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Review Article

The anesthesiologist and Covid-19 endocrinopathies

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ABSTRACT

Covid-19 disease created a havoc since 2019, affected large number of number of people over worldwide. As the second wave is receding, we will be receiving patients with the long-term effects of Covid-19 for the surgeries either for their primary disease or for the complications arising from the Covid-19. Primarily, the Covid-19 is a disease affecting the pulmonary and cardiac system, many other systems including renal, hematology, central nervous, endocrine etc. also damaged with the same. Various endocrine glands are being involved in Covid-19 disease like pancreas, thyroid, pituitary, adrenals, reproductive system etc. as they are highly expressed with ACE₂. This may even lead to the permanent damage. Because of the unfamiliarity with the disease, plausible impact on the endocrine functions is still unclear. This article elaborates various endocrine manifestations of SARS Cov and SARS Cov-2 for better understanding and management of Covid-19 recovered patients.

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1. Introduction

Corona virus disease (Covid-19) became a major pandemic after being reported first in Wuhan, China. It is caused by the severe acute respiratory syndrome corona virus 2 (SARS Cov-2), the seventh corona virus which is known to cause disease in humans. Till date, around 23 million people worldwide (2.3 crore in India) have already been affected.

The pathogenesis of Covid-19 necessitates entry of SARS Cov-2 via the respiratory system and lodgment in the lung parenchyma. Subsequently, it uses angiotensin converting enzyme 2 (ACE₂) as a receptor for entry into the host pneumocytes. The number of endocrine organs do express ACE₂, like pancreas, thyroid, adrenal, pituitary, parathyroid, testis and ovary.¹⁻⁴ The systemic viremia and an over reactive immune response contributing to the pathogenesis of the lesions in key endocrine glands. The

consequences following the interactions of SARS Cov-2 with ACE₂ expressed on these organs are expected but presently very limited data available regarding effect of virus on the endocrine system, including pancreas. As of now, assumptions made on the studies pertaining to the prior SARS outbreak (2003) and animal models.^{2,3} Changes in endocrine functions observed during the previous coronavirus outbreak with SARS Cov, led to considerable morbidity and were important predictors of mortality. Therefore, it is all-important to know the endocrinopathic impact after SARS Cov-2 illness. Recently, it has even suggested that Covid-19 could be considered as an endocrine disorder, to make sense of the nonspecific response of the immune system to the SARS Cov-2 virus.³

Manifestations of many hormonal and metabolic disturbances due to a systemic involvement of various organs by Coronavirus infection, changes in thyroid, pancreas, pituitary and adrenal glands have been reported in detail in both, SARS Cov and SARS Cov-2 infections.⁴ This

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timely presented article highlights the features of SARS induced endocrinopathy to understand and predict Covid-19 effects on target organs of the endocrine system.

2. Materials and Methods

To compile a mini-review describing possible endocrine consequences of SARS-Cov-2 infection, we performed a literature survey using Medical Subject Heading (MeSH) related to SARS-Cov-2, SARS-Cov, endocrine from electronic database PubMed from the year 2002. Manual screening of bibliographies and citations in the selected articles provided additional data. The literature review is recent until February 2021. In the framework of available literature, we discuss and explore the repercussions on endocrine system after SARS Cov-2 infection based on the experience with structurally similar SARS Cov.

