REVIEW

Alert to US physicians: DHEA, widely used as an OTC androgen supplement, may exacerbate COVID-19

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Abstract
Androgens play a fundamental role in the morbidity and mortality of COVID-19, inducing both the ACE-2 receptor to which SARS-CoV-2 binds to gain entry into the cell, and TMPRS22, the transmembrane protease that primes the viral spike protein for efficient infection. The United States stands alone among developed nations in permitting one androgen, oral DHEA, to be freely available OTC and online as a ‘dietary supplement’. DHEA is widely used by males in the US to offset the age-related decline in circulating androgens. This fact may contribute to the disparate statistics of COVID-19 morbidity and mortality in this country. In regulatory antithesis, every other developed nation regulates DHEA as a controlled substance. DHEA is an extremely potent inhibitor of glucose-6-phosphate dehydrogenase (G6PD), with uniquely unstable uncompetitive inhibition kinetics. This has particular relevance to COVID-19 because G6PD-deficient human cells have been demonstrated to be exceptionally sensitive to infection by human coronavirus. Because DHEA is lipophilic and freely passes into cells, oral DHEA bypasses the normal controls regulating androgen biology and uncompetitive G6PD inhibition. DHEA’s status as a ‘dietary supplement’ means that no clinical trials demonstrating safety have been performed, and, in the absence of physician supervision, no data on adverse events have been collected. During the current pandemic, the unrestricted availability of oral DHEA as a ‘dietary supplement’ cannot be considered safe without proof from placebo-controlled clinical trials that it is not contributing to the severity of COVID-19. US physicians may therefore wish to query their patients’ use of DHEA.

Key Words
COVID-19, SARS-CoV-2, pandemic, androgens and COVID-19, coronavirus

Introduction
COVID-19 is an acute disease that primarily targets the respiratory system, but with increasing evidence of involvement of additional organ systems. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the etiologic agent of COVID-19, uses its spike protein to bind ACE2 receptors as an entry point into the cell. ACE2 receptors are present on the surface of type 1 and type 2 pulmonary epithelial cells, but are also present on other cell types, including endothelial cells in vascular tissues throughout the body (Berger 2020, DiNicolantonio & McCarty 2020, Evans et al. 2020, Panfoli 2020). Infection with SARS-CoV-2 in humans is associated with systemic inflammatory reactions, most notably in the lung (Stawicki et al. 2020), but also in the digestive tract (Aktas & Aslim 2020, Effenberger et al. 2020, Garland et al. 2020, Hanrahan et al. 2020, Villapol 2020);
kidney (Joseph et al. 2020, Lv et al. 2020); brain (Najar et al. 2020, Vargas et al. 2020); liver (Garland et al. 2020); skin (Gisondi et al. 2020) – most likely via endothelial damage to cutaneous blood vessels (Garduño-Soto & Chorro-Parrá 2020) – and heart (Basu-Ray et al. 2020, Grimaud et al. 2020, Kochi et al. 2020, Tahir et al. 2020, Zou et al. 2020). Reports suggest that SARS-CoV-2-associated vascular endothelitis may underlie the inflammatory reactions occurring in this spectrum of organ systems (Ackermann et al. 2020, Evans et al. 2020).

The role of androgens in the morbidity and mortality of COVID-19

Males are affected more severely by COVID-19 than are females, suggesting that androgens may underlie this gender-related difference in morbidity and mortality (Bhowmick et al. 2020, Papadopoulos et al. 2020, Sharifi & Ryan 2020, Wambier & Goren 2020, Wambier et al. 2020). Indeed, treatment of prostate cancer patients with anti-androgen therapy has been reported to exert a protective effect against infection by SARS-CoV-2 (Bahmad & Abou-Kheir 2020, Montopoli et al. 2020), and women with polycystic ovarian syndrome, a condition characterized by hyperandrogenism (Yang et al. 2019), have been reported to be a potential exception to the rule that females are more resistant to the effects of SARS-CoV-2 infection than are males (Kyroù et al. 2020, Moin et al. 2020). Androgenic alopecia is prevalent in men hospitalized for COVID-19 (Goren et al. 2020, Lee et al. 2020), and the increased prevalence of prostate cancer and androgenic alopecia among African Americans correlates with the frequency of particular variants in the androgen receptor (McCoy et al. 2020).

