Dehydroepiandrosterone (DHEA): Hypes and Hopes

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REVIEW ARTICLE

Dehydroepiandrosterone (DHEA): Hypes and Hopes

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Abstract Dehydroepiandrosterone (DHEA) and its sulfated form dehydroepiandrosterone sulfate (DHEAS) are the most abundant circulating steroid hormones in humans. In animal studies, their low levels have been associated with age-related involuntary changes, including reduced lifespan. Extrapolation of animal data to humans turned DHEA into a 'superhormone' and an 'anti-aging' panacea. It has been aggressively marketed and sold in large quantities as a dietary supplement. Recent double-blind, placebo-controlled human studies provided evidence to support some of these claims. In the elderly, DHEA exerts an immunomodulatory action, increasing the number of monocytes, T cells expressing T-cell receptor gamma/delta (TCR$\gamma\delta$) and natural killer (NK) cells. It improves physical and psychological well-being, muscle strength and bone density, and reduces body fat and age-related skin atrophy stimulating procollagen/sebum production. In adrenal insufficiency, DHEA restores DHEA/DHEAS and androstenedione levels, reduces total cholesterol, improves well-being, sexual satisfaction and insulin sensitivity, and prevents loss of bone mineral density. Normal levels of CD4+CD25^{hi} and FoxP3 (forkhead box P3) are restored. In systemic lupus erythematosus, DHEA is steroid-sparing. In an unblinded study, it induced remission in the majority of patients with inflammatory bowel disease. DHEA modulates cardiovascular signalling pathways and exerts an anti-inflammatory, vasorelaxant and anti-remodelling effect. Its low levels correlate with increased cardiovascular disease and all-cause mortality. DHEA/DHEAS appear protective in asthma and allergy. It attenuates T helper 2 allergic inflammation, and reduces eosinophilia and airway hyperreactivity. Low levels of DHEAS accompany adrenal suppression. It could be used to screen for the side effects of steroids. In women, DHEA improves sexual satisfaction, fertility and age-related vaginal atrophy. Many factors are responsible for the inconsistent/negative results of some studies. Overreliance on animal models (DHEA is essentially a human molecule), different dosing protocols with non-pharmacological doses often unachievable in humans, rapid metabolism of DHEA, co-morbidities and organ-specific differences render data interpretation difficult. Nevertheless, a growing body of evidence supports the notion that DHEA is not just an overrated dietary supplement but a useful drug for some, but not all, human diseases. Large-scale randomised controlled trials are needed to fine-tune the indications and optimal dosing protocols before DHEA enters routine clinical practice.

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Key Points

Dehydroepiandrosterone/dehydroepiandrosterone sulfate (DHEA/DHEAS) are human steroid hormones but also popular nutritional supplements marketed as 'anti-aging superhormones' and used excessively around the world. Until recently their mode of action remained poorly understood.

Recent good-quality data support their potential use in medicine (allergy, adrenal insufficiency, cardiovascular and inflammatory bowel disorders, senescence) and obstetrics and gynaecology (infertility, vaginal atrophy).

For now, routine supplementation cannot be recommended until more large-scale trials clarify the indications and dosing protocols.

1 Discovery of Dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone (DHEA; 3β-hydroxyandrost-5-en-17-one; prasterone) was isolated in 1934 from male urine by Butenandt and Dannenbaum, and in 1954 from human plasma by Migeon and Plager. Dehydroepiandrosterone sulfate (DHEAS; dehydroepiandrosterone-3-sulfate), a sulfated form of DHEA was obtained by Munson, Gallagher and Koch in 1944. Ten years later, Baulieu reported that DHEAS was the most abundant steroid hormone in human plasma. Between 1934 and 1959, DHEA appeared under different chemical names: dehydroandrosterone, transdehydroandrosterone, dehydroisoandrosterone and androstenolone. The name dehydroepiandrosterone was proposed by Fieser in 1949 [1, 2].

For almost 50 years after discovery, DHEA was considered to be an inert compound involved mainly in the bioconversion of cholesterol to androgens and estrogens. There had been no large human studies until the 1990s. Only then, because of their claimed anti-aging action and therapeutic benefits in a wide array of medical conditions, did DHEA/DHEAS become of interest to the scientific community and the general public [3, 4].

2 Mechanism of Action of DHEA

DHEA acts indirectly on the peripheral sex steroid target tissues or directly as a neurosteroid, and exerts its biological effects via multiple signalling pathways reviewed in detail elsewhere [5–8]. Its classic, genomic action remains controversial as no specific nuclear DHEA/DHEAS receptor protein has been identified [5, 8, 9]. However, there is emerging evidence that DHEA and some of its metabolites either bind to and activate or antagonise peroxisome proliferator-activated receptor (PPAR)-α and receptors for pregnane X (PXR), androstanol, estrogen β (ERβ), γ-aminobutyric acid type A ($GABA_A$) and *N*-methyl-D-aspartate (NMDA). DHEA also activates the Sigma-1 receptor (Sigma-1R), a unique ligand-regulated molecular chaperone in the endoplasmic reticulum of cells expressed in the heart, kidneys, liver and brain [5, 8, 9]. There is a large body of evidence that at least some of the cardiovascular and bronchodilating effects of DHEA are non-genomic (extranuclear, non-classical, membrane-initiated) in nature [6, 7, 10–13]. In 2002, Liu and Dillon identified a plasma membrane bound, $G\alpha_i2$ and $G\alpha_i3$ protein-coupled receptor for DHEA. This further supports the concept that DHEA is not just an inactive byproduct of the adrenals but a hormone in its own right [11, 12, 14]. Two recently synthesised photoreactive DHEA analogues will allow to further purify the plasma membrane DHEA receptor, identify the elusive nuclear DHEA receptor, and expand our understanding of the physiology and pathophysiology of DHEA [15–17]. Tables 1 and 2 summarise the current knowledge of the chemistry and mechanism of action of DHEA/DHEAS [2, 18–23].

