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From Infection To Imbalance: The Endocrine Puzzle Of Long COVID

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Abstract: Long Covid (or Post-Acute Sequelae of SARS-CoV-2 infection) can have serious health consequences, and is a condition in which those who have survived the acute phase of COVID-19 continue to experience a variety of symptoms weeks or months later. This paper focuses on the impact of long covid in dysregulation of Hormones and Endocrine system In recent studies have shown transformation of several hormonal axes in individual with Long covid:

1. **Hypothalamic- Pituitary-Adrenal (HPA) Axis**
2. **Low cortisol and adrenal insufficiency which causes dizziness, fatigue and decrease in blood pressure**
3. **Hypothalamic-Pituitary-Gonadal (HPG) Axis**
4. **Low testosterone in men and irregular menstrual cycle in female leads to fatigue, irritation, erectile dysfunction, late menarche and early menopause**
5. **Antidiuretic Hormone (ADH) Imbalance**
   Diabetes insipidus causing excessive urination and dehydration
6. **Hyperthyroidism**
   inflammation followed by Hypothyroidism and damage to the gland.
7. **Chronic illness symptoms**
   due to decreased T3 levels slow metabolism and lead to lethargy and slow metabolism
8. **Blood sugar fluctuation**
   SARS-CoV-2 infect pancreatic beta cells and leads to the rise of Diabetes Mellitus (Type 1&2) and also Hypoglycemia and Hyperglycemia.

These hormonal shifts may also contribute to the chronic symptoms of Long COVID, especially widespread fatigue. The complete and thorough knowledge of these endocrine manifestations is needed to promote therapeutic approaches, better diagnostic protocols, and effective management strategies for patients with Long COVID.

Keywords: Long COVID, Endocrine Dysregulation, Hypothalamic-Pituitary-Adrenal Axis, Hypothalamic-Pituitary-Gonadal Axis, Cortisol Dysfunction, Thyroid Disorders, Insulin Resistance, Metabolic Dysregulation, Post-Viral Endocrinopathy, SARS-CoV-2, Hormonal Imbalance.

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1. INTRODUCTION

The COVID-19 pandemic which is caused by SARS-Cov-2 virus mainly causes respiratory disease. The first case was identified in Wuhan, China in late 2019 hence its name: Covid 19. It is transferred through respiratory droplets which leads to a wide range of symptoms. It enters the human body via angiotensin converting enzyme 2 receptor (ACE2) which is present in respiratory tract, heart, kidneys. The virus binds to these receptors and replication begins. In the respiratory system the virus infects the alveolar type 2 cells which leads to alveolar damage, hyaluronic acid accumulation leading to respiratory failure and in severe cases it lead to acute respiratory distress syndrome (ARDS). As for the cardiovascular system, about 12% of hospitalized patients have experienced Myocardial injury and blood clotting disorders, and around 30% of patient had experienced acute kidney injury due to viral invasion or hypoxia. Some patients' immune response experienced Cytokine storm which causes hyperinflammation leading to systemic damage and Lymphopenia.
The global spread is calculated by a basic reproduction number (Ro) which ranges from 2-3, driving rapid transmission between elderly individuals and those with comorbidities. Meaning, they were at a high risk for mortality and infection. In this review, we will be discussing the long term consequences of COVID, its effect on the bod's endocrine system, and, gland and Hormone dysregulation.
There are 4 phases in infected individual:
1. Incubation phase
2. Moderate symptomatic phase
3. Severe symptomatic phase and the last

4. Critical phase
and after all this there are recovery phase and Long covid also known as Post Acute Sequalae of SARS-CoV-2.

There is evidence that suggest, Long covid is associated with disruption in Endocrine system which leads to disruption and dysregulation of various hormones in our body.

The endocrine system plays an important role in maintenance of body's homeostasis, metabolism regulation, growth, development and reproductive functions and response to stress and disturbance in this system can lead to wide range effects on health and wellbeing. Recent findings have highlighted significant alterations in several hormonal axes in Long covid individuals that includes Hypothalamic-Pituitary-Adrenal (HPA) axis, Hypothalamic-Pituitary-Gonadal (HPG) axis, Reduced Cortisol levels, Thyroid function, Growth hormone secretions, and Reproductive hormones.

The mechanism that causes the endocrine disruptions are not completely understood. But there are several hypotheses have been proposed which includes:
Viral damage to endocrine organs in which SARS-Cov-2 virus uses ACE2 present in hypothalamus, pituitary, pancreas, thyroid, and adrenal glands to enter the cell.

1. Autoimmune response mediated by immune reactions in which immune system attacks the thyroid gland.
2. Low grade inflammation and cytokine activation which leads to disruption of hormonal balance.
3. Mitochondrial dysfunction results in ATP deficits and that results in poor functioning of endocrine organs.

This paper aims to give an overview of the endocrine changes seen in Long Covid and understanding the main mechanisms that causes the disruption and its impact on patients' wellbeing. With the help of the research findings and observation, we hope to contribute to the better knowledge and understanding of Long Covid in endocrine aspects. This study and knowledge of this topic is vital for developing treatments, diagnostic protocols, and management strategies for affected individual. Furthermore, insights from studying the endocrine manifestations of Long Covid may have a more broader implication to our understanding of the relationships between viral infection, immune response and hormonal health.