Androgens upregulate both the ACE-2 receptor to which SARS-CoV-2 binds to gain entry into the cell (Samuel et al. 2020), and the protease TMPRSS2 (type II transmembrane serine protease-2) (Clinckemalie et al. 2013, Lucas et al. 2014), which facilitates virus-host cell fusion by priming the SARS-CoV-2 spike protein, thereby increasing susceptibility to SARS-CoV-2 infection and development of severe COVID-19 (Dong et al. 2020, Ragia & Manolopoulos 2020, Stopsack et al. 2020, Strove et al. 2020). Activated androgen receptor upregulates TMPRSS2 mRNA (Wambier et al. 2020), while androgen deprivation therapy suppresses it (Bhowmick et al. 2020, Mjaess et al. 2020). In vitro elimination of TMPRSS2 activity using a protease inhibitor blocks the ability of SARS-CoV-2 to infect human cells (Hoffmann et al. 2020). The low morbidity and mortality of SARS-CoV-2 infection in very young children correlates with their pre-adrenarche developmental stage (see subsequently) (Mihalopoulos et al. 2020).

The unrestricted availability of DHEA subverts normal androgen controls that have evolved in primates, including humans

The androgen DHEA is regulated as a controlled substance in virtually every developed country in the world, with the singular exception of the United States. Until 1994, DHEA was also regulated as a controlled substance in the U.S., in the same manner as other androgens. Any proposed use required placebo-controlled, double-blind clinical trials to demonstrate safety. This changed with the passage into law of the ‘Diary Supplement Health and Education Act of 1994’. This Act exempted DHEA from clinical trials to demonstrate safety, an exemption that was based on a ‘presumption’ of safety founded entirely upon its apparent lack of toxicity in mice and rats. But humans and other primates evolved completely different androgen biology than mice and rats – biology based upon extraordinarily high levels of circulating DHEAS, and extraordinarily low levels of DHEA in the blood (five orders of magnitude lower than for DHEAS). Despite the lack of safety studies in humans, DHEA is widely available online and at retail establishments such as pharmacies and supermarkets, in dosage forms ranging up to 100 mg per capsule. It is estimated that ingestion of a single 100 mg capsule is sufficient to raise the average person’s blood levels to the supra-physiologic range. Based upon its highly touted – but unproven – anti-aging effects, DHEA is widely used in the US, particularly by men, in the belief that its ingestion will offset, without ill effects, the decline in DHEAS that occurs as a function of aging. But as illustrated in the graphical abstract, DHEAS and DHEA have completely different biological activities, blood concentrations, and toxicities (Fig. 1).

Primates are unique among mammals in having evolved an adrenal gland capable of synthesizing and secreting DHEA sulfate (DHEAS), and humans are unique among primates in having by far the highest levels of circulating DHEAS, and in completely separating adrenarche from gonadarche as a distinct developmental stage. At human adrenarche, maturation of the zona reticularis converts the adrenal gland into a DHEAS-secreting organ.

Blood levels of this androgen peak at age 25 to about 3200 ng/mL in males, and 2000 ng/mL in females,
Circulating DHEAS can be converted intracellularly to DHEA, a potent uncompetitive inhibitor of glucose-6-phosphate dehydrogenase (G6PD). Uncompetitive inhibition is otherwise unknown in natural systems because, in the presence of high levels of inhibitor and substrate, it rapidly becomes irreversible (Cornish-Bowden 1986). As Cornish-Bowden has pointed out, ‘any metabolic pathway in which uncompetitive inhibition can occur can potentially respond catastrophically to the presence of inhibitor’. G6PD is the main source for the synthesis of NADPH required for selenoprotein synthesis, a group of proteins most of which act as oxidoreductases to detoxify reactive oxygen species (ROS) (Zhang et al. 2020); and for FSP1-mediated reduction of ubiquinone to ubiquinol, required for the prevention of iron-mediated ferroptosis (Dixon et al. 2012). Uncompetitive inhibition of G6PD by DHEA thus has the potential to induce ROS/ferroptosis-mediated cell death, and this has been proposed as the basic element of a primate-specific, ‘kill switch’ tumor suppression mechanism (Nyce 2018, 2019, 2020). DHEA’s ability to powerfully inhibit G6PD has special relevance to the COVID-19 pandemic because reduction in normal G6PD activity has been shown to sensitize human cells to coronavirus infection (Wu et al. 2008).