3 DHEA: A Dietary Supplement

In the US, DHEA became available as a non-prescription drug in early 1980s. In 1985, the US FDA banned over-the-counter (OTC) sales of DHEA due to lack of health benefit and long-term safety data. The 1994 Dietary Supplement Health and Education Act allowed for certain substances to be sold without FDA approval as long as they were marketed as dietary supplements. Soon thereafter, the production of DHEA, newly recognised as a nutritional supplement, started developing at breakneck speed. Quality and quantity control was poor. Depending on the manufacturer, the quantity of DHEA varied from 0 to 150 % of the amount stated on the label. Moreover its OTC status encouraged 'off label', unlicensed use [24–28]. Currently, DHEA tablets, capsules, pessaries, creams and gels are easily available online, from health food stores and as OTC drugs. DHEA is obtained from soybean and wild yam extracts. Prasterone, an entirely synthetic form of DHEA, is also available [18, 19, 25].

4 Hopes and Hypes of DHEA

DHEA/DHEAS production in humans changes profoundly with age (Table 3) [29, 30]. At birth, circulatory levels are

Table 1 Chemistry of DHEA and DHEAS ([2, 18–22, 94, 95]

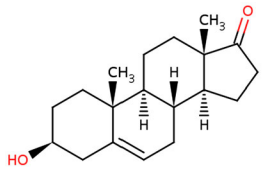
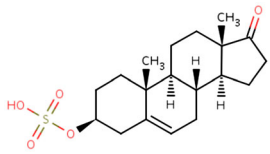
	DHEA (dehydroepiandrosterone; prasterone)	DHEAS (dehydroepiandrosterone sulfate; prasterone sulfate)
		
Chemical name	3β-hydroxyandrost-5-en-17-one	3β-hydroxyandrost-5-en-17-one 3-sulfate
Molecular formula	$C_{19}H_{28}O_2$ hydrophobic and lipophilic	$C_{19}H_{28}O_5S$ hydrophilic
Molecular weight (g/mol)	288.42442	368.49
Daily production rate	6–8 mg/day of active hormone	3.5–20 mg/day of inactivated, sulphated form
Serum concentration in adults	Males: 10.6–28.9 nmol/L	Males: 5.41–9.09 μmol/L
	Females: 9.77–26.7 nmol/L	Females: 2.23–9.20 μmol/L
Metabolic clearance rate (L/day)	~2000	5–20
Hepatic clearance	Rapid	Slow
Half-life time (h)	1–3	10–20

Table 2 Biology of DHEA and DHEAS [2, 9, 18, 19, 21–23]

	DHEA (dehydroepiandosterone; prasterone)	DHEAS (dehydroepiandosterone sulfate; prasterone sulfate)
Site of synthesis	75–90 % of DHEA synthesised in zona reticularis, remainder produced by testes, ovaries and brain	Almost exclusively in zona reticularis
Circadian variation	Pulsatile secretion, increased at night; mirrors secretion of corticotrophin	No diurnal variation
Blood carriers	95 % of DHEA and DHEAS bound to albumin; only 5 % free in blood. Albumin and sex hormone-binding globulin weakly bind DHEA but not DHEAS. Circulating DHEA (mostly in sulfated form) is highly metabolically available	
Metabolism	Bio-converted to androstenediol, androstenedione, estrone, testosterone, dihydrotestosterone and 17β-estradiol in bones, muscles, breasts, prostate, skin, adipose tissue, brain, and particularly liver from where active metabolites are released to reach peripheral targets; appears in urine as DHEAS, DHEA glucuronide and the metabolites of androstenedione and testosterone	In target tissues (brain, bone, breast and adipose tissue) undergoes continuous interconvertion with DHEA by DHEA sulfotransferases and hydroxysteroid sulfatases
Biological activity	A large reservoir of precursors for intracellular production of androgens and estrogens in non-reproductive tissues; ≥30 % of total androgens in men and 75 % of estrogens in pre-menopausal and close to 100 % in post-menopausal women produced by intracrine conversion of DHEA/DHEAS steroids in peripheral tissues	A large and stable plasma reservoir of DHEA
	Acts indirectly on peripheral sex steroid target tissues following conversion to androgens, estrogens or both, or directly as a neurosteroid via interaction with neurotransmitter receptors in the brain	
	Exerts its effect via multiple signalling pathways involving nitric oxide synthase activation, modulation of γ-amino butyric acid receptors, *N*-methyl D-aspartate, receptor sigma receptors (Sigma-1), differential expression of inflammatory factors, adhesion molecules and reactive oxygen species expression and via transformation into androgen and estrogen derivatives, e.g. androgens, estrogens, 7α and 7β DHEA, and 7α and 7β epiandrosterone derivatives acting through their specific receptors	
Clinical role	Supplementation in the elderly, menopause, ovarian dysfunction, Addison's disease, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, asthma, allergic rhinitis, urticaria, chronic obstructive pulmonary disease	Marker in Cushing's disease; screening test in asthma treated with inhaled glucorticosteroids

Table 3 DHEA and DHEAS: normal values [29, 30]

