



The role for long-term use of dehydroepiandrosterone in adrenal insufficiency

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Purpose of review

Dehydroepiandrosterone (DHEA) is an androgen produced by the zona reticularis of the adrenal gland. Patients with adrenal insufficiency will have a deficiency of DHEA. Unlike glucocorticoid and mineralocorticoid replacement, DHEA supplementation is not considered essential for life and is therefore not routinely replaced in adrenal failure. DHEA deficiency is associated with morbidity, including adverse impacts on metabolic function, quality of life and sexuality in multiple studies. The role for replacement, however, remains unclear.

Recent findings

The benefits of DHEA supplementation have been definitively demonstrated in a number of historical studies of patients with primary and secondary adrenal insufficiency. Beneficial impacts on quality of life, body composition, bone health and metabolic markers have been demonstrated. However, published data are inconsistent; controversies persist around the exact role of DHEA replacement and around which patient cohorts are most likely to benefit. There is also a paucity of recent randomized controlled trials in the medical literature to inform on optimal dose and duration of DHEA replacement in adrenal failure.

Summary

Here, we review the evidence for DHEA supplementation in patients with adrenal insufficiency. We highlight knowledge gaps in the medical literature and areas that should be prioritized for future research endeavours.

Keywords

dehydroepiandrosterone, dehydroepiandrosterone sulphate, primary adrenal insufficiency, quality of life, secondary adrenal insufficiency

INTRODUCTION

The adrenal cortex is responsible for producing glucocorticoids, mineralocorticoids and adrenal androgens, including dehydroepiandrosterone (DHEA). Glucocorticoid and androgen generation is predominantly under the control of adrenocorticotrophic hormone (ACTH) secretion from corticotroph cells of the pituitary gland. Adrenal insufficiency can be classified as primary, secondary or tertiary. Primary adrenal insufficiency (PAI) is commonly due to autoimmune-mediated destruction of the adrenal cortex also known as Addison's disease but is also caused by other processes such as mycobacterial infection, infiltrative disorders, bilateral adrenalectomy and bilateral haemorrhage [1]. Secondary adrenal insufficiency (SAI) occurs in the context of pituitary dysfunction wherein ACTH release is impaired; this may be seen with tumours of the sella or as a consequence of their treatment. Tertiary adrenal insufficiency (TAI) occurs when there is

decreased production of corticotrophin-releasing hormone (CRH) and vasopressin by the hypothalamus, which has a downstream effect on ACTH release; TAI is commonly caused by long-term exogenous administration of glucocorticoids [2]. PAI results in glucocorticoid, mineralocorticoid and adrenal androgen deficiency, whereas mineralocorticoid deficiency is not a feature of SAI and TAI due to preservation of the renin-angiotensin-aldosterone system. Glucocorticoid and mineralocorticoid replacement is therefore essential in PAI,

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KEY POINTS

- Although DHEA deficiency is a feature of both primary and secondary adrenal insufficiency, DHEA supplementation is not routine in clinical practice.
- Fifty milligrams of DHEA has generally been accepted as an appropriate replacement dose in both men and women. Mild adverse effects of DHEA replacement are predominantly due to its androgenic properties, with increased rates of acne and hirsutism reported.
- DHEA supplementation in adrenal insufficiency may improve lipid profile, bone health, patient well being and sexual function as documented in a number of short-term randomized controlled trials.
- However, the overall evidence is weak and needs to be corroborated by larger randomised control trials carried out with longer follow-up periods in heterogeneous cohorts of patients with adrenal insufficiency.

while glu-cocorticoid replacement in isolation is appropriate in SAI and TAI. DHEA replacement is not routine in adrenal insufficiency despite being a central biochemical feature of both PAI and SAI.

DHEA is produced primarily by the zona reticularis of the adrenal cortex; it is converted to DHEA sulphate (DHEAS), its inactive sulphated ester, in the liver and adrenal glands [3]. They are bound to albumin and together form the most abundant steroid

hormones in human circulation [4]; DHEA secretion increases with adrenarche and peaks by the end of the third decade [5], after which serum concentrations begin to decline. It has been postulated that low circulating levels of DHEA may be associated with cardiovascular disease (CVD), reduced bone mineral density (BMD) and increased all-cause mortality; this has resulted in a debate surrounding the potential role of DHEA replacement in the setting of PAI or SAI [6]. The objective of this review is to investigate the evidence for DHEA supplementation in patients with adrenal insufficiency.