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2. OBJECTIVE

This review aims to provide a comprehensive overview of the endocrine dysregulation caused by Long COVID by its effects on different hormonal axes, specifically the hypothalamic-pituitary-adrenal (HPA) axis, hypothalamic-pituitary-gonadal (HPG) axis, and thyroid function. The authors of this study focus on the evaluation of these defects according to the molecular level of endocrine tissues as well as the contributions of autoimmune attacks and mitochondrial dysfunction. Furthermore, the article focuses on the metabolic outcomes of Long COVID such as insulin resistance and glucose metabolism alterations alongside discussion of the potential treatment and diagnosis of the endocrine complications due to post-viral sequelae.

3. MATERIALS AND METHODS

41 articles have been analyzed for the literature review. Keywords such as Long COVID, Endocrine Dysregulation, Hypothalamic-Pituitary-Adrenal Axis, Hypothalamic-Pituitary-Gonadal Axis, Cortisol Dysfunction, Thyroid Disorders, Insulin Resistance, Metabolic Dysregulation, Post-Viral Endocrinopathy, SARS-CoV-2, Hormonal Imbalance were used for the literature searches in databases such as Google Scholar and PubMed.

4. RESULTS

Our review reveals distinct hormonal aberrations in Long COVID patients. Among these are disorders involving the HPA, HPG, and thyroid axes. Studies related to HPA function reveal a considerable decline in cortisol due to impaired activity of the HPA axis. This contributes to persistent fatigue along with immune dysregulation. Similar hypo functionality is noted in the HPG axis wherein males are given an evidence of falling testosterone levels while females demonstrated menstrual irregularities that could be linked to sexual dysfunction and gonadal hormone suppression. Conditions such as hypothyroidism and transient thyrotoxicosis are not rare at present but demonstrate more of direct viral damage to the thyroid than have otherwise been seen as purely autoimmune mediated thyroid dysfunction.

New-onset diabetes as well as insulin resistance have been reported with respect to metabolic derangement in Long COVID probably coming from the combined causes of pancreatic β-cell dysfunction, chronic inflammation, and oxidative stress. Hence, these findings call forth specific endocrine-based treatments directed at long-term sequelae of SARS-CoV-2 infection.

5. DISCUSSION

5.1 Impact of Long COVID on the Hypothalamic-Pituitary-Adrenal (HPA) Axis

- **HPA AXIS - COMPONENTS AND FUNCTION**

  The main stress response system is the hypothalamo-pituitary-adrenal (HPA) axis, and when it is activated, its main role is to release glucocorticoids, which trigger short-term physiological reactions to stress. It is mostly composed of the pituitary, adrenal, and hypothalamic glands.

  Corticotrophin-releasing hormone (CRH), its co-secretagogue arginine vasopressin (AVP), and other neuropeptides that regulate the HPA axis are produced by neurons in the paraventricular nucleus (PVN). In response to stress, the anterior pituitary gland's corticotrope cells produce and release ACTH, which increases adrenal androgens and triggers the adrenal glands to release cortisol. The synthesis and secretion of CRH, AVP, and ACTH are adversely regulated by cortisol. Numerous locations in the brain and pituitary have mineralocorticoid receptors (MRs) and/or glucocorticoid receptors (GRs), which are responsible for the negative feedback impact of cortisol.

  The body can't cope with stressful situations including infections, trauma, surgery, or extreme mental stress when there is a lack of cortisol.

  HPA AXIS REFLEX

  By suppressing the hypothalamic pituitary-adrenal axis response, SARS-CoV-2 produces less cortisol, as shown by the HPA axis reflex. The control of both innate and adaptive immune responses is impaired by this decrease in cortisol. Neurons in the PVH (a hypothalamic nucleus of the central autonomic network) release CRH in response to nerve fibers from the NTS. The thalamus, amygdala, hypothalamus, and brainstem nuclei make up the central autonomic network

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(CAN), which combines emotional, sensory, and cognitive stimuli to generate endocrine and autonomic reactions.

● The parvo-cellular PVH nucleus, which links the thalamus, amygdala, hypothalamus, and brain stem nuclei, contains hypothalamic neurons that secrete corticotrophin-releasing hormone (CRH) in response to efferent VN fibers from the NTS (nucleus tractus soliatarius). These areas work together to produce autonomic, behavioral, and endocrine responses by integrating emotional, sensory, and cognitive stimuli.

● The pituitary gland releases adrenocorticotropic hormone (ACTH) in response to CRH stimulation. After reaching the adrenal glands, ACTH stimulates the synthesis of cortisol. Through its interaction with the glucocorticoid receptor (GR), cortisol in turn prevents the activation of both adaptive immunity (spleen T cells) and innate immunity (splenic and tissue macrophages).

● As a transcription factor, glucocorticoids (GCs) bind to the cytoplasmic GR and facilitate its translocation into the nucleus. GCs reduce inflammation in a number of ways, which includes by increasing the production of IKBa protein, which inhibits the activity of nuclear factor kappa B (NF-KB), a factor that activates immune response genes. GCs also affect immune cells such as monocytes, macrophages, and T helper (Th) lymphocytes, affecting their migration, survival, and role.

According to a neurovisceral integration model, persistent alterations in cortisol production, as well as increased levels of proinflammatory cytokines and acute-phase proteins, are all resulting from impaired VN tone, which is often seen in LC patients.