	Sex	Age range (years)	DHEA range (ng/L)[a]
DHEA	Men	6–24 months	<2,500
		2–3	<630
		4–5	<930
		6–7	60–1,930
		7–9	100–2,080
		10–11	320–3,080
		14–15	930–6,040
		16–17	1,170–6,520
		18–40	1,330–7,780
		40–67	630–4,700
	Women	6–24 months	<1,990
		2–3	<630
		4–5	<1,030
		6–7	120–1,520
		7–9	140–2,350
		10–11	430–3,780
		12–13	890–6,210
		14–15	1,220–7,010
		16–17	1,420–9,000
		18–40	1,330–7,780
		40–67	630–4,700
	Sex	Age range (years)	DHEAS range (ng/ml)
DHEAS	Men	15–39	1,500–5,000
		40–49	1,000–4,000
		50–59	600–3,000
		>60	300–2,000
	Women	15–29	1,000–5,000
		30–39	600–3,500
		40–49	400–2,500
		>50	200–1,500

DHEA dehydroepiandrosterone, *DHEAS* dehydroepiandrosterone sulfate

[a] Divide by 1,000 to convert to nanograms per millilitre

high and reach maximal values between the age of 20 and 30 years. Thereafter, their concentration steadily declines. At the age of 70–80 years, peak concentrations are only 10–20 % of those in young adults. This age-related decline in DHEA secretion by adrenal cortex (adrenopause) does not affect other adrenal steroids. It is associated with many age-related involuntary changes: sarco- and osteopenia, atherosclerosis, immunosenescence, and cognitive and mood impairment [2, 9, 24–26, 29, 30]. Interestingly, DHEA concentration correlates with longevity in healthy non-human primates. Epidemiologic studies seem to suggest a similar relationship in humans [3, 31]. Understandably these observations sparked patient and doctor interest. Manufacturers of DHEA started marketing it as an agent against and a cure for aging, obesity, diabetes, cancer and heart diseases. They alleged it prolonged lifespan. Overzealous and often indiscriminate marketing by scientists and hucksters turned DHEA into a potential remedy for any illness (*cure-all* elixir), particularly in the US. It is still often advertised as a 'superhormone', 'mother of all hormones', 'hormone of youth', 'fountain of youth' or an 'anti-aging' agent [3, 4, 9, 20, 21, 32].

5 Controversies of DHEA and DHEAS

Multiple factors might be responsible for the divergent, inconsistent or even negative results of studies on the role of DHEA/DHEAS in human health and disease [9, 19, 24, 25, 33–40]:

- *Study models*: Rodent tissues respond to DHEA differently due to a lack of physiologically high levels of serum DHEA; laboratory/domestic species' low plasma DHEA levels are mainly or exclusively gonadal in origin; in contrast, human DHEA is synthesised almost entirely by the adrenals.
- *Physiology versus pharmacology*: The effects of pharmacological doses of DHEAS differ from those of its physiological concentrations because of different mechanisms of action; physiologically-produced DHEAS metabolises and activates cellular receptors; pharmacological doses may additionally impact on membrane fluidity and affect intracellular enzymes directly; moreover, in vitro studies often rely on non-physiological doses, often unachievable in humans; the effect of supranormal doses may be quite different from physiological ones and relate to a different mechanism of action
- *Metabolism*: Rapid and extensive conversion of DHEA into multiple active metabolites which could be the actual active molecular forms; it confounds the assessment of the net effects of DHEA even further.
- *Normal values in humans*: DHEA levels vary widely by age, sex and ethnicity, and are affected by day-to-day changes in corticosteroid production, alcohol intake, smoking, body mass index, medications and thyroid function; this inter- and intra-individual variability complicates the interpretation of clinical data regarding DHEA levels.
- *Age and comorbidities*: Healthy elderly have DHEA levels severalfold greater than patients with adrenal insufficiency; extrapolation of results from one group to another is difficult.
- *Organ-specific differences*: DHEA in the skin is transformed mainly into dihydrotestosterone (DHT); in the vagina to estrogens; DHEA effects can be

estrogenic or androgenic and either conducive or inhibitory to health or disease, depending on the hormonal and metabolic conditions and the responsiveness of the targeted condition to hormonal or intracrine effects.

– *Supplementation doses and route*: In clinical studies, oral doses of DHEA ranged from 25 to 200 mg/day; there is a high first-pass effect; route of administration (oral, inhaled, topical) influences the metabolism and therapeutic efficacy of DHEA, e.g. intravaginal (topical) but not oral DHEA alleviates vaginal atrophy and improves sexual function in postmenopausal women; human trials yield conflicting results due to varying study design; dose, route and duration of treatment; distinct basic clinical condition of the participants; sample size and clinical endpoints.

Finally, DHEA is an endogenous metabolite and cannot be patented. Therefore, the pharmaceutical industry is reluctant to fund expensive human studies [32]. Private and institutional sponsors are not inclined to support further research because DHEA is already commonly available as a nutraceutic (even though it is not a food) [24].

6 DHEA: Evidence from Animal and Human Studies

DHEA is a 'human' molecule as its adrenal secretion is minimal/absent in laboratory animals (including rodents) [32]. Studies on animal models are therefore not entirely reliable and most have been excluded from our review [3, 9, 19, 33, 34]. However, there are a number of good-quality, double-blind, placebo-controlled human studies investigating the role of DHEA.