PHYSIOLOGY OF ADRENAL ANDROGEN SECRETION

The adrenal glands play a key role in androgen metabolism in men and women, producing several 19 carbon (C19) steroids. DHEA and DHEAS primarily reflect adrenal androgen production [7,8]. Their secretion is under the control of ACTH released from pituitary corticotroph cells [9]. The adrenal gland is responsible for 75–90% of the body's DHEA production, synthesized via a series of cytochrome P450-dependent reactions [10]. The 17,20 lyase activity of CYP17A1 converts pregnenolone and 17-hydroxy-pregnenolone (17OH-preg) to DHEA.

Through the action of cytosolic sulfotransferase (SULT2A1), DHEA is sulphated to inactive DHEAS (Fig. 1); conversely, microsomal steroid sulphatase (STS) can hydrolyse DHEAS to DHEA [11]. 3β-

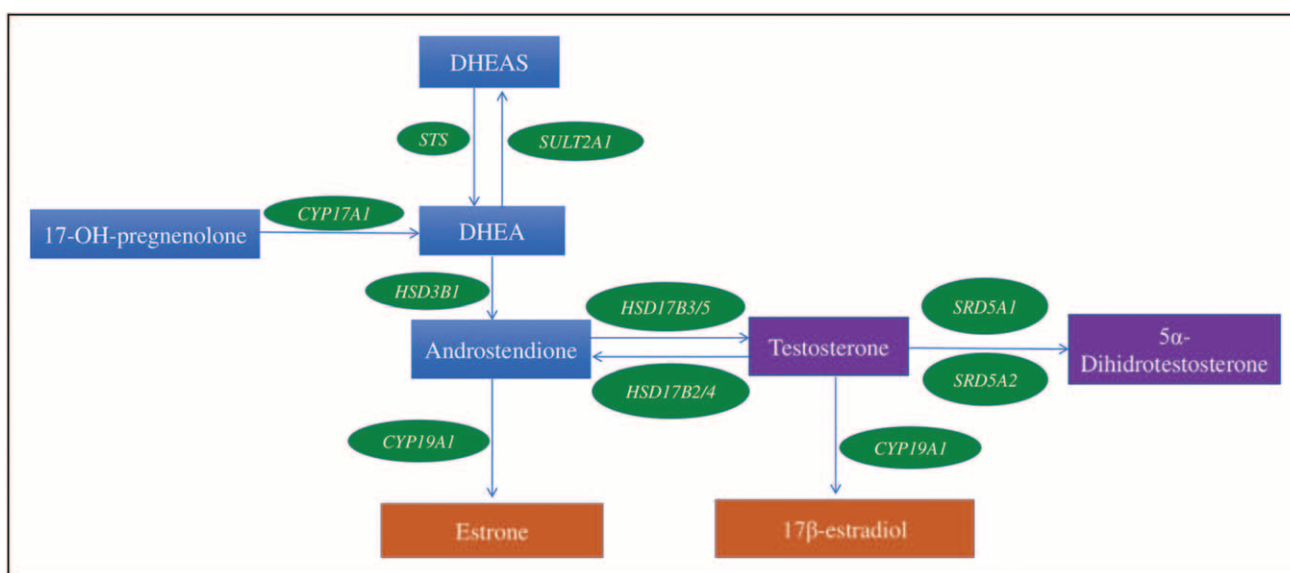


FIGURE 1. Adrenal steroidogenesis detailing key pathways of androgen biosynthesis in the adrenal cortex. CYP17A1, cytochrome P450 17A1 (17 α -hydroxylase; 17/20-lyase); CYP19A1, cytochrome P450 Family 19 Subfamily A Member 1 (aromatase); HSD17B2/3/4/5: DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulphate; Hydroxysteroid 17 β -Dehydrogenase 2/3/4/5; HSD3B1/2, 3 β -hydroxysteroid dehydrogenase type 1; SRD5A1/2, steroid 5- α reductase type 1/2; STS, steroid sulfatase, SULT2A1, sulfotransferase Family 2A Member 1.

hydroxysteroid dehydrogenase type 1 and 2 (3β HSD2) activate DHEA to androstenedione (A4) in the adrenal, ovaries and peripheral tissues; A4 is subsequently activated to more potent androgens such as testosterone (T) through the action of aldoketoreductase type 1C3 (AKR1C3) or 17-hydroxysteroid dehydrogenase type 3 (17BHSD3); the latter plays a key role in testicular T production in men. T may undergo further downstream activation to 5α -dihydrotestosterone (DHT) through the action of isoenzymes of 5α -reductase (5α R) [12,13].