PATHOPHYSIOLOGY -

- Molecular mimicry between ACTH AND SARS-CoV: SARS-CoV expresses specific amino acid sequences that function as molecular mimics of the host adrenocorticotropic hormone (ACTH). The first 24 amino acids of ACTH (ACTH1-24) are highly conserved across mammalian species, while the less conserved region is represented by ACTH25-39. The antigenically important positions for mammalian ACTH are represented by six amino acids at positions 26, 29, 31, 33, 37, and 39. SARS (and influenza virus) contain numerous permutations of amino acid sequences that are homologous to these probable ACTH key residues. Antibodies against SARS-CoV-2 may work together to compromise the body's stress response and possibly affect the cortisol response during LC.
- Direct mitochondrial damage: Its carried out by the virus, which replicates within these organelles, and the cellular oxidative imbalance, cannot be countered in individuals who develop LC. This is because their anti-inflammatory actions are inconsistent due to diminished vagal tone and direct injury to the endocrine glands of the HPA axis. Both Ach and cortisol contribute in lowering inflammation by influencing the activity of innate and cell-mediated immunity, attenuating endothelial and platelet activation, and altering mitochondrial function, which is critical for cellular energy production and anti-inflammatory actions.
- HPA axis disruption: During SARS-CoV-2 infection, both vagal signaling and axis function appear to be affected, potentially impairing HPA Axis reflex at various phases. Impairment of the VN neuro-endocrine reflex, coupled with potential direct injury to endocrine glands by SARS-CoV-2, can lead to diminished cortisol secretion, that was a characteristic of LC. As a result of this defective HPA axis feedback regulation, many patients suffered from hypercortisolism.
- When researchers looked into the autopsies of people who had died from influenza and COVID-19 infections, It was seen that all those affected by COVID-19 had adrenalitis, but only a small percentage of those affected by influenza showed signs of severe damage to the structure of the adrenal cortex. Moreover, extensive fibrosis and degeneration in the thyroid gland was something that was commonly observed in patients with COVID-19 infections that lead them to the ICU for over a week.

BIOCHEMICAL EVIDENCE OF HPA AXIS INVOLVEMENT

Leow et al. were the first to report findings to prove this. Sixty-one SARS outbreak survivors were assessed three months after they recovered and then at other intervals after that. Evidence of central hypercortisolism was found in 40% of patients; most of these cases went away in less than a year. Low dehydroepiandrosterone sulfate and central hypothyroidism were also

present in a small number of subjects. A condition of temporary hypothalamo-pituitary dysfunction might have resulted from either direct hypothalamic injury or reversible hypophysis. In reality however, autopsy studies have found the hypothalamus to have edema, neuronal degeneration, and the SARS-CoV genome. Since the pituitary and hypothalamic tissues do express ACE2, they may be viral targets.

CLINICAL IMPLICATIONS

- Patients with lymphopenia had higher serum cortisol and than those without lymphopenia. However, absence of lymphopenia in patients with COVID-19 could be used a marker of hypercortisolism (absolute or relative).
- Due of adrenal insufficiency, LC has symptoms that are similar to those of adrenal fatigue (AF). After prolonged stress or trauma, the cellular energy demand increases, making it difficult for the adrenal glands to supply to it, which leads to AF, a stress-related illness. Though recovery may take up to two years, unlike LC, AF is reversible with considerable dietary changes, supplements, and lifestyle alterations, despite the similarities in clinical presentation.
- The hypocortisolemia and hypoactivation of the HPA axis associated with long COVID are similar to the "sickness syndrome" associated with SARS. Prolonged "inadequate" cortisol secretion may prevent immune system activation, resulting in immunological dysregulation and symptoms of sickness syndrome.
- The notion is consistent with Addison's disease, which is typified by symptoms including exhaustion, weakened muscles, difficulty concentrating, brain fog, nausea, hair loss, melancholy, and anxiety. Because cortisol does not inhibit the generation of proinflammatory cytokines, Addison's illness is linked to immunological disruptions, including elevated levels of IL-6.

5.2 Thyroid Dysfunction Associated with Long COVID

ROLE OF THE THYROID GLAND

- In vertebrates, the thyroid is a butterfly-shaped endocrine gland. It is located in the neck beneath the Adam's apple or in front the trachea and larynx, and it is made up of two interconnected lobes.
- Triiodothyronine (T3), thyroxine (T4), and calcitonin, a peptide hormone, are the three hormones it secretes. Thyroid hormones affect children's growth, development, protein synthesis, and metabolic rate. Calcium homeostasis is influenced by calcitonin.
- The anterior pituitary gland secretes thyroid-stimulating hormone (TSH), which controls the release of the two thyroid hormones. The hypothalamus produces thyrotropin-releasing hormone (TRH) which regulates TSH.

HOW LONG COVID AFFECTS THE THYROID GLAND

Studies have indicated several mechanisms through which Long COVID may contribute to thyroid dysfunction:

1. **Direct viral destruction**: Thyroid follicular cells had high expression levels of two known SARS-CoV-2 entry points: transmembrane serine protease 2 (TMPRSS2) and angiotensin-converting enzyme 2 (ACE-2). Parenchymal damage caused by virus could be responsible for disturbances in thyroid function. The destruction of the thyroid parenchyma, which is characteristic of the initial phase of this disease, is associated with the release of thyroid hormones and the manifestation of a transitional phase of thyrotoxicosis.
2. **Hypothalamic-Pituitary-Thyroid Axis Disruption:** ACE-2 receptors are expressed by the thyroid and pituitary glands in addition to the lungs. Therefore, in patients with COVID-19, the hypothalamic-pituitary-thyroid axis may be directly susceptible to disruption. As a result, it may impact thyroid hormone central regulation, leading to metabolic alterations.
3. **Triggering Thyroid autoimmunity:** The viral infection itself may trigger an immunological reaction that results in a rise in antithyroid antibodies, and thus may be a primary cause of autoimmune thyroid conditions such as Graves' disease or Hashimoto's thyroiditis.