6.1 The Elderly

Morales et al. randomised 13 healthy men and 17 women aged 40–70 years to 3 months of DHEA 50 mg/day and 3 months of placebo at bedtime in a crossover manner. After 2 weeks its serum level was restored to that of young adults and was sustained throughout the trial. At 12 weeks, in the active group, there was a significant ($p < 0.005$) improvement in self-reported well-being: quality of sleep, general mood, vital energy and stress-handling, but not libido scores [41]. Around the same time, Yen et al. enrolled nine healthy men (mean age 63 years) in a 5-month, single-blind, placebo-controlled trial. Patients took nightly placebo orally for the first 2 weeks followed by oral DHEA (50 mg/day) for 20 weeks. DHEA boosted the immune system causing a biphasic increase ($p < 0.01$) in monocytes (CD14) at 2 and 20 weeks and doubling of T cells expressing the T-cell receptor gamma/delta (TCR γδ) [$p < 0.01$] after 20 weeks. An increased proliferative response to phytohemagglutinin, a T-cell-specific mitogen, occurred at 12 weeks, and a significant ($p < 0.01$) increase in serum sIL2-R and T cells expressing the interleukin (IL)-2 receptor (CD25) at 20 weeks. Additionally, DHEA replacement significantly ($p < 0.01$) increased the number of natural killer (NK) cells (CD16, CD57) by 20 weeks [42]. Subsequently, Morales et al. undertook a 1-year, randomised, double-blind, placebo-controlled, crossover trial with a 2-week 'washout' period between the 6 months of oral DHEA 100 mg/day and 6 months of placebo. Ten menopausal women (54.5 ± 1.2 years) and nine men (55.6 ± 1.9 years) entered into the study. DHEA 100 mg/day increased its serum levels from baseline: threefold ($p < 0.001$) in men and fivefold ($p < 0.001$) in women, to the levels of young adults. The treatment resulted in a fivefold increase in androstenedione (A) in women ($p < 0.001$), which was greater than the twofold elevation seen in men ($p < 0.01$). In men, there was no change in serum testosterone (T) or DHT, while in women, T levels increased fourfold ($p < 0.001$) and DHT levels threefold ($p < 0.001$) consistently with a greater intracrine androgen formation in women. In men, fat body mass decreased ($p < 0.05$) and maximal voluntary isometric strength of the lumbar extensor and quadriceps increased significantly, whereas in women only total body mass increased significantly ($p < 0.05$) [43].

At the end of the 20th century, Baulieu et al. undertook a 1-year, randomised controlled trial (RCT) of 50 mg/day of oral DHEA (prasterone) in healthy 60- to 79-year-olds. Serum DHEAS returned to young adult values after 6 months. In women, DHEA supplementation improved bone mineral density (BMD) [$p < 0.05$], mostly in trabecular zones at the femoral neck and the Ward's triangle (<70 years of age) and at upper radius (>70 years of age). No effect on bone turnover was recorded in men. A significant improvement in skin hydration, epidermal thickness, sebum production and pigmentation was noted, particularly in women over 70 years of age [44]. Another trial randomised 55 men and 58 women aged 65–75 years to a year-long course of oral DHE 50 mg/day or placebo. In the second year, a subset of participants took open-label DHEA in the same dose. During both years, all participants received vitamin D (16 μg/day) and calcium (700 mg/day). BMD was measured using dual-energy X-ray absorptiometry (DEXA). At the end of years 1 and 2, serum DHEAS level increased five- to sevenfold in the DHEA group (both sexes) but did not change in the placebo group. In older women, L2–L4 lumbar spine BMD increased ($p < 0.05$) after 6 months, and remained elevated until the end of study in the DHEA group only. There was no effect of DHEA replacement on BMD in men. No adverse effects occurred except for a slight decrease in high-density lipoprotein (HDL) in one female [45].

In 2011, a group of 136 healthy, 65- to 75-year-old volunteers of both sexes were randomised to 1 year of DHEA 50 mg/day or placebo. After completing a 12-month RCT, 112 participants volunteered to continue in an open-label study for an additional 12 months. The patients who had been randomised to DHEA replacement continued taking DHEA for a second year, while those who had been in the placebo group crossed over to DHEA replacement for 12 months. The men in the DHEA group had a small but significant ($p < 0.001$) decrease in body weight, body fat percentage and total fat mass only during the first year of DHEA replacement. DHEA significantly ($p < 0.05$) improved oral glucose tolerance test (OGTT) values, but only in patients with abnormal glucose tolerance. It persisted during the additional 12 months of open-label DHEA supplementation. A significant decrease in plasma triglycerides ($p < 0.05$) and inflammatory cytokine IL-6 ($p < 0.004$) in response to 1 year of DHEA therapy was also present. There were no serious adverse events except for acne in two women, which resolved spontaneously, and increased facial hair growth in another woman [46].

Beneficial effects of DHEA on skin function were confirmed in three studies. A pilot RCT involved 40 healthy post-menopausal women aged 55–70 years randomised to a 1 % DHEA cream or vehicle only (no active ingredient). Applications were made twice a day for 4 months to the face and the back of one hand. The other hand receiving no treatment was taken as the control. The efficacy of treatment was evaluated at 0 and 4 months, on the basis of clinical and biophysical criteria of skin aging. After 4 months, DHEA significantly increased ($p = 0.0001$) the number of active sebaceous glands and the rate of sebum production. It was perceived positively by the menopausal population usually affected by a declining sebum level. Topical DHEA improved hand skin tone ($p = 0.06$) and counteracted its papery appearance and epidermal atrophy associated with hormone-related skin aging. Moreover, although the length of wrinkles and mean wrinkle area increased significantly in the vehicle group ($p = 0.002$ and $p = 0.01$ respectively), they remained constant in the DHEA group ($p = 0.53$) [47]. The second RCT included 75 postmenopausal women aged 60–65 years treated twice daily for 13 weeks with placebo or 0.1, 0.3, 1 or 2 % DHEA cream applied to the face, arms, back of hands, upper chest and right thigh. Skin biopsies were taken before and after treatment. In the epidermis, the expression of androgen receptor was increased in all DHEA groups ($p < 0.05$). In the dermis, all concentrations significantly ($p < 0.001$) increased procollagen-1 mRNA expression, Procollagen-3 mRNA expression was significantly ($p < 0.0001$) increased only in the 2 % DHEA group. Additionally, the number of dermal fibroblasts expressing heat shock protein 47 (HSP 47), which may affect procollagen synthesis, was increased, but only in the 1 and 2 % DHEA groups [48]. In the third study, a 5 % DHEA solution was applied 12 times over 4 weeks to the buttocks of six elderly (age range 75–87 years) and five young men (age range 22–24 years), with no current or prior skin disease. DHEA increased the expression of procollagen α1 (type I) mRNA ($p < 0.05$ and $p < 0.01$, respectively) and type I procollagen protein ($p < 0.05$) in both groups. In the aged skin, only DHEA significantly decreased basal expression of matrix metalloproteinase (MMP)-1 mRNA ($p < 0.01$) and MMP-1 protein ($p < 0.05$), increased the expression of tissue inhibitor of metalloproteinases (TIMP)-1 ($p < 0.01$), induced the expressions of transforming growth factor (TGF)-β1 ($p < 0.05$) and connective tissue growth factor (CTGF) mRNA ($p < 0.05$) in cultured fibroblasts. These could be responsible for a desirable DHEA-induced procollagen synthesis in the elderly [49].

