

Long-Term Effect on Endocrine and Metabolic Disorders in the Era of Coronavirus Disease Pandemic

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ABSTRACT

The novel coronavirus disease (COVID-19) pandemic outbreak is one of the most complicated diseases which has affected the entire world severely in the last century. It is majorly associated with respiratory complications, but it has worst prognosis with co-morbidities like type 2 diabetes (T2D), obesity, hypertension, chronic kidney disease (CKD), etc. Though it is a typical virus disease and has very acute prognostic outcome; but based on observations from severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) pandemic outbreak; COVID-19 may have long-term effect on other systems of the body. So, the objective of this article to elucidate the chronic impact of COVID-19 on the endocrine and metabolic system, hence clinicians can be vigilant to detect these metabolic and endocrine complications and plan out an appropriate rehabilitation and management plan at the earliest.

Keywords: COVID-19, SARS, MERS, endocrine disorder, rehabilitation

INTRODUCTION-CORONAVIRUS PANDEMIC AS A GLOBAL CHALLENGE

Coronavirus (CoV) are positive-stranded RNA viruses with a crown-like appearance under an electron microscope (corona is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. There are seven types of human CoVs (HCoVs) identified which can cause various systemic diseases in human. First one was identified in the 1960s, while the rests were identified in this century. In the current outbreak of the pandemic responsible virus is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is also known as COVID-19, with variable clinical severity featuring respiratory and extra-respiratory manifestations; concerning acute respiratory infections about 5-10%, while the mortality rates are up to 10%.¹ Initially, it was presumed that zoonotic transmission is the mechanism of this pandemic, but subsequently, it is transmitted from human to human and symptomatic people are the most frequent source of the COVID-19 spread, even asymptomatic also can be a potential source of transmission. So, isolation of the confirmed cases is the best possible way to prevent this disease.²

The COVID-19 pandemic outbreak is probably the most commonly discussed situation amongst all people in the entire world since January 2020. The disease was first reported in Wuhan, Hubei Province, China on 31st December 2019.³ As of August 2020, there have been more 23 million confirmed cases of COVID-19 reported worldwide, with 0.8 million deaths; while in India, more than 3.1 million people have been reported with COVID-19, with ~58,000 deaths.⁴

CORONAVIRUS DISEASE AND ASSOCIATED COMORBID CONDITIONS

COVID-19 is prevalent across all age group, but frequently it is observed as a disease of elderly patients with more severity. As per initial observation, overall hospitalization rate due to COVID-19 was around 5/100,000 population; but in the elderly population, it was three times higher; which is around 15/100,000 population.⁵ 70% of these patients are either asymptomatic or have mild symptoms including mild fever, cough (dry), sore throat, nasal congestion, malaise, headache, muscle pain.

Only in 30%, there will be continuous fever with respiratory complications; that may require intensive care unit (ICU) admissions.⁶ Routinely, COVID-19 treatment is given in home with the objective of further prevention of disease. Usually, it can be managed through counselling, controlling fever, proper hydration. Detailed guidelines for critical care management for COVID-19 have been published by the WHO.⁷

Interestingly, specific comorbidities including hypertension, diabetes mellitus, obesity, chronic lung disease, renal diseases, myocardial infarction, immunosuppressive disorders, gastrointestinal disorders are frequently associated with COVID-19, which are responsible for increased risk of infection and worse outcomes with increased severity of lung injury and mortality have been reported. After 3 months of this pandemic outbreak, some initial reports from majorly affected cities like Wuhan, Lombardy, and New York City identified higher rates of hypertension, obesity and diabetes among severely ill, hospitalized COVID-19 patients.⁸ As per Garg S *et al.*, the top 3 comorbid conditions including hypertension (~50%) and metabolic conditions like obesity (~48%) and diabetes (28%) were associated with hospitalization due to COVID-19.⁵