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TYPES OF THYROID DYSFUNCTION ASSOCIATED WITH LONG COVID

1. **Euthyroid Sick Syndrome (ESS)/Nonthyroidal illness syndrome:** It consists of a series of alterations to the main part of the HPT axis and changes to the metabolism of thyroid hormones (TH) in various TH target organs. Numerous acute or chronic systemic illnesses, such as cancer, respiratory, cardiovascular, and infectious disorders, can cause NTIS.

   - It is divided into two stages: **Phase I** or the acute phase, is characterized by decreased conversion of T4 to T3, decreased synthesis of thyroid hormone-binding proteins including albumin and thyroid-binding globulin, decreased pulsatile TSH secretion, and increased thyroid hormone metabolism due to suppression of deiodinase type I activity. During **phase II**, the chronic phase, thyrotropin-releasing hormone (TRH) and TSH secretion declines as a result of increased IL-6, IL-18, and TNF-a secretion.

   - Low plasma T3, low or normal plasma T4, or elevated plasma reverse (rT3) in the presence of normal or slightly lowered and TSH are the most common hormonal alterations.It has been demonstrated that COVID-19 severity and mortality are correlated with significantly lower serum concentrations of fT3 (free T3)

   - Released during illness, cytokines are thought to be a significant predictor of NTIS because they impact many genes involved in TH metabolism.

2. **Hypothyroidism:**

   - Previous study has identified instances of primary hypothyroidism linked to COVID-19. In the THYRCOV research, hypothyroidism was discovered in just 5.2% of 287 patients admitted to a non-intensive care hospital. In particular, 5.2% (15/287) of patients in the Lania et al. trial experienced primary hypothyroidism, which was overt in 10% of cases and subclinical (i.e., FT3 and FT4 in the reference ranges) in roughly 90% of cases.

   - A recent study found that patients infected with COVID-19 who had a high level of TPO antibodies and/or a family history of thyroid disease have a considerable prevalence of subclinical hypothyroidism.

   - A small number of patients have been reported to have abnormal endocrine results at the hypothalamus or pituitary level of the HPT axis that are consistent with central hypothyroidism caused on by SARS-CoV-2 infection.

3. **Thyrotoxicosis:**

   1. **Subacute thyroiditis** (SAT)is a self-limiting thyroid disorder caused by an inflammatory process that is either viral or post-viral.

      - SAT is commonly characterized by localized hypo echogenicity in the thyroid gland, a high circulating C-reactive protein (CRP) concentration, and a high ESR. The main etiology behind this is poor thyroidal absorption of radioiodine caused by thyroid destruction and a decrease in TSH brought on by thyrotoxicosis.

      - **Three distinct phases** often characterize the clinical course of SAT: thyrotoxicosis in the initial months, followed by hypothyroidism for roughly three months, and finally euthyroidism.

      - Thyroid disorders may be caused on by virus infections through the release of antigens (through necrosis or apoptosis), the formation of altered antigens or molecular mimicry, the release of proinflammatory cytokines and chemokines, the induction of aberrant HLA-DR expression, and the activation of Toll-Like Receptors (TLRs).

      - Goiter, exhaustion, palpitations, sweating, insomnia, anxiety, tremor, and weight loss are some of the symptoms that may indicate early-onset SAT.

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- Steroid and non-steroidal anti-inflammatory medicines (NSAIDs) were successful in all patients to provide a rapid remission of thyrotoxicosis and normalization of inflammatory indicators.
- Hashimoto's thyroiditis and other autoimmune thyroid disorders may manifest clinically in COVID-19 individuals mainly due to the involvement of Th1-mediated cellular immunity and T helper (Th) 2-mediated autoantibody production.
- According to earlier research, thyroiditis during COVID-19 may be brought on by an increase in IL-6 release and/or T-cell cytotoxicity as a result of a hyperinflammatory illness.

2. **Silent thyroiditis:**

- According to the study by Lania et al., a significant portion of patients (58/287, 20.2%) who were admitted to non-intensive care units for COVID-19 had thyrotoxicosis without any neck discomfort, which most likely indicated that they had painless (silent) thyroiditis associated with COVID-19.
- An inverse and strong correlation between serum TSH and IL-6 levels was found, supporting the theory of inflammatory-mediated thyroid gland damage. Of the 58 patients with thyrotoxicosis, 31 (53.4%) had overt thyrotoxicosis, which is defined as low TSH values with FT3 and/or FT4 above the reference ranges.
- Two key characteristics that help differentiate painless thyroiditis from subacute thyroiditis are the lack of neck pain and the presence of TPOAb.

PATHOLOGICAL AND MORPHOLOGICAL CHANGES IN THYROID GLAND:

A research by Lui et al. examined 79 individuals for a median of two months following a COVID-19 diagnosis.

The thyroid gland volume was less than in control participants, according to the scientists, although the difference did not attain statistical significance. The authors discovered that **patients' thyroid gland volumes were noticeably less**. Having a greater viral load of SARS-CoV-2, particularly in men. The mechanisms underlying COVID-19's impact on the thyroid gland are not entirely understood currently.

Additionally, Yanachkova, Stankova, and Staynova's study from 2023 58 (51.3%) individuals had **nonhomogeneous, mildly hypoechoic thyroid alterations** on ultrasonography. Half of them had **poorly defined**, **hypoechoic, and poorly blood-flowing regions**. Thyroid nodules were found in 26 patients (23.1%).

TSH levels significantly decreased, according to the results of a longitudinal comparison of TSH levels at two months (baseline) and at the follow-up one month later.

Histological analysis of the thyroid has shown **widespread apoptosis** in place of a **lymphocytic infiltrate**, indicating destructive thyroiditis, which may be the cause of thyrotoxicosis.