6.2 Adrenal Insufficiency

A 4-month crossover RCT studied 24 women aged 42 ± 9 years with adrenal insufficiency of 9 ± 2 years' duration who received, in random order, oral DHEA 50 mg/day and placebo, with a 1-month washout period. DHEA significantly ($p < 0.001$) raised the initially low serum concentrations of DHEA, DHEAS and A into the normal range. Serum T and DHT concentrations increased to a low–normal range. Compared with placebo, DHEA significantly decreased total ($p = 0.02$) and HDL cholesterol ($p = 009$) and improved overall well-being. DHEA significant reduced the scores on the 90-item symptom checklist for depression ($p = 0.05$) and anxiety ($p = 0.09$), and increased the frequency of sexual thoughts or fantasies ($p = 0.006$), sexual interest ($p = 0.002$) and satisfaction with both mental and physical aspects of sexuality ($p = 0.009$ and $p = 0.02$, respectively) [50].

Another 1-year RCT enrolled 106 subjects (median age 46 years; 62 females) with Addison's disease. Patients received oral micronized DHEA 50 mg/day or placebo for 12 months. In both sexes, serum DHEAS rose markedly within 1 month to the physiological range for young adults, and was maintained throughout the study period. It fell back to a low baseline level a month after discontinuing DHEA. There was a similar rise in A during DHEA treatment in both sexes, with T increasing to low–normal levels in females only ($p < 0.001$). DHEA replacement therapy reversed ongoing loss of BMD at the femoral neck ($p = 0.05$); significantly enhanced total body ($p = 0.02$) and truncal ($p = 0.017$) lean mass with no change in fat mass; and significantly improved ($p = 0.0004$) the score for the emotional dimension of health in the Short Form 36

Health Survey (SF-36). There was no significant beneficial effect on fatigue, memory, verbal fluency, visual search accuracy, libido and sexual function. Females receiving DHEA reported increased occurrence of skin spots, greasy skin, and axillary hair growth [51].

A single-centre, crossover RCT included 28 hypoadrenal women (mean age 50.2 ± 2.87 years) who received oral DHEA 50 mg/day or placebo for 12 weeks. DHEA replacement significantly ($p < 0.00001$) increased DHEAS, total T and A, and reduced total cholesterol ($p < 0.005$), triglycerides ($p < 0.011$), low-density lipoprotein (LDL) cholesterol ($p < 0.05$) and HDL cholesterol ($p < 0.005$). There was a significant reduction in fasting plasma insulin ($p < 0.06$) and increase in insulin sensitivity in hypoadrenal women. It had no effect on body weight, fat mass or free fat mass [52].

A study from Cambridge, UK, included ten patients (five females; mean age 41 years) with Addison's disease of a mean duration of 16 years (5–34) who received DHEA 50 mg/day for 12 weeks. All patients continued their standard treatment with corticosteroids, fludrocortisone and, in seven cases, thyroxin. The pre-DHEA supplementation number of circulating regulatory T cells was reduced. Oral DHEA restored normal levels of regulatory $CD4^{+}CD25^{hi}$ (high staining) T cells after 4 weeks. At 12 weeks, there was an increased expression of FoxP3 (forkhead box P3), a constitutive transcriptional factor necessary for $CD4^{+}CD25^{hi}$ lymphocyte function. The number of peripheral NK ($CD3^{-}CD56^{+}$) and NKT ($CD3^{+}CD56^{+}$) cells reduced significantly ($p < 0.05$). Homeostatic lymphocyte proliferation increased. There was also an increase in constitutive, but reduction in stimulated, $CD4^{+}$ T-cell regulation. At 4 weeks, levels of interferon (IFN)-γ ($p < 0.01$), IL-5, IL-10 and TGF-β ($p < 0.05$) rose [53].

6.3 Systemic Lupus Erythematosus and Inflammatory Bowel Diseases

A Taiwanese multicenter RCT included 120 adult women with active systemic lupus erythematosus (SLE) who received oral DHEA (200 mg/day; $n = 61$) or placebo ($n = 59$) for 24 weeks. Although there was no significant difference in the SLE activity measure (SLAM) score between the two groups, significantly fewer patients in the DHEA group had disease flare-ups ($p = 0.044$). The mean change in patients' global assessment was statistically significant between the DHEA and placebo groups ($p = 0.005$). DHEA was well-tolerated [54].