2.1. Changes in pancreas and diabetes mellitus

Many viruses, such as Enteroviruses, Coxsackie B virus, Retro-viruses, Rubella, Mumps, Cytomegalovirus, Epstein-Barr and Varicella Zoster virus have been incriminated in the development of diabetes mellitus (DM) in humans.⁴⁻⁶ Presently, Coronavirus has also been reported to cause diabetes in animal and human studies.⁴ Direct viral damage due to coronavirus to pancreas leading to diarrhoea and transient diabetes mellitus simultaneously was reported in the case report earlier.⁷ The stronger expression of ACE₂ in pancreatic endocrine tissue compared with the exocrine tissue may explain the extent of tissue damage by SARS-Cov, also being proven in autopsy findings.^{8,9} Thus, due to damaged pancreatic islets, acute insulin dependent diabetes mellitus may occur by SARS Cov viruses but not acute pancreatitis. Yang et al reported development of new onset diabetes in 51% of SARS Cov patients who had no previous diabetes and received no steroid treatment during illness.⁸ In addition to, direct β -cell damage, alterations in self- antigens and subsequent immune-mediated destruction of β -cells could be implicated.² Therefore, SARS Cov (and perhaps SARS Cov-2) could be potential environmental triggers for the development of type 1 DM. The process may be accentuated by a systemic pro-inflammatory milieu, as evident by high amounts of interleukin-1 β , monocyte chemoattractant protein-1 (MCP-1) and inducible protein-10 even in patients with mild Covid-19. Covid-19 could also lead to worsening of insulin resistance in patients with pre-existing type 2 diabetes mellitus (T2DM).² Recent studies have indicated fear of de novo onset of severe DM and diabetic ketoacidosis among patients with Covid-19 who were formerly healthy and non-diabetic.⁴ Apart from inducing a plethora of cytokines, SARS Cov increases serum levels of fetuin A, a glycoprotein that has been linked with impaired insulin sensitivity.¹⁰ Moreover, Covid-19 is often

associated with hypokalemia; this has been attributed to downregulation of pulmonary ACE₂, reduced angiotensin-II degradation and subsequent increased aldosterone secretion.¹¹ Hypokalemia, in turn, can worsen glucose control in patients with pre-existing T1DM and T2DM. During the present Covid-19 pandemic, mild pancreatitis (diagnosed on the basis of elevated serum amylase and/or lipase) has been described in patients with severe Covid-19.¹² This may be attributable to the direct viral invasion or the systemic inflammatory response.¹³ Table 3 summarises possible effects of endocrine impact post Covid-19.

Examination of beta cell injury and insulinopenia has been initiated by a global CoviDiab registry in those without pre-existing DM and in whom SARS Cov-2 is the only etiological factor.¹⁴ This data suggest the importance of monitoring of endocrine dysfunction in patients affected with Covid 19.

2.2. Thyroid dysfunction

Destruction of the follicular epithelium with extensive exfoliation of apoptotic cells into the follicular lumen of the thyroid gland was seen in patients affected by the SARS Cov. Thyroid follicular damage was occasionally very severe, associated with complete loss of parafollicular C cells as shown by total absence of calcitonin immunostaining. This explains why decreased serum T₃ and T₄ in 94% and 46%, respectively, in a group of patients with SARS Cov during the acute phase of the disease, followed by persistence of low-serum T₃ and T₄ in 90% and 38% among convalescent cases. Low level of thyroid stimulating hormone (TSH) is also reported by the author.¹⁵ Marked destruction of the follicular and parafollicular cells of the thyroid was also observed in autopsies of patients with SARS Cov.³ This derangement can be due to direct viral destructive effects or immune mediated mechanisms precipitated by Covid-19. Current literature favours Covid-19 also leads to infliction of pituitary lesions leading to secondary thyroid and adrenal insufficiency as observed by SARS Cov, earlier reported by Leow et al.¹⁶ This could be treated by levothyroxine and hydrocortisone replacement.³ This divergence are reported to be transient and fully resolved after 3-6 months.^{3,4} Greater impact on hypothalamus-pituitary-thyroid (HPT) axis is suspected with Covid-19 after discovering ACE₂ mRNA in thyroid cells.¹⁷ This also explains Covid 19 related acute thyroiditis or De-Quervain's thyroiditis, often seen with viral diseases. Now, sub-acute thyroiditis is considered to be a sequelae closely associated with Covid-19.¹⁸ Primary hypothyroidism due to autoimmune thyroiditis is also reported after "cytokine storm" induced by SARS Cov-2. Covid-19 can act as an autoimmune-trigger of latent or new-onset disease as well a trigger for new cases or relapses of Graves' disease.¹⁸ The parafollicular cell damage might lead to low levels of serum calcitonin, which

has been proposed as a probable reason for development of osteonecrosis of femoral head seen in recovered patients with SARS. So, the common thyroid manifestations of Covid-19 are thyrotoxicosis, Grave's orbitopathy, and or hypothyroidism.³ A recent report from Italy on a young female who recovered from SARS Cov-2 describes the first reported case of subacute thyroiditis sequentially followed by this viral infection.¹⁹ Furthermore, occurrence of subacute thyroiditis among nine patients positive for SARS CoV-2, after the remission of Covid-19 in six patients (about 65%), with a time interval ranging from 17 to 40 days from remission of Covid-19 has been reported.

