACTH
2. After obtaining an informed consent, the patient will have baseline tests including:
  - a) FT4, TSH, T3, ANTI TPO Ab and anti Thyroglobulin Abs
  - b) Baseline cortisol and ACTH followed by synacthen 250 mcg iv bolus and measurement of serum cortisol at 30 and 60 minutes

Testing will be done only once if the results are normal and will be repeated second time after 3-4 days if the result is abnormal.

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