A GL701 Lupus Study enrolled 191 female SLE patients (mean age 40 years) from 18 US centres. All patients were receiving prednisone (10–30 mg/day). They were randomly assigned to receive placebo, 100 or 200 mg/day prasterone (GL701, Genelabs, CA, USA) administered as four capsules every morning for at least 7 months. In patients with active SLE (SLE disease activity index [SLEDAI] >2), the number of days on prednisone <7.5 mg/day was significantly higher in the prasterone 200-mg group compared with placebo ($p < 0.015$). A reduction in HDL level occurred in the 200-mg group compared with placebo ($p = 0.002$), while reductions in LDL, total cholesterol and triglycerides occurred in all groups. Adverse events—acne, hirsutism, menstrual abnormalities (spotting, metrorrhagia) or abdominal pain—were transient, generally mild and did not require discontinuation of the drug [55].

A 2003 German study reported that DHEA was clinically effective in seven patients with refractory Crohn's disease and 13 with ulcerative colitis (UC) [aged 18–45 years]. This small, unblinded, phase II pilot study without placebo included only patients with active disease (Crohn's disease activity index [CDAI] >150 and clinical activity index [CAI] >4, respectively). Serum concentrations of DHEAS increased significantly ($p < 0.001$) during the treatment period in all patients irrespective of sex. In 86 % of Crohn's patients the mean CDAI decreased from 242 ± 51 to 111 ± 106 points ($p = 0.0012$), and patients went into remission (CDAI <150). Sixty-one percent of UC patients responded to treatment with a decrease in CAI of >4 points. Six patients went into remission (CAI <4). The mean number of liquid stools, bloody diarrhoea and abdominal pain decreased significantly in UC, but not Crohn's patients. No patients withdrew from the study. Side effects—intermittent nausea, colds, hoarseness or herpes labialis—were sporadic and resolved during or shortly after DHEA treatment [56]. Unfortunately these encouraging preliminary data have not been followed up with a large RCT, which precludes the standard use of DHEA in inflammatory bowel disease.

6.4 Cardiovascular Diseases

The evidence for a protective role of DHEA in vascular inflammation, atherosclerosis and elevated pulmonary vascular resistance was observed in many animal studies but only a few human clinical studies [7, 10, 34]. DHEA exerts its beneficial anti-remodelling, anti-inflammatory and vasorelaxant action-modulating membrane potential values, ion channels, endothelial nitric oxide (NO) production, oxidative stress, cell proliferation and apoptosis. It impacts on many signalling pathways: 3-phosphoinositide-dependent kinase/Akt/endothelial NO synthase (PI3K/Akt/eNOS), Akt/glycogen-synthase-kinase-3β/nuclear factor of activated T cells (Akt/GSK-3-β/NFAT), PI3K/NFAT, cyclic guanosine monophosphate (cGMP), RhoA signalling G protein/Rho kinases (RhoA/ROCK) or nuclear factor

kappa B (NF-κB) [7, 10, 57, 58]. A recently published Women's Ischemia Syndrome Evaluation (WISE) observational study included 270 postmenopausal women. Lower DHEAS level significantly correlated with a higher cardiovascular disease (CVD) mortality ($p = 0.011$) and all-cause mortality ($p = 0.011$) [59].

6.5 Asthma and Allergic Diseases

Despite an increased understanding of the mechanism of DHEA/DHEAS action, its effects on asthma, atopic dermatitis or chronic urticaria (CU) are still poorly understood [17, 44]. In animal models it appears to be an important immunomodulatory hormone despite its minimal secretion [9, 32, 60–63]. DHEA attenuates *Dermatophagoides farinae*-induced airway response in BALB/c mice with established asthma, significantly reducing eosinophil and lymphocyte count and IgE, IL-4 and IL-5 T helper 2 (Th2) cytokine levels in bronchoalveolar lavage (BAL) or serum [60]. In ovalbumin (OVA)-sensitised mice, DHEA works synergistically with Bacillus Calmette–Guérin (BCG), reducing BAL eosinophilia and airway hyperresponsiveness (AHR) [61]. DHEA suppresses methacholine-induced airway hypersensitivity and decreases eosinophil infiltration in the lungs of OVA-sensitised mice [62]. In the tracheal rings from non-sensitised and sensitised guinea pigs, DHEA elicits a concentration-dependent airway smooth muscle (ASM)-relaxing effect on contraction induced by potassium chloride, carbachole or OVA, as well as a marked preventive effect on the Ca^{2+}-induced contraction. Administration of DHEA in sensitised guinea pigs suppresses OVA-induced bronchospasm in a dose-response manner. DHEA acts as a 'bronchoactive' steroid that induces ASM relaxation. DHEA inhibits Ca^{2+}-induced ASM contraction by blocking, at least in part, voltage-dependent calcium channels (VDCC) and receptor-operated calcium channels (ROCC), as well as store-operated Ca^{2+} entry (SOCE) [11].