2.3. Pituitary gland dysfunction

Gradual development of hypocortisolism is reported in SARS Cov survivors as a late complication over a period of weeks after the onset of infection, possibly due to direct or immune mediated hypophysitis.¹⁶ Post viral hypocortisolism routinely manifested by low mood, low energy levels as well as dizziness and drastic improvement is seen with the cortisol replacement.¹⁶ Rich expression of ACE₂ and TMPRSS₂ (transmembrane protease serine 2) in the hypothalamus especially in paraventricular nucleus, makes it the highly probable target in SARS Cov-2 infection.^{3,20–22} Possibility of damage to hypothalamo-pituitary-adrenal (HPA) axis with hypocortisolism shall be expected in patients with Covid-19 considering the high frequency of neurological involvement with complains of unexplained fatigue, lassitude, malaise, orthostatic dizziness, anorexia and apathy.^{1,2} Affection of HPA axis more frequently reported than the HPT axis.⁴ Recovery of HPA axis is being demonstrated within 1 year in majority who were affected in SARS epidemic in 2003. Evidence regarding molecular mimicry of SARS Cov-2 with ACTH is lacking as reported with SARS- Cov limiting the corticosteroid stress response. Still, SARS Cov-2 proteins are highly homologous to the original SARS Cov, patients with severe Covid-19 may be more prone to develop critical illness related corticosteroid insufficiency (CIRCI).^{2,18}

2.4. Adrenal gland dysfunction

Presence of adrenal necrosis, vasculitis of small veins of adrenal medulla, and adrenal infiltration with monocytes and lymphocytes found in autopsies during this Covid-19 epidemic.²³ Present data suggest the adrenals are a frequent site of Covid-19 related lesions in the body based on radiological and autopsy evidence.^{24–27} So, clinician must be aware about possibility of hypocortisolism in patients post Covid-19. To establish the diagnosis, first checking of a morning cortisol level at 8 AM, at least 24 hours after the last dose of glucocorticoids is recommended. Based on the morning cortisol result, a corticotropin

stimulation test may be warranted as shown in Table 1.²⁸ Covid-19 is usually associated with hypokalemia due to pulmonary ACE₂ downregulation, decreased angiotensin-II depletion and enhanced secretion of aldosterone hormone from the adrenal glands. Moreover, a noticeable association between hypernatremia, hypokalemia, and hyporeninemic-hypoaldosteronism with new onset of hypertension among Covid-19 patients also being reported.¹⁸ Findings also suggested low levels of dehydroepiandrosterone sulphate (DHEAS) in 13.1% patients after adjusting for age, sex and menopausal status. DHEAS replacement could be beneficial in those having the deficiency.⁴

Table 1: Interpretation of morning cortisol and morning corticotropin test

Test	Recommendation
1) Morning corticotropin test: Cortisol (8AM, at least 24 h after last corticosteroid)	
<5 mg/dl	Give supplemental corticosteroids
5-10 mg/dl	Consider corticotropin stimulation test vs empiric supplemental corticosteroids
>10 mg/dl	No supplemental corticosteroids needed
2) Corticotropin (ACTH) stimulation test: Cortisol (30-60 min after giving 250 mg corticotropin)	
<18 mg/dl	Give supplemental corticosteroids
=18 mg/dl	No supplemental corticosteroids needed

Who does not need supplemental Corticosteroids?

The following groups do not require any additional perioperative corticosteroids because suppression of the HPA axis is unlikely:

1. Patients who have been taking corticosteroids less than 3 weeks.
2. Patients who are taking less than the equivalent of 5 mg of prednisone daily (assuming they had not been taking higher doses previously).
3. Patients undergoing superficial procedures (eg, cataract extraction, biopsy, dental surgery).