Pathological abnormalities in the thyroid gland and other organs have been found in post-mortem studies of people who died from COVID-19. Surprisingly, nevertheless, **no serious thyroid follicular destruction** have been found.

COVID MEDICATIONS COULD AFFECT THE THYROID GLAND:

- When evaluating the impact of COVID-19 on thyroid function, it is also important to consider the effects of several drugs employed in the treatment of the virus. Antiplatelet medicines, anticoagulants, and corticosteroids are commonly used to treat COVID-19 infection due to its multisystemic involvement, endothelial dysfunction, inflammation, and vascular and thrombotic events.

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- Acetylsalicylic acid, for instance, causes changes in plasma protein binding that result in higher free hormone fractions, changed fT4 to fT3 conversion, and consequently momentarily decreased TSH levels. Thyroid hormone synthesis eventually declines as a result of this.
- Numerous other investigations have demonstrated that pharmacological glucocorticoid administration causes an initial decrease in TSH secretion in both humans and rats, which resolves upon glucocorticoid withdrawal. One notion is that glucocorticoids have the ability to directly inhibit the hypothalamic release of TSH-releasing factor (TRH). Moreover, it has been demonstrated that the human hypothalamus paraventricular nucleus's expression of TRH mRNA is decreased by high-dose glucocorticoids. Due to pituitary axis suppression, dexamethasone therapy also lowers endogenous TSH levels. It also lowers active fT3 levels, potentially by inhibiting conversion processes, plasma protein binding, and deiodinase activity.
- Additionally, thyroid hormones are displaced from their binding proteins by heparin. TSH levels slightly decline as a result, but fT4 and fT3 levels rise. Heparin primarily affects the thyroid gland by interfering with the determination of serum levels of free thyroid hormone. Intravenous heparin administration has been shown to cause a five-fold increase in FT4 concentration in as little as two to fifteen minutes.

5.3 Sex Hormone Imbalances and Reproductive Health Implications

Long covid has an important impact on the human reproductive system and particularly disrupting hormone balance in both women and men. These hormone imbalances affect the reproductive health and the duration of long covid, which leads to the symptoms like hormonal imbalance such as menopause, hypogonadism and other endocrine disorder which further complicates the recovery of the patient.

Impact of SARS-CoV-2 on Menstrual Cycle:

- SARS- CoV-2 uses the receptor called ACE2 receptors, which are found in the ovaries and in uterine tissues.
- The virus utilizes these receptors to infiltrate into the ovaries, which can disrupt follicular development, oocyte maturation and hormonal regulation, and thus leads to menstrual irregularities.
- Furthermore, psychological stress as a result of long covid can interfere with hypothalamic-pituitary-gonadal (HPG) axis dysfunction, which can lead to menstrual cycle irregularities.

Impact of Renin- Angiotensin System (RAS) on Female Reproductive Health:

- Renin-Angiotensin System plays an important role in reproductive health. The Angiotensin-Converting Enzyme, which converts angiotensin 1 to angiotensin 2, to regulate vascular tone and reproductive function. Angiotensin 2 helps with the uterine blood flow, embryo implantation, and steroid hormone synthesis. Lastly Angiotensin (1-7) which has an opposite effect of Angiotensin 2, promotes vasodilation and endometrial health.
- Since ACE2 receptors are found in the ovarian tissues, viral infection may interrupt follicular maturation, hormonal imbalance and fertility.
- Imbalance between Angiotensin 2 and Angiotensin (1-7) can impair reproductive function and increase oxidative stress, which can affect the quality of oocyte.

Hormonal Disruption and their impact on Reproductive Health.

- Hormonal disruption affects menstrual cycle, fertility and pregnancy.
- Inflammation due to viral infection can affect the hypothalamic-pituitary-gonadal (HPG) axis, which disturbs the gonadotropin release and ovarian function.

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- This inflammation reduces the quality of the oocyte and affect follicular development hence leading to lower fertilization rates.
- Inflammatory cytokines suppress the function of the ovary and impair estrogen production. If there is an increased activity of these cytokines, implantation becomes difficult and success rate of early pregnancy reduces.

Long COVID and Perimenopause and Menopause:

- Long COVID and Perimenopause present common symptoms that overlap each other such as headaches, fatigue, dizziness, palpitations, muscle aches, brain fog and poor concentration.
- Women in the age of 40-60 years are at higher risk of Long COVID.
- Women with long COVID often complain of menstrual irregularities which affects its frequency, duration and intensity of the period.
- Long Covid in women may exacerbate the hormonal imbalance, which could lead to menopausal symptoms and thus prolonging their recovery.
- Menopausal symptoms should be recognized and treated when identified, as this could improve both physical and mental health and reduce long-term risks (eg: cardiovascular diseases, osteoporosis, type 2 diabetes).

Impact of SARS-CoV-2 in Male Reproductive Health:

- Long COVID is a high stress disease, such viral infection triggers immune response, which leads to an increase in oxidative stress (OS) and reactive oxygen species (ROS), causing impairment of sperm function.
- SARS-CoV2 causes infection of male accessory glands which are seminal vesicle and prostrate, and this infection reduces the semen quality and fertility.
- The virus attacks the germ cell line or spermatogonia which causes the failure of healthy sperm production. Moreover, the infection causes inflammation which leads to tissue and cellular damage in the testes and disrupts sex hormone secretion.
- The number of Leydig cells or testosterone-producing cell is reduced in patient with covid infection, leading to low testosterone levels. This low testosterone level causes disruption of hypothalamic-pituitary-gonadal (HPG) axis. The SARS-CoV2 virus replicates in these Leydig cell which causes hypogonadotropic hypogonadism.