There is an age-related pattern of DHEA secretion [5,9]. Foetal adrenal gland synthesis of DHEA results in high levels at birth, dropping rapidly thereafter. DHEA concentrations rise during adrenarche, which typically correlates to ages between 6 and 10 years, in tandem with maturation of the zona reticularis. DHEA and DHEAS levels rise until they reach a peak typically around the third decade, following which there is a slow decline dropping to 10–20% of peak levels by the eighth decade, a process sometimes referred to as adrenopause [14,15]. Circulating levels of DHEAS display a sexually dimorphic pattern, with two-fold higher levels found in men compared with women around age 25–30 years [16].

Destruction of the adrenal cortex in PAI leads to loss of 17OH-pregnenolone production, along with impaired 17, 20-lyase activity this significantly reduces DHEA synthesis [17]. ACTH is required for adrenal steroidogenesis and resultant DHEA production; therefore, DHEA deficiency in SAI is due to lack of ACTH stimulus in the adrenal cortex, as ACTH stimulation activates CYP17 transcription [18,19].

IMPACT OF DEHDROEPIANDROSTERONE SUPPLEMENTATION ON HEALTH OUTCOMES IN ADRENAL INSUFFICIENCY

Pharmacokinetics and safety profile

Several studies demonstrated that 50 mg daily of DHEA is an appropriate dose to restore plasma DHEA to normal circulating levels (Table 1) [20–23,24[■],25[■]]. Higher doses may cause supraphysiological levels of circulating DHEA, leading to androgenic side effects particularly in women [20,21,26]. Older patients may require a lower replacement dose and, conversely, young men may require higher doses [27[■]].

DHEA has a good safety profile and replacement is generally well tolerated; however, several side effects have been documented, most of which are a consequence of androgen excess. The main reported side effects were seborrhoea and acne in women [22,25[■],27[■],28,29], but an increase in apo-

crine sweat production [22] and hirsutism has also been reported [28]. Gastrointestinal side effects are another possible adverse reaction [28,30] and mildly deranged liver function has also been reported [29]. It appears to be generally better tolerated in men and with less risk of over replacement and unwanted androgenic side effects [26].

Ageing and cognition

Mortality rates for patients with PAI and SAI are significantly higher than that of the general population [31]. These findings have led to the hypothesis that DHEA replacement may be beneficial in preventing certain chronic diseases independent of adrenal function. Furthermore, the Baltimore Longitudinal Study of Aging suggested that higher levels of DHEA were associated with longevity in patients without adrenal insufficiency [6]. To date, there is no convincing evidence to suggest DHEA supplementation improves cognition in either PAI or SAI [32,33].

Quality of life

Patients with PAI despite receiving optimal glucocorticoid and mineralocorticoid replacement subjectively report poorer quality of life (QoL) compared with the general population [27[■],34] and women report poorer QoL than men [35]. QoL is typically measured using standardized questionnaires self-reported by patients, which makes it an inherently unreliable measurement. Several studies have reported a beneficial effect on patient QoL with regards to depressive symptoms, anxiety, exhaustion, obsessive-compulsive traits and hostility in PAI and SAI [27[■],29,36,37[■]]. This finding, however, was not consistently reported in the literature; many studies showed no significant improvement in patient-reported QoL. It is not clear in the literature whether replacement has distinct effects in PAI compared with SAI [24[■],35,37[■]].

Bone health

Patients with adrenal insufficiency may have accelerated BMD loss [38] likely due to exogenous glucocorticoids; however, a deficiency in adrenal androgens may also play a role [39]. DHEA impacts bone metabolism, as osteoblasts express both an androgen receptor and aromatase, implying a possible direct androgenic effect or a secondary impact due to conversion of DHEA-derived A4 and T to estrone (E1) and oestradiol (E2), respectively [40]. Oestrogens play an important role in bone health and deficiency may lead to premature BMD loss.

