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REVIEW

Dehydroepiandrosterone administration in humans: evidence based?

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ABSTRACT

Dehydroepiandrosterone (DHEA) and its ester dehydroepiandrosterone sulphate (DHEAS) are produced by the adrenal glands. These hormones are inactive precursors that are transformed into active sex steroids in peripheral target tissues. After a peak in early adulthood, there is a marked decrease in plasma concentrations throughout adult life. These hormones are thought to affect mood and well-being, have neurosteroid effects and may influence the immune system. Animal experiments suggest that DHEA has many other effects, including anticancer, immune-enhancing, neurotropic and general antiageing effects, but information based on studies in humans is limited. In female patients with adrenal insufficiency, treatment with DHEA replacement doses of 20 to 50 mg results in improvements in mood, quality of life and libido. These studies usually lasted only a few months, so the effect of chronic DHEA treatment or its effectiveness in male patients is not known. Some studies suggest a favourable effect of pharmacological doses of DHEA in the treatment of depression. DHEA may have a very limited effect on cognitive function in elderly people, and some studies suggest a beneficial immunomodulatory effect of DHEA in patients with autoimmune diseases, but further studies are warranted before introducing DHEA for these indications in clinical practice.

KEYWORDS

Adrenal insufficiency, autoimmune diseases, cognitive function, DHEA, mood, well-being

INTRODUCTION

Dehydroepiandrosterone (DHEA) and its ester dehydroepiandrosterone sulphate (DHEAS) are the main secretory products of the adrenal zona reticularis, and are known as 'adrenal androgens'. DHEA is lipophilic, and can be converted to DHEAS by activity of the enzyme sulphotransferase in the liver and adrenal glands. DHEAS is the hydrophilic storage form that circulates in the blood, bound to albumin. DHEAS can be converted into DHEA by activity of the enzyme sulphatase in peripheral tissues. DHEA and DHEAS are inactive androgen precursors that are transformed into active sex steroids in peripheral target tissues, e.g. hair follicles, prostate, external genitalia, adipose tissue and the brain. These transformations depend on the tissue activity of metabolising enzymes and result in the production of active androgens (androstenedione, testosterone) and oestrogens (oestradiol and oestrone). In men, about 50% of androgens are derived from adrenal precursor steroids. In premenopausal women, about 75% of oestrogen synthesis occurs in peripheral target cells, and this is almost 100% in postmenopausal women.[1] The sex steroids that are derived from intracellular conversion of DHEA have their action mainly within the cells in which they are produced.

The production of DHEA(S) shows a strong association with age. Serum concentrations of these androgens are low during the prepubertal period, and reach a peak in early adulthood. This is followed by a decline throughout adult life, at the 7th decade the concentrations are only 10 to 20% of the earlier individual peak concentrations.[2,3] In contrast, cortisol levels in men and women show a progressive increase (20% overall) with ageing.[4] It has been suggested that the decrease in cortisol/DHEA ratio may cause a meta-

bolic shift towards a catabolic state during ageing and may negatively affect the cognitive function in the elderly.[4,5] DHEA crosses the blood-brain barrier and may act in the brain as a neurosteroid via effects on neurotransmitter function. A specific nuclear hormone receptor for DHEA has not been identified, but DHEA may act on the N-methyl-D-aspartate (NMDA) receptor as a modulator of the response to NMDA or as an allosteric antagonist at the level of the γ-aminobutyric acid (GABA) receptor.[6] DHEA increases neuronal excitability and initiates alterations in synaptic transmission in the hippocampus. Cognitive processes may therefore be influenced by DHEA.[7] Animal experiments suggest that DHEA has many effects, including anticancer, immune-enhancing, neurotropic and general antiageing effects. However, most experiments with DHEA(S) have been performed in rodents, which have little circulating DHEA(S). Therefore, as DHEA physiology in humans is clearly different from that in nonprimate mammals, these experiments are of limited significance for humans.[8] In the next paragraphs we focus on studies on the effects of DHEA administration in various conditions in humans.

DHEA REPLACEMENT IN ADRENAL INSUFFICIENCY

In patients with adrenal insufficiency, health-related quality of life is impaired despite adequate glucocorticoid and mineralocorticoid replacement.[9] As these patients are DHEA deplete, several studies have assessed the effects of DHEA administration in adrenal insufficiency. The most important are discussed below (see also *table 1*).
In a double-blind, placebo-controlled, crossover study, 24 women with primary or secondary adrenal insufficiency received 50 mg of DHEA or placebo orally, each for four months. Psychological and sexual functioning were evaluated using several validated questionnaires. Treatment with DHEA for four months resulted in significant improvements as compared with placebo. The greatest improvements occurred in the scores for depression and anxiety, compatible with a neurosteroidal action of DHEA. Sexuality improved as well. This was accompanied by an increase in peripheral androgen synthesis, as serum concentrations of DHEA(S), and testosterone returned to the normal range, while serum concentrations of sex hormone-binding globulin, and total and high-density cholesterol decreased. Side effects were transient and mild. The same authors did not find an effect of DHEA on carbohydrate metabolism, body composition or serum insulin.[10] DHEA administration did result in a significant increase in osteocalcin as compared with placebo, suggesting an osteoanabolic effect of DHEA. There was a nonsignificant improvement in physical capacity, and sense of well-being and self-perception improved significantly after four months of DHEA treatment. [11]

