Does dehydroepiandrosterone sulfate have a role in COVID-19 prognosis and treatment?

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The pathophysiology of COVID comprises an exaggerated pro-inflammatory response. Hypothalamic-pituitary-adrenal (HPA) axis has a crucial role in various inflammatory conditions and modulated immunological response. Limited evidence is available regarding the incidence and the effect of HPA dysfunction in COVID-19. Although the cortisol levels have only been estimated in a few studies, the dehydroepiandrosterone sulfate (DHEAS) release from the adrenal gland has not been explored yet. In this mini review, the authors discuss the role of dehydroepiandrosterone (DHEA) and DHEAS in the acute stress response and immunological modulation. Various effects of DHEAS have been demonstrated in different diseases. The specific inhibitory effect of DHEA on interleukin 6 (IL-6) could be of paramount importance in COVID-19. Further, DHEA supplementation has already been proposed in inflammatory conditions, like rheumatoid arthritis. DHEAS levels in COVID-19 may help to understand the HPA axis dysfunction as well as the possibility of repurposing DHEA as a drug for mitigating the pro-inflammatory COVID-19.

Key words: COVID-19, hypothalamic-pituitary-adrenal axis, DHEA, DHEAS, cortisol

Acute respiratory distress syndrome (ARDS) and cytokine storm are important causes leading to mortality in COVID-19. The immune response to COVID-19 and the host stress response are modulated by the alterations of the hypothalamic-pituitary-adrenal (HPA) axis. Medium to small doses of glucocorticoids facilitates the suppression of the development of cytokine storm (Xiang et al. 2020). In a recent meta-analysis of clinical trials, a lowered 28-day all-cause mortality has been demonstrated on the administration of systemic glucocorticoids (WHO REACT Working group et al. 2020). However, SARS-CoV (2003) has been shown to suppress the cortisol stress response in the host by targeting the host adrenocorticotrophic hormone (ACTH) (Pal 2020). The molecular mimicry resulting from the viral peptides structurally similar to ACTH has been proposed to have a role in adrenal insufficiency

in COVID-19 (Garg et al. 2020). Currently, limited evidence is available regarding the alterations of the HPA axis in COVID-19 infection.

Dehydroepiandrosterone and dehydroepiandrosterone sulfate

Dehydroepiandrosterone (DHEA) is synthesized by zona reticularis of the adrenal cortex from 17 α -hydroxypregnenolone on ACTH stimulation (Bentley et al. 2019). This androgenic steroid is sulfated to form dehydroepiandrosterone sulfate in the adrenals and peripheral tissues (Figure 1). The enzyme sulfotransferase converts DHEA to dehydroepiandrosterone sulfate (DHEAS). DHEAS has an immunostimulatory and antiglucocorticoid effects. Since cortisol and DHEAS are secreted in coordination and have opposing effects, the ratios of both

Figure 1. Schematic representation of pathway for dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) synthesis.

have been advocated (Tsai et al. 2017). Furthermore, DHEA also acts as a precursor for other steroids, like androstenedione, testosterone, and estrogen. Normal levels of DHEA and DHEAS vary over time. Age-specific changes in the blood levels of both manifest as a decline with the progression of age (Chen and Parker 2004). The higher circulatory levels of biologically inactive DHEAS provide a consistent pool that can be converted in the endoplasmic reticulum by steroid sulfatase to DHEA (Bentley et al. 2019). The linear interconversion of DHEA to DHEAS makes it an excellent serum proxy marker for DHEA availability (Rosenfeld et al. 1972).

The alterations in blood levels of DHEA and DHEAS have been associated with a multitude of diseases. Decreased serum levels of DHEAS were associated with an increased incidence of coronary heart disease (Thijs et al. 2003). Further, a lowered DHEAS has been found to correlate with all-causes of the mortality (Phillips et al. 2010). However, polycystic ovarian disease and non-classical congenital adrenal hyperplasia are some conditions associated with elevated DHEA levels (Goodarzi et al. 2015). The decrease in DHEAS levels with the progression of age with relatively stable cortisol levels, widens the imbalance between the two hormones (Phillips et al.

2010). Suppressed levels of DHEAS and higher ratios of cortisol to DHEAS correlated with frailty in older people (Baylis et al. 2013). In addition, a multitude of inflammatory conditions, including rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, inflammatory bowel disease, have been associated with the decreased DHEAS levels (Andus et al. 1996; Straub et al. 1997).