Table 1. Summary of published articles examining the use of dehydroepiandrosterone replacement in adrenal insufficiency

Title	Dose and duration	Population	Outcomes
			Metabolic
Effects of dehydroepiandrosterone sulphate (DHEAS) replacement on insulin action and quality of life in hypopituitary females: a double-blind, placebo-controlled study (McHenry <i>et al</i> , 2012 [24 [■]])	50 mg/day for 12 weeks	N= 14 hypopituitary hypoadrenal women	<ul style="list-style-type: none"> • No change in HbA1c, fasting glucose or insulin • No difference in insulin action • ↓ Triglycerides
Long-term DHEA substitution in female adrenocortical failure, body composition, muscle function, and bone metabolism: a randomized trial (Christiansen <i>et al</i> , 2011 [25 [■]])	50 mg/day for 6 months	N= 10 hypoadrenal women (PAI and SAI)	<ul style="list-style-type: none"> • ↑ Lean body mass • No change in fat mass/distribution or BMI and waist-hip ratio • No effect on metabolism
Effect of Dehydroepiandrosterone Replacement on Lipoprotein Profile in Hypoadrenal Women (Srinivasan <i>et al</i> , 2009 [23])	50 mg/day for 3 months	N=33 hypoadrenal women	<ul style="list-style-type: none"> • No effect on body weight, fat mass, fasting glucose • ↓ Fasting insulin levels • ↓ Total cholesterol and HDL (more significant ↓. in large HDL particles)
Long-term DHEA replacement in primary adrenal insufficiency: a randomized, controlled trial (Gurnell <i>et al</i> , 2008 [27 [■]])	50 mg/day for 12 months	N= 106 (44 men and 62 women with Addison's disease)	<ul style="list-style-type: none"> • No effect on lipid profile or thyroid function
Dehydroepiandrosterone substitution in female adrenal failure: no impact on endothelial function and cardiovascular parameters despite normalization of androgen status (Christiansen <i>et al</i> , 2007 [68])	50 mg/day for 6 months	N= 10 women with adrenal insufficiency	<ul style="list-style-type: none"> • BMI and waist circumference were unchanged • No effect on cardiac output • No change in lipid profile
Effects of dehydroepiandrosterone (DHEA) supplementation on hormonal, metabolic and behavioral status in patients with hypoadrenalism (Libe <i>et al</i> , 2004 [37 [■]])	50 mg/day for 4 months	N=20 (13 men, 7 women) with PAI and SAI	<ul style="list-style-type: none"> • In AD total cholesterol and LDL ↓ • Slight ↓ in triglycerides • No change in insulin/glucose levels/ insulin sensitivity/ thyroid hormones • ↓ Body fat%
Replacement of dehydroepiandrosterone in adrenal failure: no benefit for subjective health status and sexuality in a 9-month, randomized, parallel group clinical trial (Livls <i>et al</i> , 2003 [47])	25 mg/day for 9 months	N=39 women with adrenal failure	<ul style="list-style-type: none"> • No effect on lipids
Dehydroepiandrosterone Replacement in Women with Adrenal Insufficiency: Effects on Body Composition, Serum Leptin, Bone Turnover, and Exercise Capacity (Callies <i>et al</i> , 2001 [46])	50 mg/daily for 4 months	N= 24 women with adrenal insufficiency (14 with PAI and 10 with SAI)	<ul style="list-style-type: none"> • No change in BMI, waist to hip ratio, fat mass, lean mass or basal metabolic rate • ↓ in serum leptin • No effect noted on metabolism or exercise capacity
Oral dehydroepiandrosterone (DHEA) replacement therapy in women with Addison's disease (Gebre-Medhin <i>et al</i> , 2000 [22])	50 mg/day (n=5) and 200 mg/day (n=4) for 3 months	Women with Addison's disease (n=9)	<ul style="list-style-type: none"> • ↓ LDL in both groups • No change in s-insulin levels or tissue sensitivity • No effect on body composition
Dehydroepiandrosterone replacement in women with adrenal insufficiency (Arlt <i>et al</i> , 1999 [29])	50 mg/day for 4 months	Women with adrenal insufficiency N= 24 (14 PAI, 10 SAI)	<ul style="list-style-type: none"> • HDL concentrations ↓
			Bone health
Long-term DHEA substitution in female adrenocortical failure, body composition, muscle function, and bone metabolism: a randomized trial (Christiansen <i>et al</i> , 2011 [25 [■]])	50 mg/day for 6 months	N= 10 hypoadrenal women (PAI and SAI)	<ul style="list-style-type: none"> • ↑PTH
Long-term DHEA replacement in primary adrenal insufficiency: a randomized, controlled trial (Gurnell <i>et al</i> , 2008 [27 [■]])	50 mg/day for 12 months	N= 106 (44 men and 62 women with Addison's disease)	<ul style="list-style-type: none"> • ↑BMD in men with AI
Effects of dehydroepiandrosterone (DHEA) supplementation on hormonal, metabolic and behavioral status in patients with hypoadrenalism (Libe <i>et al</i> , 2004 [37 [■]])	50 mg/day for 4 months	N= 20 (13 men, 7 women) with PAI and SAI	<ul style="list-style-type: none"> • ↓ in osteocalcin levels