In another blinded, crossover study in 39 patients with Addison's disease, the effect of an oral daily dose of 50 mg DHEA for 12 weeks was evaluated. This was the only

Table 1 *DHEA therapy in adrenal insufficiency*

Study	**Arlt *et al.*[10] Callies *et al.*[11]**	**Hunt *et al.*[12]**	**Johannson *et al.*[13]**	**Løvås *et al.*[14]**
Subjects	24 women	24 women, 15 men	38 women	39 women
Age range (years)	23-59	25-69	25-65	18-70
Diagnosis	Primary and secondary AI	Primary AI	Secondary AI	Primary and secondary AI
Study design	1	1	2	2
Duration of DHEA therapy	9 months	7 months	6 months	9 months
Daily DHEA dose	50 mg	50 mg	30 mg (<45 years) 20 mg (>45 years)	25 mg
Results				
Body composition	No change	No change	No change	
Lipids	Decrease TC and HDL-C	No change	No change	No change
Bone markers and BMD	Increase osteocalcin level	BMD no change Osteocalcin level unchanged	Osteocalcin level unchanged	Osteocalcin and deoxypyridinoline unchanged
Mood/well-being	Improvement in scores for depression and anxiety	Self-esteem improved	No change	No change
Sexuality	Improved	No change	No change	No change

1 = double=blind, placebo-controlled, randomised, cross-over; 2 = double-blind, placebo-controlled, parallel; AI = adrenal insufficiency; BMD = bone mineral density; DHEA = dehydroepiandrosterone; HDL-C = high-density lipoprotein cholesterol; TC = total cholesterol.

study that also included men. DHEA administration resulted in significant improvement in some aspects of psychological functioning, such as self-esteem, and in improvements in mood and fatigue, especially in the evening. DHEA had no effect on libido and sexual function, memory or cognition. Further, no effect on bone metabolism was found, the authors attributed this to the short duration of treatment.[12]

In another study, 38 women with adrenal insufficiency due to hypopituitarism were treated with oral DHEA for six months in a randomised, placebo-controlled, double-blind study, followed by a six-month open treatment period. The DHEA dose was 30 mg/day when <45 years, and 20 mg/day when >45 years. The primary goal was to study the effect on quality of life, well-being and behaviour. Treatment with DHEA did not result in a change in general well-being as compared with baseline, but the partner questionnaire did reveal an overall improvement in the DHEA-treated group. Compared with placebo, DHEA treatment did not influence sexual interest and activity, whereas during the open phase most women reported an increase. No changes in glucose metabolism, lipoproteins, IGF-1, coagulation parameters, body composition or bone metabolism were observed.[13]

Løvås *et al*. treated 39 women with adrenal insufficiency with either placebo or DHEA, 25 mg/day for nine months.[14] In the DHEA group the levels of DHEAS, androstenedione and testosterone significantly increased as compared with baseline. Health status or sexuality did not improve in the DHEA group as compared with the placebo group. Several side effects, including sweating, hirsutism, acne and itching occurred more often in the DHEA group than in the placebo group.

To define a suitable replacement dose, nine patients with Addison's disease were randomised to oral DHEA 50 mg (n=5) or 200 mg (n=4) daily for three months. Oral doses of 50 mg/day increased circulating levels of DHEA from subnormal to the upper part of the reference range for young individuals, the 200 mg dose resulted in supra-physiological levels, suggesting that 50 mg/day is a replacement dose, and 200 mg/day a pharmacological dose. Five of the nine participants experienced a marked increase in psychological and general well-being. However, from the report it cannot be derived which dosage these five participants used.[15]

In conclusion, trials on DHEA replacement in patients with adrenal insufficiency have mainly been performed in female patients and usually lasted only a few months. Improvements in mood, health-related quality of life and libido were seen in some but not all studies and only if DHEA doses of 50 mg were administered. No convincing effects on bone density, body composition or serum lipid levels were found, and no long-term studies have been carried out to assess the possible effect of DHEA in either replacement or pharmacological dose on the incidence of cancer or cardiovascular disease.