Since it is a global pandemic and more than 90% of the affected persons will finally recover from the acute phase, we can expect a large number of the population who would be recovering from the acute illness soon and would be having many short-term and long-term morbidities. Long-term outcomes and sequel of COVID-19 are difficult to predict at present, but we can extrapolate the knowledge acquired from previous respiratory outbreaks produced by coronaviruses like the SARS (severe acute respiratory syndrome) CoV of 2003 and the MERS CoV of 2012.⁹

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2 AND LONG-TERM IMPACT ON ENDOCRINE AND METABOLIC DISORDERS

Currently, it is very difficult to predict long term outcome of COVID-19 in various systems of the body, but we can assess the short term and long-term respiratory sequelae of COVID-19 to be on similar to that of individuals affected with previous coronavirus pandemics like the SARS and MERS. There are studies to suggest a significant residual damage in the pulmonary parenchyma with impairment in surface area of gas exchange in 15.5% and 24% of survivors of SARS after 6 months and 2 years after recovery respectively.^{10,11} Zhang *et al.* in their observational follow-up study of SARS survivors, showed that though the imaging abnormalities on computerized tomography (CT) scan had improved significantly after 2 years of the acute illness, but subtle diffusion abnormalities persisted after 15 years of follow-up.¹² Apart from this, SARS and MERS induced mental stress, psychological distress and reduced quality of life have been observed not only 1 year and 4 years post-illness but the emotional and mental health remained lower than controls even 12 years later.^{13,14} These findings signify the importance of evaluation of long-term effect of COVID-19 on endocrine system-related diseases in survivors.

In the last 8 months, COVID-19 and its association with the elder age group, hypertension, diabetes, obesity, chronic lung disease, etc. are frequently observed. The affection of COVID-19 with renin-angiotensin system (RAS) axis, beta cell dysfunction and insulin resistance leading to diabetes, abnormalities in lipid profile and long-term derangements of various metabolomes, glucocorticoid axis and thyroid gland abnormalities are important causes of our concern.

Role of Renin-Angiotensin System Axis

SARS-CoV and SARS-CoV-2 utilize angiotensin-converting enzyme 2 (ACE2) as receptors for internalization into the host cell. SARS-CoV-2 down-regulates the ACE2 pathway and up-regulates the more inflammatory ACE 1 pathway.¹⁵ Apart from respiratory alveolar epithelial cells, ACE2 is expressed in several other locations like heart, endothelium, renal tubular epithelium, intestinal epithelium, and pancreas. The long-term consequences of RAS axis being affected by COVID-19, its subsequent recovery and role of ACE inhibitors and DPP4 inhibitors are yet to be ascertained in long run.¹⁶

Lipid Profile, Metabolomes and Cancer Markers

COVID-19 infection caused a lowering of serum low-density lipoprotein (LDL) cholesterol in majority and it decreased progressively from mild to moderate to severe disease. Serum LDL cholesterol has been proposed to be a biomarker for severity of illness. Atherogenic dyslipidaemia was noted in 68% of the SARS survivors as compared to 40% of the healthy controls. A study on lipid metabolism and other metabolomes in recovered SARS patients 12 years after the acute illness have noticed raised triglyceride and very-low density lipoproteins (VLDL) levels apart from a significant rise in the levels of serum metabolomes, namely phosphatidylinositol and lysophosphatidylinositol (LPI). There are many cancer markers which have

been significantly increased in patients suffering from COVID-19. A severe rise in these cancer biomarkers raise an alarm of potential malignancy in COVID-19 patients especially in long term survivors.^{17,18}

Diabetes

Diabetes and COVID-19 share a bidirectional link. Though the morbidities and complications of COVID-19 infection have been increased significantly with pre-existing diabetes, the emergence of new-onset diabetes in these patients have been a spotlight of research. Whether the hyperglycaemia during the acute illness is transient or permanent is yet to be ascertained. To address these findings, an international group has formed a global registry in the name of CoviDIAB Project of patients with COVID-19-related diabetes. The goal of the registry is to study the new-onset diabetes that is defined by hyperglycaemia, confirmed COVID-19 infection, no prior history of diabetes, and a history of a normal glycosylated haemoglobin level.¹⁹