Normal human physiology has evolved a three-part safety mechanism that prevents uncompetitive inhibition of G6PD from becoming unleashed in normal cells. First and foremost, blood levels of DHEA are kept extremely low, five orders of magnitude lower than for DHEAS. Second, DHEAS requires subsequent de-sulfation by steroid sulfatase (SS) before it becomes the uncompetitive G6PD inhibitor DHEA. Unlike hydrophilic DHEAS, lipophilic DHEA freely diffuses across cell membranes. Oral DHEA thus bypasses this three-part safety mechanism that evolved to protect normal cells from uncompetitive inhibition of G6PD (Fig. 2).

The effect of long-term exposure of humans to doses of oral DHEA that raise serum concentrations to levels above the physiologic range has not been studied. In dogs, such dosing can cause a systemic inflammatory reaction that does not occur in mice or rats (Nyce 2017a), a finding that might be explained by the fact that the canine adrenal gland more closely models the human – that is, unlike murine species, DHEAS is primarily secreted by the adrenal gland in female dogs (Mongillo et al. 2014). There is additional evidence from studies in canines that endothelial tissues are particularly sensitive to the effects of oral DHEA, possibly due to the tissue-specific expression of endothelial nitric oxide synthase (eNOS) (Nyce 2017b).

To produce nitric oxide (NO) and maintain vascular tone, eNOS must remain ‘coupled’, which means that the NADPH-dependent production of tetrahydrobiopterin (BH4) – a critical cofactor for eNOS activity – must be maintained. In endothelial cells in which uncompetitive inhibition of G6PD by oral DHEA has led to the depletion of intracellular NADPH, and loss of NADPH has depleted BH4, eNOS becomes ‘uncoupled’, and instead of NO, the highly reactive peroxide, peroxynitrate, is formed instead (Radi 2018). As with ROS, several selenoproteins – which

Figure 1
DHEAS and DHEA are the Dr Jekyll and Mr Hyde of androgen biology.

Figure 2
Oral DHEA subverts the controls that have evolved in human androgen biology, and may exacerbate COVID-19 by facilitating viral entry, and by precipitating vascular endothelialitis. OATP, organic anion transport protein; SS, steroid sulfatase.
are also dependent upon NADPH for their synthesis – are required for peroxynitrate detoxification. If this finding of endothelial hypersensitivity to DHEA translates from dogs to humans, men consuming oral DHEA might increase endothelial peroxynitrite levels via enos uncoupling, simultaneously with a reduction in the ability of those endothelial cells to synthesize protective selenoproteins. Elevation of circulating DHEA levels much beyond its normal ultralow blood level of 18.5 nM may thus be particularly toxic to endothelial cells, which have a low threshold for interference with their redox controls. In subjects with SARS-Cov-2 infection, supraphysiologic serum concentrations of DHEA may enhance or precipitate the vascular endothelialitis observed with such infection (Ackermann et al. 2020, Evans et al. 2020).