Although animal models replicate many features of human asthma, extrapolation of animal data and translation from bench to bedside remains problematic. Moreover, the absence of a truly chronic animal model of asthma is a major limiting factor [64]. However, there are a few scientifically rigorous and methodically correct human studies confirming the immunomodulatory action of DHEA/DHEAS in allergic diseases. The beneficial effect of DHEA on Th2-associated cytokines was reported more than a decade ago by Tabata et al. in 47 adult males with atopic dermatitis. Preincubation of peripheral blood mononuclear cells (PBMC) with DHEA significantly ($p < 0.05$) reduced IL-4 and increased IL-2 production by concanavalin A-stimulated PBMC. IL-5 production also showed a tendency to decrease but it was not significantly affected by preincubation of PBMC with DHEA [65]. In 2008, Choi et al. [63] showed that DHEA suppressed both Th1 and Th2 responses, with a Th1 bias, and the degree of suppression was associated with the severity of AHR or atopy. In 21 subjects (20.2 ± 0.4 years) with a positive metacholine challenge, DHEA added to concanavalin A-stimulated PBMC significantly suppressed IL-10, IL-5 and IFN-γ production in a dose-dependent manner (all $p < 0.001$) and tended to increase the IFN-γ/IL-5 ratio ($p = 0.087$). Cytokine suppression was significantly related to AHR, serum total IgE levels, and skin reactivity to house dust mites [63]. The other study investigated the effect of DHEAS on cells involved in the pathogenesis of asthma and chronic obstructive pulmonary disease (COPD)—human ASM cells (HASM) and pulmonary human neutrophils (PMN). DHEAS dose-dependently inhibited chemotaxis of PMN and HASM, but had little effect on the phosphorylation levels of the canonical positive regulators of cell migration—Akt kinase, extracellular signal-regulated protein kinases 1/2 (ERK 1/2), p38 mitogen-activated protein kinase (MAPK) or protein kinase C (PKC). Treatment of neutrophils with DHEAS inhibited PMN chemotaxis and migration, suggesting that DHEAS may attenuate airway inflammation in both diseases [66]. Finally, a single, multicentre, double-blind, placebo-controlled RCT assessed the efficacy of DHEAS suspension (GenaFlow; Epigenesis Pharmaceuticals, Cranbury, NJ, USA) in subjects with poorly-controlled moderate-to-severe asthma. Nebulised DHEAS 70 mg/day led to a statistically significant improvement in the Asthma Control Questionnaire (ACQ) after 6 weeks. Asthma symptom scores, the proportion of symptom-free days and nights, were not statistically significant but had positive trends [67].

DHEA had a beneficial effect on atopic dermatitis-like skin lesions in BALB/c mice sensitised and challenged with 0.5 % 1-chloro-2,4-dinitrobenzene and treated topically for 15 days with DHEA 50 or 100 mg/kg (Sigma–Aldrich, St. Louis, MO, USA) [groups A50 and A100] or fed DHEA 50 or 100 mg/kg (groups B50 and B100). Both forms of DHEA significantly decreased ear thickness, skin erythema and scaling, and suppressed ear swelling. They also significantly reduced eosinophil and mast-cell infiltration in the skin and ears, particularly the A100 and B100 groups. IgE, IgG1, IL-4 and tumour necrosis factor (TNF)-α levels were significantly suppressed compared with the sensitised control group. The extent of improvement did not differ significantly between topical and oral DHEA administration. In the same study, TNFα-stimulated inflammatory human keratinocytes (HaCat cells) were pretreated with DHEA which suppressed the expression of proinflammatory cytokines IL-6, IL-8, macrophage-derived chemokine (MDC), monocyte chemotactic protein (MCP)-

1, thymus and activation regulated chemokine (TARC), phosphorylation of IκB-α, ERK1/2, p38, and c-Jun N-terminal kinase (JNK) and nuclear translocation of p56 in a significant and concentration-dependent manner. The authors concluded that DHEA ameliorated inflammatory symptoms in female BALB/c mice by significantly blocking inflammation-associated signaling pathways, including IκB-α and MAPK phosphorylation and nuclear translocation of NF-κB p65 [68].

Data from Kasperska-Zajac et al. [69, 70] suggest that DHEA may play a role in urticarial inflammation as, irrespective of sex and age, serum DHEAS concentration was low in CU. In these patients, it correlated negatively with the anxiety levels and depression intensity but positively with the total sense of coherence (SOC). It might suggest that DHEAS decline in CU is a phenomenon secondary to the psychological distress common in CU [71]. However, due to the scarcity of experimental and clinical data, the role of DHEAS in urticaria warrants further studies [23, 69–73].

In mice, DHEA seems to oppose the action of glucocorticosteroids (GC). In vivo pre-treatment with DHEA 60 mg/kg/day for 3 days antagonised the profound suppression of in vitro blastogenic response seen in T and B lymphocytes after a single injection of dexamethasone (DEX). Pretreatment with DHEA also significantly reduced DEX-induced thymic and splenic atrophy. Splenic lymphocytes from DHEA-treated mice were markedly more resistant to in vitro suppression of blastogenesis by DEX at 10^{-6} to 10^{-8} M compared with lymphocytes from control mice [74]. Suppression of IL-2 production and augmentation of IL-4 production in mice treated with 5 mg corticosterone was reversed by in vivo treatment with 5 mg of DHEA, or the use of 5 mg corticosterone with 5 mg DHEA [75]. DHEA, in contrast to DEX, did not suppress growth factors involved in bone formation—vascular endothelial growth factor (VEGF), fibroblast growth factor-5 (FGF-5) and insulin-like growth factor-binding protein 3 (IGFBP3). However, DHEA suppressed expression of the DEX-induced receptor activator of the NF-κB ligand (RANKL) and reversed the DEX-induced increase in RANKL/OPG ratio (osteoprotegerin, the decoy receptor for RANKL), suggesting that it can inhibit the catabolic action of GCs on the skeleton. Finally DHEA, similar to DEX, reduced the expression of several proinflammatory/resorptive cytokines—IL-6, IL-4 and IFN-γ [76]. Interaction of DHEA and cortisol seems relevant for the expression of the scaffold protein receptor for activated C kinase 1 (RACK-1). DHEA 100 nM almost completely counteracted the effect of cortisol on RACK-1 proteins as early as 16 h after treatment. DHEA significantly reduced the inhibitory effects of cortisol on guanine nucleotide-binding protein (G Protein), β polypeptide 2-like (GNB2L1) luciferase promoter activity which contains a putative consensus glucocorticoid responsive element (GRE) only at 72 h of study. DHEA also prevented cortisol inhibitory effects, restoring TNFα release to control values after 16 h of treatment, indicating that DHEA not only counteracts the effect of cortisol on RACK-1 expression but also has opposite effects to cortisol on immune functionality [77]. Long-term exposure to DHEA seems to affect the transcriptional activity of the GC receptor (GR) because 72 h of incubation with DHEA diminishes GR-dependent expression of the reporter gene ErbB-2 mRNA and protein, abates cellular proliferation and inhibits association of GR to a standard GRE sequence. In conditions where DEX promotes nuclear translocation and transcriptional activation of GR, DHEA enables a slow GR nuclear translocation but inhibits its DNA binding in the dimeric active form [35]. Thus far, the steroid sparing effect of DHEA has only been confirmed in SLE. However, these results might prove DHEA and its analogues to be useful in other inflammatory disorders requiring chronic GC therapy—asthma, atopic dermatitis, severe chronic spontaneous or autoimmune urticaria and COPD [23, 55, 78, 79]. Unfortunately, none of the combinations of DHEA with GCs, inhaled β2 agonists/anticholinergics, antihistamines and anti-IgE patented in the US between 1999 and 2005 have been studied in RCTs [23, 78, 80]. Because of its long-term stability and highly significant correlation with cortisol and ACTH levels, DHEAS, but not DHEA, might become a new marker for the diagnosis and follow up of Cushing's disease, particularly in the preoperative phase. Moreover, DHEAS might be used as a screening test for the adverse effects of long-term inhaled GC in asthma. Low or a significantly decreased serum DHEAS points at adrenocortical suppression and a higher risk of systemic side effects such as osteoporosis [2, 22, 81].