Table 1 (Continued)

Title	Dose and duration	Population	Outcomes
Replacement of dehydroepiandrosterone in adrenal failure: no benefit for subjective health status and sexuality in a 9-month, randomized, parallel group clinical trial (Livls <i>et al</i> , 2003 [47])	25 mg/day for 9 months	N= 39 women with adrenal failure	<ul style="list-style-type: none"> • No change in markers of bone metabolism
			Quality of life
Effects of dehydroepiandrosterone sulphate (DHEAS) replacement on insulin action and quality of life in hypopituitary females: a double-blind, placebo-controlled study (McHenry <i>et al</i> , 2012 [24 [■]])	50 mg/day for 12 weeks	N= 14 hypopituitary hypoadrenal women	<ul style="list-style-type: none"> • No effect on QoL questionnaires
Effect of Dehydroepiandrosterone Replacement on Lipoprotein Profile in Hypoadrenal Women (Srinivasan <i>et al</i> , 2009 [23])	50 mg/day for 3 months	N= 33 hypoadrenal women	<ul style="list-style-type: none"> • No effect on IGF-1 levels
Long-term DHEA replacement in primary adrenal insufficiency: a randomized, controlled trial (Gurnell <i>et al</i> , 2008 [27 [■]])	50 mg/day for 12 months	N= 106 (44 men and 62 women with Addison's disease)	<ul style="list-style-type: none"> • ↑IGF-1 in women
Effects of dehydroepiandrosterone (DHEA) supplementation on hormonal, metabolic and behavioral status in patients with hypoadrenalism (Libe <i>et al</i> , 2004 [37 [■]])	50 mg/day for 4 months	N= 20 (13 men, 7 women) with PAI and SAI	<ul style="list-style-type: none"> • ↓ hostility reported by women in the SCL-90 questionnaire • No change in growth hormone/IGF-1 levels
Replacement of dehydroepiandrosterone in adrenal failure: no benefit for subjective health status and sexuality in a 9-month, randomized, parallel group clinical trial (Livls <i>et al</i> , 2003 [47])	25 mg/day for 9 months	N= 39 women with adrenal failure	<ul style="list-style-type: none"> • No change in IGF-1
DHEA replacement in women with adrenal insufficiency- pharmacokinetics, bioconversion and clinical effects on well being, sexuality and cognition (Arlt <i>et al</i> , 2000 [33])	50 mg/day for 4 months	N= 24 hypoadrenal women (14 with PAI and 10 with SAI)	<ul style="list-style-type: none"> • No effect on cognition • ↑IGF-1 in women with PAI • ↑Well being (anxiety, depression, exhaustion)
Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double-blind trial (Hunt <i>et al</i> , 2000 [32])	50 mg/day for 3 months	39 patients with Addison's disease (15 men and 24 women)	<ul style="list-style-type: none"> • Improved well being (↓.GHQ score) • No effect on cognitive function
Dehydroepiandrosterone replacement in women with adrenal insufficiency (Arlt <i>et al</i> , 1999 [29])	50 mg/day for 4 months	Women with adrenal insufficiency N= 24 (14 PAI, 10 SAI)	<ul style="list-style-type: none"> • ↓ in the scores in the global severity index, on the revised version of the 90-item Symptom Checklist (depression, anxiety, obsessive-compulsive traits, hostility), the Hospital Anxiety and Depression Scale, and on the short form of the Giessen Complaint List subscale (exhaustion). • Serum IGF-I ↑ in women with PAI
			Sex steroid metabolism and sexual function
Effects of dehydroepiandrosterone sulphate (DHEAS) replacement on insulin action and quality of life in hypopituitary females: a double-blind, placebo-controlled study (McHenry <i>et al</i> , 2012 [24 [■]])	50 mg/day for 12 weeks	N= 14 hypopituitary hypoadrenal women	<ul style="list-style-type: none"> • Possible improvement in sexual function • DHEAS and A4 ↑ to normal levels
Long-term DHEA substitution in female adrenocortical failure, body composition, muscle function, and bone metabolism: a randomized trial (Christiansen <i>et al</i> , 2011 [25 [■]])	50 mg/day for 6 months	N= 10 hypoadrenal women (PAI and SAI)	<ul style="list-style-type: none"> • ↑DHEA, DHEAS, A4, T & free T to normal range • No effect on oestradiol or SHBG levels.
Effect of Dehydroepiandrosterone Replacement on Lipoprotein Profile in Hypoadrenal Women (Srinivasan <i>et al</i> , 2009 [23])	50 mg/day for 3 months	N= 33 hypoadrenal women	<ul style="list-style-type: none"> • ↑DHEA and T
Long-term DHEA replacement in primary adrenal insufficiency: a randomized, controlled trial (Gurnell <i>et al</i> , 2008 [27 [■]])	50 mg/day for 12 months	N= 106 (44 men and 62 women with Addison's Disease)	<ul style="list-style-type: none"> • ↑ DHEA and DHEAS to the normal range • ↑A4 • In women only ↑ T to low normal levels but no change in SHBG • In males no change in T, SHBG or oestradiol
Dehydroepiandrosterone substitution in female adrenal failure: no impact on endothelial function and cardiovascular parameters despite normalization of androgen status (Christiansen <i>et al</i> , 2007 [68])	50 mg/day for 6 months	N= 10 women with adrenal insufficiency	<ul style="list-style-type: none"> • ↑ DHEA/ DHEAS/ A4/ T/ free T all increased to normal levels