Perioperative corticosteroid supplementation always depends on the type of surgery as different surgeries lead to different increase in cortisol production.²⁹ Recommendations on the amount of supplementary corticosteroids are not based on randomized controlled trial data but rather expert opinion based on physiologic data as outlined in Table 2.²⁸

Table 2: Recommended perioperative steroid replacement

Type of Surgery	Example	Suggested Corticosteroid Dose
Superficial	Dental Surgery/Biopsy	Not required
Minor	Hernia repair/Hand surgery	25mg IV* before incision
Moderate	Hysterectomy/Joint replacement	50mg IV Hydrocortisone before incision, then 25mg IV 8hourly for 1-2 days
Major	Cardiopulmonary By-pass	100mg IV Hydrocortisone before incision, then 50mg IV 8hourly for 2-3 days
Prolonged surgery/ Surgeries that involves delayed oral intake	Trauma	100mg IV Hydrocortisone before incision, then 50mg IV 8hourly for 2-3 days

*IV – Intravenously

Table 3: Effects of SARS-CoV-2 on the endocrine system

Possible mechanisms of target organ changes	Effect on hormonal axis	Clinical features	Perioperative investigations and management
Direct viral injury on ACE ₂ expressing islet cells ⁹	Possible hypoinsulinemia	Hyperglycemia	Dose adjustment of Insulin Requires frequent monitoring of blood sugar and titration of Insulin Monitoring of complications like ketoacidosis
Due to glycosylates ACE ₂ and viral S protein, facilitating viral entry ⁸	Stress response up-regulates cortisol, growth hormone, and adrenergic activity with hyperglycemic effects	Hyperglycemia	
Pancreatitis : direct viral injury, response to systemic inflammation, immune mediated injury ¹²		Minimal or no symptoms	
Destruction of follicular and parafollicular cells of thyroid	Primary hypothyroidism	Look for Hypothyroid features	High TSH and low free T ₄ Require Thyroxine replacement
Hypophysitis/ hypothalamic involvement ¹⁶	Secondary hypothyroidism	Look for Hypothyroid features	Low TSH and free T ₄ Require Thyroxine replacement
Decreased activity of type 1 deiodinase (decreased T ₄ to T ₃ conversion), increased activity of type 3 deiodinase (increased T ₃ catabolism), and down-regulation of hypothalamic pituitary axis ³⁰	Sick euthyroidism	Clinically not significant	Difficulty in differentiating during acute illness as associated with low T ₄ , T ₃ and TSH Test TSH and free T ₄ following recovery to differentiate from secondary (central) hypothyroidism
Hypophysitis resulting from infiltration by virus ¹⁶	Impaired ACTH/ cortisol production	Postviral syndromes ¹⁶ like c/o fatigue, lassitude, weakness, malaise, orthostatic dizziness, anorexia, anxiety, depression and apathy	Cosyntropin/ ACTH stimulation test Monitor serum cortisol and ACTH ⁴ Require Hydrocortisone replacement ⁴
Hypothalamic involvement ¹⁶	Low thyroid hormones sometimes with low TSH		TSH and free T ₄ If deficient, hormone replacement in physiological doses ¹⁶
Adrenal necrosis and vasculitis from direct cytopathic effect or inflammatory response ²³	Hypocortisolism	Postural hypotension Persistently low blood pressure Hypokalemia and Hyponatremia	Serum 8 AM cortisol level Cosyntropin/ACTH stimulation test Require Hydrocortisone replacement Require corrective measures

2.5. Bone and parathyroid dysfunction

No data exist on ACE₂ expression, viral invasion or inflammation of the parathyroid glands, or alterations in parathyroid hormone or calcium homeostasis with the exception of interest in the possible role of vitamin D in mitigating Covid-19 disease.^{1,31} Most of the focus has been on access to therapy during the pandemic. Despite of hypocalcemia being reported in patients with severe illnesses, no published data are available regarding Covid-19 disease severity and serum calcium levels. But, possibility of association between hypocalcemia and Covid-19 disease severity and prognosis could not be ruled out.