Acute stress response

DHEAS has been shown to have an important role in inflammatory diseases and critically ill patients. A decreased DHEAS with elevated cortisol and high cortisol to DHEA ratio has been observed in severely ill patients. An extremely low level of DHEAS has been observed in patients in septic shock (Beishuizen et al. 2002). Cortisol, in critically ill patients, has been demonstrated to have a time-dependent response with an initial increase in levels followed by a state of adrenal suppression initiated by the suppressed levels of ACTH by the feedback loop (Teblick et al. 2019). The cortisol to DHEA ratio has been shown to be significantly increased in nonsurvivors in patients with septic shock (Arlt et al. 2006). Low DHEAS/cortisol ratios have been corre-

lated with the severity of inflammation. It also serves as a prognostic marker in cirrhotic patients with concurrent septic shock (Tsai et al. 2017). Further, in patients with severe sepsis, the ratio has been found to be significantly lowered in both survivors and nonsurvivors (Marx et al. 2003). Hence, in critical illness, DHEAS has been proposed as an early sign of impending exhaustion of the adrenal reserve. The cortisol/DHEAS ratio has been considered to be a predictor of long-term mortality in septic patients (De Castro et al. 2019).

Lower DHEAS has been observed in both ulcerative colitis and Crohn's disease. In Crohn's disease patients, low DHEAS, and high serum cortisol levels were associated with higher humoral inflammatory activity (Straub et al. 1998a). Patients with polymyalgia rheumatica/giant cell arteritis with new-onset active disease have also significantly lower levels of DHEAS, despite the inappropriately normal cortisol levels (Narvaez et al. 2006). Interestingly, DHEA has been found to be more sensitive to HPA axis stimulation than cortisol (Arvat et al. 2000). Contrastingly, a lower cortisol-to-DHEAS ratio with enlarged adrenal glands has been observed in fetuses exposed to intraamniotic inflammation (Buhimschi et al. 2008). This suppressed response to inflammation in fetuses has been proposed to be a part of a complex adaptive stress response modulated in anticipation of birth by premature fetuses (Buhimschi et al. 2008).

Severe acute respiratory syndrome (SARS) in SARS-associated coronavirus affects the HPA axis during the course of infection. Multiple studies have observed an elevation in cortisol levels in COVID-19 patients (Ramezani et al. 2020; Tan et al. 2020). Tan et al. (2020) have demonstrated the association between high cortisol levels and mortality. However, the prognostic role of cortisol in COVID-19 has been under debate due to the interindividual variability of cortisol secretion in response to stress, the circadian nature of its secretion, and the non-uniformity of cortisol released in response to various modes of stress (Choy 2020; Pal et al. 2020; Rajcani et al. 2020). The data regarding the association of DHEAS with HPA axis abnormality and mortality in COVID-19 is sparse. Further studies should be undertaken to assess the role of DHEAS, which has lesser variability and non-pulsatile nature, as a prognostic marker in COVID-19.

Infection and immunity

DHEA affects the immune response in the body suppressing the expression of various proinflamma-

tory cytokines (Du et al. 2001; Choi et al. 2008). DHEA has also been shown to have a specific inhibitory effect on interleukin-6 (IL-6) secretion (Marx et al. 2003). In chronic inflammation, DHEAS and DHEA have been found to be decreased and had a negative correlation with IL-6 levels (Straub et al. 2002). The suppressed levels of both DHEA and DHEAS have been associated with systemic lupus erythematosus (Suzuki et al. 1995; McMurray and May 2003).

The levels of DHEAS have been assessed in multiple infections. The DHEAS levels have been found to be decreased in human immunodeficiency virus (HIV) patients. Low CD4 T cell counts, although do not correlate with cortisol levels, exhibited a good correlation with low DHEAS levels in HIV patients (de la Torre et al. 1997). DHEAS levels were lower in hepatitis C virus (HCV) coinfecting HIV patients (Mauboussin et al. 2004). Multiple studies have observed decreased DHEA and DHEAS in patients with tuberculosis (Santucci et al. 2011; Fernandez et al. 2020) and schistosoma infection intensity was lower in patients with high concentrations of DHEAS (Kurtis et al. 2006).

The immune-modulatory effects of DHEA lead to accentuated type 1 T helper (Th1) response. DHEA is a potent enhancer of interleukin-2 (IL-2) secretion from Th1 cells and negatively regulates the production of the type 2 T helper (Th2) cytokines IL-6 (Suzuki et al. 1991). T lymphocytes, on exposure to DHEA, have exhibited heightened cytotoxicity (Suzuki et al. 1991). In addition, DHEA directly modulates the function of the neutrophils by stimulating the synthesis of reactive oxygen species (ROS) via NADPH oxidase activation (Radford et al. 2010). Similarly, DHEA exposure lowers the activation threshold of Monocytes leading to the more effective clearing of infectious agents (McLachlan et al. 1996). Concurrently, DHEA and DHEAS have been shown to inversely correlates with serum IL-6 levels (Cutolo et al. 2002). DHEA concentration-dependent inhibition of IL-6 production from peripheral blood mononuclear cells has also been demonstrated (Straub et al. 1998b).