Table 1 (Continued)

Title	Dose and duration	Population	Outcomes
Effects of dehydroepiandrosterone (DHEA) supplementation on hormonal, metabolic and behavioural status in patients with hypoadrenalism (Libe <i>et al</i> , 2004 [37 [■]])	50 mg/day for 4 months	N=20 (13 men, 7 women) with PAI and SAI	<ul style="list-style-type: none"> • ↑ DHEAS • ↑T, A4 in women • No difference in free androgen index (except in hypoadrenal women ↑) • No change in gonadal axis
Replacement of dehydroepiandrosterone in adrenal failure: no benefit for subjective health status and sexuality in a 9-month, randomized, parallel group clinical trial (Lhüs <i>et al</i> , 2003 [47])	25 mg/day for 9 months	N=39 women with adrenal failure	<ul style="list-style-type: none"> • ↑ DHEA/DHEAS/A4/T • No effect on sexuality
DHEA replacement in women with adrenal insufficiency- pharmacokinetics, bioconversion and clinical effects on well being, sexuality and cognition (Arlt <i>et al</i> , 2000 [33])	50 mg/day for 4 months	N=24 hypoadrenal women (14 with PAI and 10 with SAI)	<ul style="list-style-type: none"> • ↑DHEA, DHEAS, T • ↓.SHBG • ↑Sexual interest and satisfaction
Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double-blind trial (Hunt <i>et al.</i> , 2000 [32])	50 mg/day for 3 months	39 patients with Addison's disease (15 men and 24 women)	<ul style="list-style-type: none"> • In both men and women DHEA and DHEAS ↑ to normal levels. • In females only ↑ in total testosterone and ↓ in SHBG • No effect on sexual function
Oral dehydroepiandrosterone (DHEA) replacement therapy in women with Addison's disease (Gebre-Medhin <i>et al</i> , 2000 [22])	50 mg/day (n=5) and 200 mg/day (n=4) for 3 months	Women with Addison's disease (n=9)	<ul style="list-style-type: none"> • Levels of DHEA and DHEAS after 1 2 weeks on 200 mg were ↑ compared to the 50 mg group. • In both 200 mg and 50 mg groups androstenedione, testosterone & testosterone/SHBG ratio increased to levels seen in normal individuals.
Dehydroepiandrosterone replacement in women with adrenal insufficiency (Arlt <i>et al</i> , 1999 [29])	50 mg/day for 4 months	Women with adrenal insufficiency N=24 (14 PAI, 10 SAI)	<ul style="list-style-type: none"> • Serum DHEA, DHEAS, & androstenedione concentrations ↑ to the normal range. • ↑ scores in visual-analogue scales for sexuality, ↑ frequency of sexual thoughts/fantasies/sexual interest

Only studies including DHEA replacement in patients with adrenal insufficiency were included.