6.6 Ovarian Dysfunction and Vaginal Atrophy

Fusi et al. investigated the effect of 12 weeks of micronized DHEA 75 mg before a long stimulation protocol for in vitro fertilisation (IVF). It improved the ovarian function allowing for unexpected spontaneous pregnancies among young poor responders [82]. Labrie et al. focused on vaginal atrophy. All concentrations of intravaginal prasterone (0.25, 0.5, 1.0 %) used in a phase III, 12-week RCT in 216 postmenopausal women induced a highly significant beneficial change in the percentage of vaginal parabasal and superficial cells, vaginal secretions, colour, epithelial surface thickness, epithelial integrity and vaginal pH. The second trial evaluated the effect of 12 weeks of daily intravaginal prasterone on sexual dysfunction—desire/interest, arousal, orgasm and pain at sexual activity—in 216 postmenopausal women with moderate to severe vaginal

atrophy. A time- and dose-dependent improvement in all domains of sexual function was observed. At 12 weeks, 1.0 % DHEA compared with placebo exerted a relatively beneficial effect on sexual function in women and improved desire ($p = 0.0257$), arousal/sensation ($p = 0.006$) and arousal/lubrication ($p = 0.0014$), orgasm ($p = 0.047$) and dryness during intercourse ($p = 0.0001$) [83, 84].

7 DHEA Replacement: When?

As yet, there is not enough evidence to recommend routine use of DHEA in day-to-day clinical practice. Recent meta-analyses have produced conflicting results. Alkatib et al. [37] confirmed a small but clinically trivial improvement in health-related quality of life, depression, anxiety and sexual function scores in elderly women with adrenal insufficiency treated with oral DHEA. Davis et al. [85] concluded that oral DHEA in postmenopausal women did not improve sexual function, well-being, cognitive performance or lipid and carbohydrate metabolism. In elderly men, DHEA supplementation was associated with a small but significant reduction of fat mass but no effect on lipid and bone metabolism, glycaemia, sexual function and quality of life [86]. Nevertheless, there are groups who might benefit from DHEA supplementation. Patients with adrenal insufficiency with persistently and seriously impaired quality of life despite optimal conventional gluco- and mineralocorticoid replacement might be one of those [19, 24, 26, 87]. DHEA appears promising in some forms of CVD and hypoxic pulmonary hypertension linked to COPD, but additional large, multicentre, clinical studies are required. [6, 7]. Based on recently published studies, DHEA seems beneficial in female infertility as it raises fecundity and fertility [82, 88–91]. These contrast with two small meta-analyses that failed to detect any significant difference in pregnancy and miscarriage rates between those pre-treated with DHEA and those who were not. Therefore, it is too early to recommend the routine use of DHEA as an adjuvant to controlled ovarian stimulation in IVF [92, 93]. However, its replacement may be recommended in men and women with severe and disabling signs of adrenopause but not in healthy elderly men and women. In other cases, replacement remains experimental [9, 19, 21, 25, 26]. The recommended oral dose of DHEA ranges from 25 to 50 mg/day. Tablets need to be taken at bedtime to stimulate the circadian rise in DHEA secretion in the last hours of the night [20, 25, 32]. If patients opt for DHEA supplementation, potential risks and side effects need to be discussed [19, 32]. These are generally mild and transient; androgenic skin side effects—greasy skin, acne, and increased facial, axillary and pubic hair growth—are among the most common. Understandably, DHEA supplementation is contraindicated in patients with sex steroid-dependent prostate, breast and endometrial cancers [24, 25, 45, 46, 50, 51]. During supplementation, especially in the elderly, DHEAS and its androgenic and estrogenic metabolite levels should be measured at least annually to minimise the risk of breast or prostate cancer. Prostate-specific antigen test and mammography should be carried out according to current guidelines [19, 20, 25, 32].

8 Conclusions

A growing body of evidence challenges the notion that DHEA and its metabolites are merely a worthless dietary supplement with no proven health benefits. It is becoming evident that DHEA might be of value in gynaecology, endocrinology, rheumatology, dermatology and allergy. However, more large-scale, well-designed RCT studies are warranted before it enters routine clinical practice. Indications, optimal dosage and duration of treatment need to be determined. This will require a multidisciplinary effort of the medical, pharmaceutical, patient, regulatory and scientific communities [24, 32, 40].

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