In some of the case reports, COVID-19 was responsible for precipitating acute complication of diabetic ketoacidosis (DKA). Reddy PK *et al.* observed that some patients who were hospitalized with either new-onset of diabetes or with some other comorbid conditions; were also diagnosed with precipitation of DKA.²⁰ In those two cases, interleukin 6 (IL-6) levels is elevated in both DKA and COVID-19, which may be an important prognostic factor. The possible mechanism may be aggressive damage to beta cells of the pancreas or abnormal secretion of insulin due to downregulation of ACE2 cells in the pancreas.²⁰ In the current scenario, there is no major change is recommended for the management of diabetes with COVID-19, but strict glycaemic control is at most important, which can be achieved by extensive anti-diabetic medications. But for long-term control, metformin has shown its beneficial effect by reducing mortality in these types of patients.²¹ Other anti-diabetic drugs are also recommended, but need to address clinical outcomes and predictors in the case of SARS-CoV-2 exposure with long-term effect.²²

Hypocortisolism

Irrespective of the use of glucocorticoids during acute SAARS event, endocrine evaluation of survivors at one year have revealed the presence of hypocortisolism in around 39% individuals.²³ Reversible hypophysitis or direct hypothalamic effect leading to the hypothalamic-pituitary-adrenal (HPA) axis suppression have been proposed to be the responsible mechanism. HPA axis dysfunction of the majority resolved within a year but one should be careful about its long-term implications. The hypocortisolism probably explains the persistence of weakness, fatigue and poor quality of life long after recovery from the acute infection. Evaluation of the HPA axis in follow-up visits should be done to rule out central adrenal insufficiency, in COVID-19 patients as well.

Thyroid Diseases

In one observational study of SARS, 7% hypothyroidism was reported in survivors, with histopathological changes including altered follicular architecture with distortion, dilatation, and collapse.^{24,25} Initial stage of subacute thyroiditis with a raised level of inflammatory markers may also lead to hypothyroidism on long-term follow-up. At the moment there are no data suggesting that thyroid patients are at higher risk of COVID-19, but this requires further research and data analysis.²⁶

Rehabilitation Strategy

Since we are expecting a mammoth number of people recovering after the COVID-19 infection, our state, nation and the entire world need to foresee, what short term and long-term complications these COVID-19 survivors may have in future and accordingly robust planning and strategy need to be kept in place. The goal is to improve discharged COVID-19 patients' breathing difficulties and dysfunctions, reduce complications, relieve anxiety and depression, reduce disability rate, restore the capacity for routine activities as much as possible and improve quality of life. Apart from respiratory function and physical rehabilitation a strong psychological and emotional support and rehabilitation is a must for all COVID-19 survivors.^{27,28}

Endovigilance is the key to prevent any diabetes and endocrine-related complications in the long run. Both the patient and the physician should be absolutely vigilant for any new onset dysglycaemia and diabetes and if detected, need to be treated. Thyroid function evaluation can be done at the recovery phase and long run as there are evidences of thyroiditis and hypothyroidism in the previous respiratory pandemics. Evaluation of the HPA axis is to be done in any COVID-19 survivor, presenting with extreme fatigue, anaemia, low blood pressure and altered electrolytes. Since there are evidences for dyslipidaemia in both acute infection and in long-term, COVID-19 survivors are to be actively screened for any lipid abnormalities and atherosclerotic cardiovascular diseases.²⁹

CONCLUSION

Though COVID-19 is an acute viral infection predominantly affecting the respiratory system, it has long term metabolic and endocrine implications. Being a global pandemic with a high rate of recovery, it is expected to find many long-term metabolic complications in a vast number of COVID-19 survivors. Hence, it is prudent to be vigilant to detect these metabolic and endocrine complications and plan out a robust rehabilitation and management plan at the earliest.

DECLARATION OF CONFLICTING INTERESTS

The author declares absence of any conflict of interest.

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