A4, androstenedione; AD, Addison's disease; BMD, bone mineral density; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulphate; GHQ, General Health Questionnaire; HDL, high-density lipoprotein; IGF1, insulin-like growth factor-1; LDL, low-density lipoprotein; PAI, primary adrenal insufficiency; PTH, parathyroid hormone; SAI, secondary adrenal insufficiency; SCL-90, Symptom Checklist 90; SHBG, sex hormone binding globulin; T, testosterone.

Several studies have found DHEA supplementation to increase BMD in patients with adrenal insufficiency [27²²,39]. The largest study involving DHEA replacement in men with adrenal insufficiency was carried out by Gurnell *et al.* [27²²]. They reported an increase in BMD in men with Addison's disease who were treated with 50 mg daily of DHEA [27²²]. Most studies did not find a benefit; however, they were carried out over a relatively short follow-up period [25²,41].

Lipid metabolism

Long-term glucocorticoid use has metabolic implications, including obesity, hyperlipidaemia and diabetes, and is, therefore, a risk factor for CVD [42]. Patients with adrenal insufficiency have a higher risk of CVD and mortality, which could be attributed to long-term glucocorticoid replacement, but DHEA deficiency could conceivably play an additional aetiological role. Bergthorsdottir *et al.* [43] observed a significant increase in death in patients with PAI partially due to CVD amongst other diseases (malignancy and infectious diseases).

Several studies suggest that DHEA replacement in adrenal insufficiency may lead to a more metabolically favourable lipid profile, with reductions in total cholesterol, low-density lipoprotein (LDL) and triglycerides in hypoadrenal patients [23,24²,30]. DHEA replacement has also been reported to reduce high-density lipoprotein (HDL) due to the suppressive effects of androgens on HDL cholesterol [23,28–30]. As a result, it is unclear if DHEA replacement in PAI and SAI does in fact lead to an improved lipid profile given the fact that the cardioprotective effects of HDL cholesterol may be diminished [23,29].

Insulin sensitivity and body composition

Exogenous glucocorticoid replacement in adrenal insufficiency can drive significant metabolic morbidity, including impaired glucose tolerance and increased body fat mass, despite glucocorticoid replacement aiming to be near physiological. The effect of DHEA on glucose homeostasis is not fully understood, but it appears to have an impact on insulin sensitivity and insulin secretion in animal studies [44]. DHEA is found at lower circulating levels in patients with impaired fasting glucose and type 2 diabetes mellitus (T2DM) [45]. However, in patients with PAI and SAI, several studies have found no difference in insulin action, HbA1c, fasting glucose or insulin secretion in patients receiving DHEA supplementation compared with placebo [22,24²,37²]. The effects of DHEA on body composition in patients

with PAI and SAI, including decreased fat mass and increased lean body mass, have been reported in several studies [25²,26,27²²,37²]; however, not all studies reproduced these findings [22,28,46,47].

Sexual function

DHEA is believed to play a role in libido and sexual function. It is therefore plausible that DHEA replacement may improve sexual wellbeing in women with adrenal insufficiency. Circulating T levels are almost undetectable in women with Addison's disease and bilateral adrenalectomy, highlighting the important role played by adrenal androgens as substrate for ovarian and peripheral T production [48].

There are limited and conflicting studies investigating the benefit of DHEA in adrenal insufficiency; therefore, the data must be considered inconclusive [24²,27²²,34]. Arlt *et al.* [29] found there to be an increase in the frequency of sexual thoughts and sexual satisfaction in women with adrenal insufficiency after DHEA replacement, which increased the longer the patient remained on treatment (Table 1) [33].