5.4 Metabolic Dysregulation: Insulin Resistance and Glucose Metabolism

Patients with Long covid has shown significant health concerns due to metabolic dysregulations, in particular Insulin Resistance and Glucose Metabolism. Non-diabetic patients who later got diagnosed with Long COVID presented with elevated blood glucose level, insulin resistance and advancing into Type 2 Diabetes.

Insulin Resistance in Long COVID:

- Patients with Long COVID developed Insulin Resistance (IR) within a year of Infection, particularly Patients with predisposing risk factors like Obesity and Metabolic Syndrome. These Patients had elevated blood glucose level and leading to risk of Insulin Resistance and affecting Glucose Metabolism.
- Inflammatory Markers, like high-sensitivity C-reactive protein (hs-CRP) and Erythrocyte Sedimentation Rate (ESR) were elevated during COVID infection. These inflammatory markers were negatively correlated with Insulin sensitivity, which then suggests that, during acute COVID infection, the immune response leads to metabolic disturbances.

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- Cytokines like IL-6 and TNF-α have prolonged activation and release during both Acute Infection and Long COVID, leading to disruption of Insulin signaling which causes Insulin Resistance. This further worsens endothelial dysfunction and vascular inflammation, which may impair glucose uptake in tissues.

Glucose Metabolism Dysregulation in Long COVID:

- Fasting Blood Glucose is often elevated in patients with Long COVID, and they may develop hyperglycemia. Most patients after one year after recovery from the infection, hyperglycemia progresses to Type 2 diabetes.
- This sustained increase in blood glucose leads to direct metabolic alterations which are caused by persistent inflammation and immune dysregulation often associated with Long COVID.
- A significant risk factor for long covid is Obesity. After one year after recovery from SARS-CoV2 around 62% of patients with over the BMI of 30kg/m² had increased blood glucose level leading to glucose metabolism disturbance with visceral fat causing Insulin Resistance in Long COVID patients.
- Long COVID patients with obesity have dysfunctional adipose tissues, which may further impair Insulin sensitivity leading to abnormal glucose metabolism and increasing the risk of developing Diabetes.

Mechanism Linking Long COVID to Metabolic Dysregulation:

- Acute COVID-19 infections cause exaggerated response from immune cells like monocytes, macrophages and neutrophils which can lead to pancreatic damage and insulin secretion impairment which often results in Insulin Resistance. This Hyperinflammatory state leads to metabolic changes in Long COVID.
- SARS-CoV-2 targets the adipose tissue and pancreatic islet which produces Insulin and thus affects the Insulin sensitivity, which leads to reduced Insulin production and function.
- Patients with severe COVID-19 infection may have low cortisol level due to adrenal insufficiency and this can interrupt metabolic processes like lipolysis and adipogenesis. This further results in metabolic dysfunction and causes Insulin Resistance in Long COVID patients.

Mechanism Linking COVID-19 to Type 2 Diabetes Development:

- Glucose metabolism and insulin sensitivity are regulated by ACE2 receptors which are expressed in pancreatic β cells. These receptors are vulnerable to viral attacks, allowing the virus to enter and disrupting normal insulin secretion and glucose regulation.
- The viral infection causes mitochondrial dysfunction, which leads to increased reactive oxygen species (ROS) production. This increase in ROS results in production of oxidative stress promoting β-cell apoptosis and causing Insulin Resistance.
- The SARS-CoV-2 infection disrupts the function of ACE2 receptors, which leads to overactivation of renin-angiotensin-aldosterone system (RAAS), thus increasing the angiotensin 2 levels which causes the activation of NF-KB pathway leading to inflammation, activation of NADPH oxidase leading to Oxidative stress and lastly vasoconstriction and endothelial dysfunction which impairs pancreatic and muscle glucose uptake.
- The increased level of angiotensin 2 reduces insulin sensitivity by inhibiting the Insulin receptor phosphorylation, which then leads to impaired glucose uptake in muscles and adipose tissues resulting in hyperglycemia.
- Islet amyloid polypeptide (IAPP) deposition in β-cells in common in patients with Type 2 Diabetes Mellitus. During SARS-CoV-2 infection this amyloid deposition increases leading to β-cell dysfunction, this then causes progressive β-cell loss resulting in alteration of glucose metabolism.

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5.5 Alterations in Cortisol and Stress Response Mechanisms

Cortisol is a glucocorticoid hormone that released by the adrenal glands. Cortisol is widely known as the "stress hormone." However, it has many important effects and functions throughout the body including:

- Regulating the body's stress response
- Regulating metabolism
- Suppressing inflammation
- Regulating blood pressure
- Increasing and regulating blood sugar
- Helping control the sleep-wake cycle

Cortisol concentrations fluctuate during the day, typically peaking early in the morning after waking followed by a rapid decline during the day. Normal values for a blood sample taken at 8 in the morning are 140 to 690 nmol/L.

CORTISOL DYSREGULATION AND ASSOCIATION WITH STRESS RESPONSE

In Long COVID, serum cortisol levels are generally decreased (hypocortisolemia), suggesting a dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis as discussed in an earlier section. In a study we reviewed on probable COVID-19-infected cases with no symptoms of adrenal insufficiency and/or glucocorticoid therapy, baseline serum cortisol levels were measured within 48 hours of the patients' admission. In their investigation, patients with COVID-19 infection had a median serum cortisol concentration of 619 nmol/L compared to 519 nmol/L in those who were not infected with COVID-19. The ideal cortisol cutoff was determined using maximally selected rank statistics. Patients with COVID-19 whose baseline cortisol concentration was equal to or less than 744 nmol/L (268 patients [67%]) had a median survival of 36 days, whereas patients with COVID-19 whose cortisol value was more than 744 nmol/L (135 patients [33%]) had a median survival of 15 days.
Multivariable analysis showed that a doubling of cortisol concentration was associated with a significant 42% increase in the hazard of mortality.

