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MINI REVIEW: ASSOCIATION BETWEEN SERUM CORTISOL LEVELS AND COVID-19 DISEASE

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ABSTRACT

Serum cortisol concentration indicates the severity of the underlying condition. More severe disease results in increased cortisol concentrations in the blood, increasing the probability of a catastrophic outcome. A high level of serum cortisol is found in patients with community-acquired pneumonia, and these patients are more likely to develop major complications and death. Corticosteroids are endogenous hormones that are produced by the hypothalamus pituitary adrenal pathway, which is involved for stress response. Considering, known risk factors of endocrine disturbance, there has been minimal discussion on measuring the serum cortisol concentration in COVID-19 patients. SARS-CoV-2 mediated pathogenetic pathways, may also affect endogenous steroid synthesis, particularly cortisol. For the purpose of improving survival rate in severe COVID-19 individuals, we discuss briefly about the current and new findings in the support of measuring the serum cortisol levels in severe COVID-19 individuals and facilitate better treatment management in this article.

KEYWORDS: Cortisol; COVID-19; adrenal gland; Sars-CoV-2, Glucocorticoid.

INTRODUCTION

The COVID-19 pandemic is a global catastrophe that has devastated impact on global societies and is still continuing. Due to high rates of infectious disease and death rates in COVID-19 patients, any method of enhancing the diagnosis and treatment to prevent the spread of infection and morbidity is a positive step (1). Cortisol, a stress hormone, is expected to increase in infected individuals. More severe the infections, then there is more inherent stress and the level of cortisol is higher in the bloodstream. As a result, researchers discovered that elevated blood cortisol is risk factor in individuals who had acquired pneumonia in the community (2). Cortisol elevation is a vital part of the immune response to stress, causing adapting change in metabolic energy, cardiovascular functioning, and immunological modulation. COVID-19 effect on cortisol is still unknown. Because of mimicry, it was proposed that SARS-CoV, which preceded to SARS-CoV-2 may act as an immune-response to adreno-corticotropic hormone. SARS-CoV-2, may increase death rates by triggering cortisol deficiency associated with critical disease (3).

CORTISOLAND COVID-19

A cytokine storm is a hyper-active immune response associated with increased serum concentrations containing anti-inflammatory markers. Cytokine storms can progress to fulminant lung inflammation, commonly known as respiratory failure, or inflammatory responses that can lead to multiple organ damage in the severe cases (4).

The administration of corticosteroids also known as systemic steroids to treat COVID-19 inflammation has already been debatable. With systemic administration of steroids, there is a potential risk of increasing lymphocytopenia, which is a critical feature in individuals with severe COVID-19 (5). Adrenal insufficiency, hyperglycemia and hypernatremia may limit the usage of steroids in COVID-19 individuals having comorbidity such as myopathy, muscular wasting and mental problems (6).

Cortisol is an important steroid hormone secreted by the hypothalamus pituitary adrenergic pathway, which is responsible for maintaining physiological homeostasis (7). Acute physiological stress caused by illness or the use of a ventilator can result in dysregulation of the HPA axis and hypercortisolemia in COVID-19 individuals (8). Free serum cortisol levels in severe COVID-19 individuals have significant function in the HPA-axis malfunction. The

proposed mechanisms for acute stress-induced hypercortisolemia in these individuals include decreased serum protein binding and prolonged inhibition of metabolic breakdown, both of which result in elevated free blood cortisol concentrations (9). Hypercortisolemia can disrupt the physiologic innate immune response to viral infections, which has possibility of increasing chances of viral respiratory illnesses such as COVID-19 (10).

The pathogen responsible for SARS-CoV-2 has attach to the angiotensin-converting enzyme-2 (ACE-2) protein in the human epithelial-cells, allowing it to enter the cells more readily. Additionally, ACE-2 acted as a cell entrance receptor for SARS that caused SARS outbreak in 2002 (11). Transmembrane protease serine-2 (TMPRSS-2) or cathepsin-L (CTSL) are the proteolytic enzymes co-expression that allow the virus entry in to the host-cell through the ACE-2 receptor. Adrenal gland secretory cells have been shown to express the genes ACE2 and TMPRSS2/CTSL (12). The endothelial cells of blood vessels exhibit receptors for virus entry, which is reported that they are released into the blood circulation when the virus infects the cell wall (13). Because the adrenal gland has a high level of vascularity, hence it is susceptible to infection due to SARS-CoV-2 that penetrates the blood vessel of the gland and causes infection. In patients with COVID-19, virus-mediated adrenal cortical damage may result in hypocortisolemia, which may need the administration of exogenous steroid therapy (13). According to the information now available that the laboratory data currently available in COVID-19 patients did not reveal significant evident adrenal-insufficiency in the current scenario (14).

The survival benefits of dexamethasone low-dose in severely ill COVID-19 patients, which have been seen in multiple studies, are currently unknown. One study concluded that the dosage and severity of the disease were the most important determinants of the survival advantage associated with steroids in sepsis patients who were receiving critical care (15). Because high inflammation causes lymphocytopenia and thus an increase in mortality, the unexpected benefits of steroids in COVID-19 related to their anti-inflammatory effects (5).