FUNCTIONAL HYPOADRENALISM: CRITICAL ILLNESS AND BURNS

Functional hypoadrenalism or functional adrenal insufficiency (FAI) is defined as adrenal deficiency in the setting of critical illness. Cortisol delivers glucose to peripheral tissues, and in most illnesses or in the postoperative phase, the stress response leads to a compensatory increase [49]. Arlt *et al.* [50] reported a dissociation between DHEA and DHEAS levels in patients with severe sepsis and trauma; although DHEA levels increased significantly in sepsis, they dropped in the context of severe trauma, indicating that the specific underlying cause of critical illness is likely to play a role in physiological and pathophysiological disturbances. However, in most critically ill patients, severe disease is inversely correlated with DHEA levels, and an increased cortisol: DHEA hints that there may be a role for DHEA replacement in severe sepsis or it may be used as a surrogate marker of disease. In rodent studies, DHEA replacement has been shown to improve mortality in sepsis and critical illness [51]. In burn victims, DHEA is typically lower than healthy controls [52,53]. In fact, DHEA replacement in mice has been shown to prevent the progression of dermal ischaemia after a burn injury and studies are ongoing in humans [54].

DHEA supplementation in patients with adrenal insufficiency in the context of critical illness has not been investigated. Foster *et al.* [55] examined

patients without adrenal insufficiency presenting with severe trauma and noted a decrease in both DHEA and DHEAS and an increased DHEA/DHEAS ratio, which persisted for several months post injury; however, this study did not investigate whether DHEA supplementation would be beneficial. A study investigating whether DHEA supplementation in trauma patients who do not have adrenal insufficiency restores circulating androgens to normal levels and the immune response to DHEA replacement is currently in the recruitment phase [56]. Further research is required to clarify if DHEA supplementation in patients with adrenal insufficiency who are critically unwell would benefit from DHEA replacement is required.

ROLE OF DEHDROEPIANDROSTERONE IN FERTILITY

DHEA is produced by the ovarian theca cells and is essential for ovulation. It is converted to A4, which is a precursor of E1 and E2. Oestrogens activate the hypothalamic-pituitary axis and release of luteinizing hormone (LH). It is this LH surge that triggers ovulation [57]. Therefore, it has been hypothesized that DHEA supplementation may lead to improved ovulatory function and egg quality [58,59]. The link between DHEA and improved ovarian reserve was first reported by Casson *et al.* [60]; more recent studies have been carried out that corroborate these findings [61]. In certain cases, women with poor ovarian reserve undergoing in-vitro fertilisation may undergo a trial of DHEA treatment [62]. A meta-analysis found DHEA treatment increased the likelihood of successful conception and reduced abortion rates [63]. Lebbe *et al.* [64] noted that follicles with reduced DHEA exposure were growth restricted compared with control follicles; conversely, the authors found follicle developmental arrest when exposed to increased androgen concentrations, similar to polycystic ovary syndrome. However, currently, the National Institute for Health and Care Excellence advises against the use of DHEA in fertility treatments [65].

Primary ovarian insufficiency (POI) is more common in women with adrenal insufficiency and may be as prevalent as 1: 10 [64]. Women with adrenal insufficiency often struggle with conception and are less likely to have successful pregnancies; the reasons for this are unclear and likely multifactorial; however, it is plausible that DHEA deficiency may play a role. There is minimal evidence in the literature to support the use of DHEA replacement in women with adrenal insufficiency as part of their fertility treatments [66]. This represents an area

requiring significant future research to improve fertility outcomes in women with PAI and SAI.

CONCLUSION

Low levels of circulating DHEA may be associated with CVD, T2DM and reduced QoL in patients with and without adrenal insufficiency. It is not clear whether long-term exogenous DHEA mitigates the risk of these complications in adrenal failure. Relatively few studies involving patients with PAI and SAI have been carried out in humans, most with a relatively short follow-up period and small patient numbers, and relatively few randomized controlled trials have been conducted since 2012. As such, it is difficult to draw conclusions around long-term health benefits. Shorter-term studies cannot definitively confirm long-term impacts on these physiological parameters, and adequately powered trials over longer periods of time are needed to assess this further. In fact, the Endocrine Society and several other medical societies appointed a task force to investigate the safety and possible clinical uses of DHEA replacement, the consensus recommendation being that currently there is not enough evidence to support the routine use of DHEA in women with adrenal insufficiency [67]. In summary, the evidence for DHEA replacement in adrenal insufficiency is weak, and larger randomized control trials with longer follow up and adequate sample sizes are warranted to support claims regarding long-term health benefits.

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Conflicts of interest

The authors have nothing to declare.

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