Whereas in acute COVID-19, increased serum cortisol (hypercortisolemia) is observed as an adaptive survival mechanism to stimulate changes in metabolism, cardiovascular function, and immune regulation via the HPA axis to overcome the psychological and physiological stress caused by Covid-19. Stress has the ability to reduce cortisol metabolism and cortisol-binding globulin (CBG) metabolism, resulting in increased cortisol function.

LINKING HPA AXIS DYSFUNCTION AND CORTISOL DYSREGULATION IN LONG COVID

Cortisol production is regulated by the hypothalamic-pituitary-adrenal (HPA) axis. In healthy individuals, plasma cortisol secretion is controlled by the release of adrenocorticotropic hormone (ACTH) released by the pituitary gland. ACTH secretion, in turn is regulated by corticotrophin-releasing hormone (CRH) produced by the hypothalamus. To prevent possible side effects of Glucocorticoid overexposure in peripheral tissues most of the plasma cortisol is bound to corticosteroid-binding globulin (CBG). During sepsis due to COVID, there is often an impairment of HPA function. In some patients, reduced glucocorticoid metabolism and depletion of CBG'S enhance cortisol bioavailability, which might inhibit ACTH release as a consequence of the negative feedback mechanism. Furthermore, a significant number of patients develop critical illness-related corticosteroid insufficiency (CIRCI), which outlines an inadequate level of morning cortisol. Hypercortisolism is mostly presented as the main hormonal disease diagnosed in patients with COVID-19 after three months of recovery. A study reviewed revealed that subjects with moderate-to-severe COVID-19 infection have statistically more frequent hypocortisolemia compared to subjects with mild COVID-19 infection. According to recent research, ACTH and SARS-CoV-2 share similarities in certain amino acid sequences. This suggests that COVID-19 infection may encourage the formation of cross-reacting antibodies, which could deactivate endogenous ACTH and kill cells that secrete ACTH. In addition to this, a direct injury on the adrenal cortex, due to the expression of ACE2 receptors in the zona fasciculata and reticularis, impairs the glucocorticoid synthesis.

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PROLONGED CORTICOSTEROID USE IN LONG COVID

It is, indeed well known that a prolonged treatment with high corticosteroid doses enhances COVID19 – associated mortality through induction of immune deficiency, enhanced risk of secondary infections, and development of HPA axis dysfunction. It may also lead to high risk of adrenal insufficiency that may take up to 6 months to revert. In COVID-19 patients, development of cortisol deficiency can be a result of both the steroid treatment or the virus itself.

5.6 Long-Term Consequences of Endocrine Dysregulation in Long COVID

ACE2 receptors have been found in a number of endocrine glands, including the pancreas, thyroid gland, adrenal glands, ovaries, and testes. The presence of the ACE2 receptors on the endocrine system hints at alternations in endocrine function caused by SARS-CoV-2. Several endocrine disorders such as autoimmune thyroiditis, male infertility , adrenal insufficiency and diabetes have been reported in association with post-COVID-19 disease.
In accordance with numerous articles, a brief overview of endocrine complications have been summarized below:

1. **THYROID GLAND DYSFUNCTION:**
   According to a study reviewed, significantly higher levels of thyroid-stimulating hormone (TSH) and anti-thyroid peroxidase (aTPO) antibodies and lower free triiodothyronine (FT3) and free tetraiodothyronine FT4 levels were found in the case group examined six months after COVID-19 compared to the control group consisting of age and sex-matched individuals before the COVID-19 pandemic. This study indicated potential autoimmune hypothyroidism in patients recovered from COVID-19.
   Several reports of subacute thyroiditis, autoimmune thyroiditis, and HPA axis dysfunction after SARS-CoV2 infection have also been published.
2. **TESTES**
   Male patients that recovered from COVID-19 had significantly lower levels of testosterone potentially due to direct damage to the Leydig cells, which were observed during the acute phase of COVID-19.
   Evaluation of male reproductive health after three months from COVID-19 infection showed the presence of erectile dysfunction in one-third of tested subjects.
3. **ADRENAL INSUFFICIENCY**
   It was observed that the prolonged use of steroids for several weeks to treat COVID-19, in some cases, led to acute adrenal insufficiency. Findings also show that SARS-CoV-2 can be found in the adrenal glands of deceased COVID-19 patients and can infect adrenal cells in laboratory settings. Thus it is reasonable to assume that COVID-19 may cause long term damage to the adrenal glands.
4. **GLUCOSE METABOLISM**
   In both healthy and obese individuals, an increasing amount of research has shown that COVID-19 infection can cause insulin resistance, hyperglycemia, and even diabetes. According to a new study, people without diabetes may be more susceptible to insulin resistance if they have COVID-19. This could result from a number of things, such as immunological dysfunction and inflammation brought on by the virus or the adverse effects of Glucocorticosteroid therapy for COVID-19. This study also revealed that at 3- and 6-month follow-ups after infection, fasting levels of C-peptide and HOMA for beta cell function were significantly increased implying high insulin resistance.
   The COVID-19 infection may also trigger the presentation of new diabetes mellitus cases. Recent clinical evidence has suggested an effect of SARS-CoV-2 with presentation of diabetic ketoacidosis (DKA) and hyperosmolarity, usually requiring higher doses of insulin to be controlled.
   SARS-CoV-2 can also cause the damage of the pancreatic islets subsequently resulting in loss of insulin secretory capacity. Pancreatic islets express ACE2, facilitating damage during the infection. A study that presented data from both human pancreatic islet cultures and COVID-19 full-body postmortem examinations indicated that SARS-CoV-2 infects and replicates in human islets, inducing morphological, transcriptional, and functional changes with subsequent reduction of insulin-secretory granules and impairment of glucose-dependent insulin secretion of β cells

The possibility of permanent dysregulation of glucose homeostasis or an increased predisposition to developing overt diabetes in COVID-19 survivors remains under investigation. Long-term studies are needed to determine the full scope of these late complications.