During this pandemic, the concern remains over difficulties in accessing hospital or clinic administered osteoporotic drugs, particularly denosumab (Prolia), which has detrimental effects with delays of more than 6 months between dose administration.³¹ Current data doesn't suggest an increased risk of viral infections when denosumab is used for the treatment of osteoporosis. However, hypocalcemia is known to be associated with infections; recently report of Covid-19 patients showed worsening of clinical outcome with lower calcium levels.³² The widespread distribution of the vitamin D receptor in most tissues throughout the body initiated the interest in vitamin D as a possible tool in the armamentarium of Covid-19 treatment stems. Role of vitamin D has been implicated in innate and adaptive immune responses. It helps to maintain cell physical barrier integrity through tight junctions, gap junctions, and adherents junctions. Enhancement of cellular innate immunity by vitamin D is partly through the induction of antimicrobial peptides. The preferential increase in the expression of anti-inflammatory cytokines while reducing the expression of pro-inflammatory cytokines reported after vitamin D which are all beneficial in Covid-19.³³ Prior to the Covid-19 pandemic, there had been interest in investigating the impact of vitamin D supplementation on the risk of respiratory infections. Although the data around use of vitamin D and infection prevention is inconclusive, a recent meta-analysis using individual data points conclude that oral vitamin D3 supplementation reduced the risk of acute respiratory tract infections (OR 0.88%). More pronounced effect was seen when baseline 25-hydroxyvitamin D levels were less than 25 ng/ml. Protective effects were mainly found in individuals receiving daily or weekly vitamin D without additional bolus doses.³¹

In the current Covid-19 pandemic, there are some data suggesting that European countries (including Northern latitude locations) with lower mean vitamin D levels had higher rates of infection and mortality related to Covid-19. Thus, although the data are inconclusive, it would be advisable to ensure sufficient levels of vitamin D and initiate supplementation where needed, especially the elderly who have a higher risk of vitamin D deficiency.

The recommendation of supplementation with 1000 to 4000 IU/day of vitamin D and a serum 25(OH)D concentration of 30 ng/ml or higher has already been given by the Endocrine Society.³¹

2.6. Reproductive axis dysfunction

ACE₂ and Neuropilin 1 (NRP₁) are also expressed in the testis in abundance. The release of TMPRSS₂ in prostasomes secreted into semen from the prostate during ejaculation together with ACE₂ present on the sperm plasma membrane would thus allow SARS CoV-2 to infect sperm cells.³⁴ Men with symptoms consistent with acute orchitis in some male cases of SARS were reported previously.³⁵ Similarly, at least one case of orchitis has been documented in a young man with Covid-19.³⁶

Injury to seminiferous tubules, vacuolation of Sertoli cells, reduction in Leydig cells, and lymphocytic infiltrates in 11 of 12 deceased males, of whom one had demonstrable SARS Cov-2 by RTPCR within testicular tissues already recorded on post-mortem examination. Mechanism of inhibition of sperm motility, permanent damage to the testis, and decreased fertility by SARS Cov-2 remains undetermined.³⁷ Impaired spermatogenesis and androgen synthesis, male hypogonadism and subfertility is reported so far after SARS Cov-2. So, follow-up after recovery from acute infection is recommended.¹ Possibility of a sexual route of transmission could not be ruled out looking to this finding together with the significantly high rates of Covid-19 infection between sex-partners but strong evidences are still lacking.³⁸

In females, ACE₂ is found in the ovary, uterus, placenta, vagina, and breast tissues. Expression of ACE₂ established in ovarian stroma, granulosa cells, and oocytes and ACE₂ mRNA has been shown to be detectable in the ovaries of premenopausal and postmenopausal women.³⁹ Unlike males, TMPRSS₂ appears to be absent in human oocytes which means that infection of the female germline by SARS Cov-2 is rather improbable except in the situation where the ovum is fertilized by an infected spermatozoon. Despite such theoretical concerns, any published literature of teratogenic effects and embryopathy directly attributable to SARS Cov-2 are still awaited.

3. Conclusion

Although, Covid-19 is widespread, many endocrine manifestations are still far from being explicated. Further research required to report chronic endocrine sequelae following Covid-19 pandemic. New onset DM and chances of diabetic ketoacidosis are high in patients post Covid-19. Adrenal gland and thyroid gland changes are commonly observed in patients post Covid-19. Hypocortisolism, primary/secondary hypothyroidism or sick-euthyroidism should be looked for. Central hypothyroidism and

hypoadrenalism due to the disruption of the HPT and HPA axes should be suspected post Covid-19. Knowledge of Covid-19 endocrinopathy is highly required for an anesthesiologist for better perioperative management as these cases require special consideration during preoperative evaluation and postoperative management. Initial assessment should focus on establishing the patient's current status, i.e., the degree of glycemic control for patients with diabetes, thyroid function for patients with thyroid disease, and risk of HPA axis suppression for patients receiving long-term corticosteroid therapy. This assessment will lead subsequent perioperative recommendations.

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None.

5. Conflict of Interest

The authors declare no conflict of interest.

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