The excessive activation of the immune system in COVID-19 is associated with an increase of cytokines (De Biasi et al. 2020). As a result, COVID-19 has been associated with a significant increase in proinflammatory cytokines, especially IL-6 (Chen et al. 2020; Huang et al. 2020). IL-6 and C-reactive protein (CRP) effectively assessed the disease severity and predicted outcome in COVID-19 patients (Liu et al. 2020). Severe COVID-19 disease is characterized by IL-6-mediated lymphopenia and sustained

cytokine production (Giamarellos-Bourboulis *et al.* 2020). COVID-19 pneumonia with ARDS, characterized by hyperinflammatory syndrome responded with significant clinical improvement to IL-6 inhibitor, Tocilizumab (Toniati *et al.* 2020). Tocilizumab also reduced ICU admissions and mortality in severe SARS-CoV-2 pneumonia patients (Klopfenstein *et al.* 2020). Patients with COVID-19 also have lower levels of regulatory T cells, which has been accentuated in severe cases (Qin *et al.* 2020). Single-cell transcriptomic analysis revealed that COVID-19 patients had a decreased number of the protective polyfunctional Th1 cells among SARS-CoV-2-reactive CD4⁺ T cells (Meckiff *et al.* 2020). In addition, impaired CoV-2-specific Th1-type cellular immunity has been attributed to varying severity of the disease (Sattler *et al.* 2020). The potential of DHEA to blunt immunological response, suppress IL-6 levels, and increase Tregs makes it an attractive target to be explored for its therapeutic efficacy. Animal models have demonstrated that DHEA treatment can lead to decreased mRNA levels of tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), IL-6, and interferon-gamma (IFN- γ) via MAPK and NF- κ B signaling pathways (Cao *et al.* 2020; Zhao *et al.* 2020).

Dexamethasone, a synthetic glucocorticoid, has been demonstrated to have effectiveness in reducing 28-day mortality in patients receiving respiratory support (RECOVERY Collaborative Group *et al.* 2021). However, the recent bioinformatics analysis revealed that the IL-6 pathway is not involved in the beneficial effect of dexamethasone in COVID-19 (Sharma 2021). Similarly, computational analysis has demonstrated a more stable bond formation between dexamethasone and glucocorticoid receptor when compared with IL-6 (Fadaka *et al.* 2020). In addition, Ciampa *et al.* (2021) have demonstrated the ineffectiveness of dexamethasone in significantly altering cytokine levels. Hence, DHEA should be explored for its effectiveness in targeting the increased IL-6 levels in COVID-19 patients, which may not be addressed by dexamethasone treatment.

DHEA supplementation

The supplementation of DHEA has already been associated with significant antiglucocorticoid and immunomodulatory actions. DHEA has antiglucocorticoid actions and has been demonstrated in numerous tissues (Browne *et al.* 1992; Kimonides *et al.* 1999; Hu *et al.* 2000). DHEA has a protective action against glucocorticoid-induced thymic involution and suppression of lymphocyte proliferation

(May *et al.* 1990; Blauer *et al.* 1991). Supplementation with DHEA has been shown to reverse the suppression of IL-2 synthesis by glucocorticoids (Daynes *et al.* 1990). DHEA supplementation has been shown to have a significant effect on the modulation of pro-inflammatory cytokine levels in the reduction of lupus flares (Chang *et al.* 2004). Oral DHEA replacement in Addison's disease leads to restoration of levels of regulatory T cells and the decrease in the NK cells (Coles *et al.* 2005). The inhibitory effect of DHEA analogs in viral multiplication has been demonstrated in influenza A virus infection where it inhibited the viral infection in the post-attachment stage (Yang *et al.* 2016).

Synthetic DHEA (Prasterone) therapy has been already explored in the treatment of depression and schizophrenia (Wolkowitz *et al.* 1997; Ritsner and Strous 2010). A synthetic analog of a metabolite of DHEA has been shown to reduce the established disease in the rodent models of rheumatoid arthritis (Offner *et al.* 2009). The use of synthetic analog in the mouse model also demonstrated a decrease in proinflammatory cytokines and increases in T reg cells (Auci *et al.* 2007). A daily dose of DHEA at 50 mg showed an enhanced activation of immune functions in elderly individuals with low serum DHEA levels (Khorram *et al.* 1997). In individuals with lower DHEAS concentrations, influenza vaccination when supplemented with a one-time dose of DHEAS showed an enhanced antibody response against the specific Hemophilus Influenza antigen (Degelau *et al.* 1997). The evidence from other viral diseases justifies the attempts that the therapeutic efficacy of DHEA and its analogs in COVID-19 disease may be taken into account.

Conclusion

The assessment of DHEAS in COVID-19 patients may be explored to understand its prognostic capability with respect to severe COVID-19 disease and HPA axis abnormality in comparison to the current cortisol estimation. Besides, the repurposing of DHEA as an adjuvant therapy may be assessed for its therapeutic benefits in COVID-19 in view of its immunomodulatory properties exhibited in other autoimmune and viral diseases. However, the evolving immune landscape in COVID-19 and the emerging evidence with respect to host immune response as well as the mode of perturbations of HPA axis in COVID-19, would be crucial in evaluating the immunological benefits of DHEAS in COVID-19.

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