5.7 Therapeutic Strategies and Future Directions in Managing Hormonal Changes

The COVID-19 pandemic may have lasted less than two years, but it has had various effects on human life, casting a long shadow. Long-term sequelae of COVID continue to affect the systemic well-being of millions of patients, causing an overload of the existing healthcare resources. Going forward, the medical community needs to take a multi-pronged approach to tackle this complex issue, as well as furthering research into the topic.

Research Gap

While extensive research has been carried out over the past few years into COVID-19 and its impact, most of it understandably focuses on symptomatic management and other algorithmic approaches. Further progress is the need of the hour, with a particular focus on systemic sequelae that may lie dormant.

Improved Multidisciplinary Care

Diabetologists, endocrinologists and GPs need to undertake a continued coordinated approach towards the long-term endocrine health of COVID patients. The presence of comorbidities is a particularly prevalent factor to be taken into consideration, as it significantly affects recovery of endocrine function.

Lifestyle Modifications: a Potential Resource

This era of clinical endocrinology is not just about treating pre-existing conditions- Preventive health is the need of the hour. However, the changing diet composition, sedentary routines and personal habits of patients pose a serious threat. These lifestyle patterns have been identified as key causal agents behind numerous endocrinopathies like Type 2 Diabetes and infertility. Improving these factors offers a simple and straightforward way to retard the progression of endocrine disease.

Specifically, omega3 fatty acids and vitamins counter viral-induced inflammation not only during acute infection, but also counter long COVID in various ways. Apart from preserving brain structure via alterations in phospholipid metabolism, these ‘good fats’ also reduce oxidative stress. Furthermore, they partially undo the deleterious effects on the Renin-Angiotensin-Aldosterone System (RAAS) by long-standing COVID.

Continuous Monitoring of Gonadal Function

Fertility rates have followed a general pattern of decline over the past few decades, with numerous etiologies that need to be identified and managed in different ways. Thus, the impact of COVID-19 infection on gonadal function is of vital importance, both in male and female factor infertility.

While there has been a demonstrable decrease in Testosterone levels during the acute phase of COVID infection, there exists very little evidence to suggest any persistent decline in gonadal function.

Ovarian function, however, has shown more concrete association. In an international survey with long-term COVID-19 patients, more than one-third reported alterations to their menstrual cycle in the months following the infection, including the development of irregular periods, unusually heavy periods, and postmenopausal bleeding.

Going forward, the impact of COVID infection over a period of five to ten years is still unknown. So, continuous monitoring must be upheld, with periodic assessments of gonadal function/hormone levels.

Specific Anti-inflammatory Molecules

While broad management modalities have their own utility, present-day healthcare also features a tailored approach for each and every patient. Unsurprisingly, the latest developments in endocrine health reflect the same pattern.

One particularly interesting example is the use of individual molecules that target specific components of the inflammatory pathway. Tocilizumab, a monoclonal antibody against IL-6R, is currently being tested in a multicentric study in Italy. The drug previously found use in Wuhan during the acute phase of the pandemic. While initial results are promising, the currently available data is too limited to draw broad conclusions from.

A newer modality details the use of anti-2019nCoV-specific T lymphocytes against long-standing COVID infection. These increase the preparation of T-cell products as adjunct therapy. If brought into general practice, these drugs would help approach COVID-induced endocrine dysfunction on a case-by-case basis, leading to improved effectiveness of treatment and an overall better prognosis.

6. CONCLUSION

Long COVID appears to affect the functioning of the endocrine system in many ways, via numerous mechanisms.

Both Long COVID disease and treatments have been shown to affect the thyroid gland- both by direct destruction and indirect suppression. Interference of Long COVID with both male and female reproductive functioning has been demonstrated, possibly via the generation of reactive oxygen species (ROS). Insulin Resistance and overall dysregulation of glucose metabolism has also been observed, particularly in patients with pre-existing risk factors.

Furthermore, Long COVID suppresses the secretion of cortisol, a key mediator in response to stress/infections. This can lead to chronic immune suppression, predisposing the body to develop further infections. Long-term steroid therapy for COVID infection can also paradoxically lead to increased mortality.

Future directives aim to tackle lifestyle modifications, and new studies have pioneered the use of specific immunomodulators to tackle Long COVID-associated endocrine dysfunction. Specifically, Tocilizumab (anti-IL6R monoclonal antibody) and anti-Covid lymphocytes have proven to be immense breakthroughs in this field of research. Other projects have focused on the use of Janus Kinase inhibitors (JAKs) to counteract the effects of Long COVID on the endocrine system.

However, COVID is a relatively new phenomenon, and much remains to be discovered about its longer-term implications on the multiple facets of human health. Plenty of research is needed to investigate the mechanisms behind endocrine dysregulation, and to suggest measures to counteract the damage and ensure better patient well-being. When it comes to the future of healthcare, a thorough understanding and standardized approach to this chronic infection will undoubtedly be a key weapon in our arsenal.

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DISCLOSURE

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Ethical approval was not required for this study

Declaration of patient consent

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Conflicts of interest

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