The compounding effects of diabetes and G6PD deficiency upon androgen-enhanced COVID-19 morbidity and mortality

Taken together, these facts suggest that DHEA may potentiate SARS-CoV-2-induced vascular endothelialitis, contributing to multi-organ inflammatory reactions. This effect may be further magnified in diabetic patients, since G6PD activity is already significantly reduced in them (Heymann et al. 2012, Mahmoud & Nor El-Din 2013), lowering the threshold at which DHEA could induce ROS/peroxynitrite-mediated endothelial cell death and ensuing vascular endothelialitis. Poor glycemic control observed in many diabetic patients could further compound the effects of DHEA, since it would elevate G6P levels, the G6PD substrate required for uncompetitive inhibition of G6PD to become irreversible. Diabetes with poor glycemic control has reached epidemic proportions in both the Hispanic (Loganathan et al. 2017, Aguayo-Mazzucato et al. 2019) and African American (Marshall 2005) communities, which both have experienced disproportionately high levels of COVID-19 morbidity and mortality (Moore et al. 2020).

G6PD deficiency, the most common inherited genetic disease, would also lower the threshold at which DHEA-induced, ROS/RNS-mediated vascular endothelialitis could occur. It has already been demonstrated in ex vivo studies that G6PD-deficient cells are more vulnerable to human coronavirus infection than are G6PD normal cells (Wu et al. 2008) – which is also further evidence that self-administration of the uncompetitive G6PD inhibitor DHEA will increase vulnerability to SARS-CoV-2 infection.

African Americans and people of Hispanic origin, who endure increased morbidity and mortality from COVID-19, are disproportionately affected by both G6PD deficiency and diabetes (Carter et al. 1996, Levine et al. 2001, Wong et al. 2002), albeit the latter due primarily to socioeconomic status rather than genetic factors (Signorello et al. 2007). G6PD deficiency and diabetes are linked in additional ways. Thus, levels of glycated hemoglobin, HbA1c, are used to diagnose type 2 diabetes. A recent study demonstrated that the common G6PD variant rs1050828 is associated with lower HbA1c in African Americans, and that 650,000 African Americans with diabetes will remain undiagnosed when screened by HbA1c if this G6PD genetic information is not taken into account (Wheeler et al. 2017). A similar situation appears to occur in people of Hispanic origin, and in American Indians (Moon et al. 2019). Persons of Middle Eastern descent are also at higher risk for G6PD deficiency than other groups. G6PD deficiency is also more common among males than females, since it is an X-linked recessive hereditary disease. Finally, ketosis-prone diabetes, which predominantly occurs in males of West African descent, shows a high prevalence of G6PD deficiency without G6PD mutation (Sobngwi et al. 2005). This relatively occult form of diabetes/G6PD deficiency could therefore also potentiate the effects of DHEA consumption in African Americans with SARS-CoV-2 infection. The bottom line is that both diabetes and G6PD deficiency, maladies particularly afflicting the African American community, intersect as variables that could potentiate androgen enhancement of SARS-CoV-2 driven vascular endothelialitis.

Conclusion

DHEA’s status as a ‘dietary supplement’ – a status for this androgen that is unique to the US – means that no clinical trials demonstrating safety have been performed, and, in the absence of physician supervision, no data on adverse events have been or are being collected. This is particularly troubling in the era of COVID-19, the severity of which is known to be associated with androgen exposure. The unrestricted consumption of DHEA as a ‘dietary supplement’ in the US may therefore represent an unappreciated risk factor for the development of severe forms of COVID-19. DHEA’s uncompetitive mechanism of inhibition of G6PD – remarkable for its unstable kinetics, which can rapidly become ‘catastrophic’ in the presence of...
increasing intracellular concentrations of G6P (such as occur in diabetes) – should be a red flag that self-dosing in the absence of physician supervision is contraindicated during the COVID-19 pandemic; particularly in subjects in whom diabetes and/or G6PD deficiency are present as co-morbidities. It would therefore seem prudent for regulatory authorities to consider suspending OTC availability of oral DHEA unless it can be proven in placebo-controlled, randomized, double-blind clinical trials that it is not contributing to the morbidity and mortality of COVID-19 in the United States. To avoid – or to determine the etiology of – inflammatory reactions occurring in COVID-19 patients, physicians in the US may wish to query use or abuse of DHEA in their workup of patient histories, and more routinely request lab analyses of DHEA (not DHEAS) serum levels.

Declaration of interest
The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Alert to physicians treating COVID-19


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