Given the high probability of HPA axis dysregulation in COVID-19 patients (13), estimating serum cortisol concentrations may be important in choosing lot of patients, especially for patients in the Intensive Care Unit (ICU). Steroids are commonly researched in COVID-19 patients; however, the lack of relevant literature suggests that blood cortisol levels have not been closely monitored. Despite the strong theoretical justification, due to lack of sufficient data, it will be advisable to address this topic through properly conducted research to determine whether serum cortisol can also be utilized to access COVID-19 individuals. Higher blood cortisol concentrations were linked to increased mortality in COVID-19 patients, were recently report by Tan et al. The researchers found that COVID-19 patients had a much greater cortisol response to stress than those who did not have COVID-19. After adjustment of age, comorbidities and laboratory tests, a double of cortisol levels was significantly correlated with 42 percent increase in the risk of death. Patients with cortisol levels more than 744nmol/L in the cohort had a significantly lower median survival rate. The study did not mention the severity of the condition. Both multivariate and survival analyses would have shown cortisol predictability after adjustment of disease severity (14).

GLUCOCORTICOID TREATMENT IN COVID-19 INFECTION

The role of serum cortisol to guide glucocorticoid treatment in COVID-19 patients is controversial and impracticable. When compared to prolonged mechanical ventilator or oxygen therapy, the landmark RECOVERY research discovered that utilizing low-dose dexamethasone was observed to lower twenty-eight-day death in COVID-19 patients (16). Even though dexamethasone was not demonstrated to be effective in severe COVID-19 individuals, it was discovered that the medication was useful in these people. The serum cortisol level was used to guide corticosteroid therapy and found positive association in patients with critical illness-related corticosteroid insufficiency (CIRCI). COVID-19 was also issued, which may cause hypocortisolism due to molecular mimicry and cause hypocortisolism in patients with critical illness (17); however, as Tan et al., point out that CIRCI is not the common in COVID-19 setting (14). Because cortisol testing in severe illness is unreliable, clinicians choose septic shock in patients those are vasopressor-dependent or who are resistant to fluid-resuscitation, instead of the measuring the serum cortisol level (18).

Predictive value in serum cortisol levels for the diagnosis of community-acquired- pneumonia has studied widely. Poor outcomes and death in persons who have community-acquired pneumonia are predicted by their cortisol levels, which are completely independent predictors (2). The variation of cortisol dynamics in response of the stress, serum cortisol is rarely employed as diagnostic in community-acquired-pneumonia in routine clinical practice. The researchers have not yet excluded out the

possibility of inherent corticosteroid deficiency due to severe illness that would increase cortisol level greater than 248nmol/L 60 minutes after tetracosactide delivery (18). According the Surviving Sepsis Campaign guideline recommends intravenously cortisol -200 mg/day instead of serum cortisol in order to improve their survival (19).

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) working team recently merged information from seven studies (RECOVERY, REMAP-CAP, CoDEX, CAPE COVID, and three more trials) comprising one thousand seven hundred three participants and found that patients assigned to corticosteroids had a reduced 28-day mortality. There was no difference in mortality between dexamethasone and hydrocortisone administration, showing that the benefit was due to a general class impact of glucocorticoids rather than a specific corticosteroid. No difference in the mortality is found among the patients, who had fewer versus over than seven days of problems at randomization, or between patients who had fewer versus over than seven days of complaints at randomization (20).

It implies that treatment with steroids is definitely related with benefit in severely ill COVID-19 patients, whereas the precise threshold at which a given patient should be taken corticosteroids is still up for debate. It should be noted that, contrary to popular, patients suffering from either endogenous or exogenous hypercortisolism are not protected from developing cardiovascular disease. The treatment in the COVID-19 patients is not much effective, despite the fact that corticosteroids have anti-inflammatory characteristics with only mild adverse effects, as a result, persistent hypercortisolism can lead to serious negative events such as cardio-metabolic complications, as well as inhibition of the HPA axis, that are detrimental in the treatment of COVID-19 infection.

CONCLUSION

Monitoring the serum cortisol level in the COVID-19 patients is beneficial because of the possibility of substantial serum variations and their impact on survival outcomes. As a stress hormone, cortisol can be used to determine the severity of a disease. Clinical research on COVID-19 patients monitor the blood cortisol levels in these patients and compare this information to survival outcomes to see if blood cortisol concentrations are correlated with patient survival. Higher the level of cortisol in the circulation, the more it will chance of morbidity and mortality risks. Furthermore, based on glucocorticoid therapy on levels of serum cortisol is an impracticable concept that has yet to be supported by strong data. As a result, we suggest that regular blood cortisol monitoring in individuals with COVID-19 is useless and should be undertaken.

CONFLICT OF INTEREST: No conflict of interest.

ABBREVIATION

TMPRSS2	Transmembrane protease serine
CTSL	Cathepsin-L
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
ACE	Angiotensin-Converting-Enzyme
HPA axis	Hypothalamic pituitary adrenergic axis

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