EFFECT OF DHEA REPLACEMENT ON MOOD, WELL-BEING AND COGNITION

Ageing results in a decline in concentrations of DHEA, which may have physiological significance.[4] Morales *et al*. demonstrated an improvement in self-reported physical and psychological well-being in middle-aged and elderly men and women after administration of a daily dose of 50 mg DHEA for three months.[16] The same group also did a study on the effects of a DHEA 100 mg/day, but in this report the effect of this higher DHEA dose on well-being was not mentioned.[17] In a double-blind cross-over study, 22 healthy male volunteers received four months of DHEA (50 mg/day) and four months placebo treatment. In these healthy men with age-related physiological decline of DHEA secretion, no obvious benefit of DHEA replacement was found.[18] Wolkowitz *et al*. randomised 22 subjects with a major depression to receive either DHEA (30-90 mg/day) or placebo for six weeks.[19] They concluded that patients treated with DHEA showed a greater anti-depressant response (an overall enhancement of mood scores by 30.5%) than those who were treated with placebo. In a recently published study, six weeks of DHEA therapy in a pharmacological dose (90 mg/day for three weeks and 450 mg/day for three weeks), was compared with placebo for six weeks in men (n=23) and women (n=23) aged 45 to 65 years with midlife-onset major or minor depression. DHEA administration in a pharmacological dose was associated with a significant improvement compared with both baseline ($p<0.01$) and placebo treatment ($p<0.01$).[20]

The mechanism of the possible antidepressant effect of DHEA is unclear. DHEA crosses the blood-brain barrier and may interact directly with brain function by affecting serotonin and/or GABA receptors. Secondly, in brain cells DHEA is a precursor for testosterone and oestrogen formation, and increases in the levels of these hormones can enhance mood. Another theory suggests that a normal DHEA/cortisol ratio is required for a good balance between anabolic and catabolic steroid effects. Cortisol levels are increased in major depression, so DHEA administration may restore this ratio.[21]

DHEA ADMINISTRATION TO IMPROVE COGNITIVE FUNCTION IN ELDERLY PEOPLE

Serum levels of DHEA(S) decrease during ageing, resulting in a progressive decrease in the serum DHEA(S)/cortisol

ratio. It has been hypothesised that this may impair cognitive function. DHEA administration may restore the DHEA(S)/cortisol ratio, thus potentially improving cognitive function and preventing neurotoxic effects of cortisol. This hypothesis resulted in four placebo-controlled clinical trials that investigated the effect of DHEA administration on cognitive function in elderly people. These studies were reviewed by Huppert *et al.*[22] All four studies used a daily oral DHEA dose of 50 mg, for periods lasting less than three months. Few significant changes were found. In one study DHEA improved immediate and delayed recall in a visual memory test compared with placebo, while no improvement in a verbal memory test, nor in four other cognitive tests was seen.[23] Another study found a deterioration in a test following a psychological stressor in the placebo group, which was not seen in the DHEA group.[24] The other studies did not demonstrate any beneficial effects of DHEA administration.[25,26] The overall conclusion of Huppert *et al.* was that there is very limited evidence for a beneficial effect of a daily oral dose of 50 mg DHEA on cognitive function in elderly people.[22] Using a higher dose of 100 mg DHEA a day for three months, Flynn *et al.* did not find clinically meaningful changes in 39 healthy elderly men either.[27]

DHEA ADMINISTRATION IN POSTMENOPAUSAL WOMEN

In women the synthesis of DHEA occurs mainly in the adrenal cortex and DHEA serves as the main precursor of active oestrogens in postmenopausal women. The reduction in DHEA(S) formation by the adrenals during ageing results in a reduction in the formation of androgens and oestrogens in peripheral tissues. It has been suggested that this could influence well-being and the occurrence of osteoporosis, obesity and insulin resistance in postmenopausal women. In the last few years several trials have assessed whether administration of DHEA would improve interest in sex, sexual satisfaction, quality of life or osteoporosis in postmenopausal women. Barnhart *et al.* found no difference in improvements in mood, libido, cognition, memory or well-being after treatment with DHEA (50 mg/day for three months) *vs* placebo in 60 perimenopausal women.[25] Genazzani *et al.* studied the effect of oral administration of 25 mg DHEA daily in 20 postmenopausal women in a 12-month prospective study that was not blinded or randomised.[28] They found an increase in the circulating levels of all DHEA-derived steroids, osteocalcin, as well as growth hormone and IGF-1 during DHEA supplementation. An improvement in psychological functioning was also found. These authors concluded that DHEA administration may be considered in postmenopausal women.

DHEA ADMINISTRATION IN PATIENTS WITH AUTOIMMUNE DISEASES

Because of its immunomodulatory effects in animal studies, DHEA administration has been studied as a potential pharmacological tool in the treatment of human autoimmune diseases. In 21 patients with severe systemic lupus erythematosus (SLE), DHEA administration (200 mg/day *vs* placebo for six months) was added to conventional treatment. DHEA administration had a beneficial effect on lupus outcomes and protected against steroid-induced osteopenia.[29] This effect on bone density could not be confirmed by Hartkamp *et al.*[30] Chang *et al.* investigated 120 adult women with active lupus, who were treated with DHEA, 200 mg/day or placebo, for 24 weeks.[31] They found a reduction in disease flares and the patients perceived a decrease in disease activity. Side effects (acne, hirsutism) were mild.

CONCLUSION

DHEA is an adrenal androgen for which many effects in different clinical situations have been postulated. Many studies have been performed to assess the importance of DHEA administration. In most studies in patients with adrenal insufficiency, oral DHEA replacement is biochemically effective, well tolerated and associated with some improvement in well-being, mood and fatigue. This may at least partly be mediated by neurosteroid effects of DHEA. However, all studies have been small and short term, and studies in adrenal insufficiency have mainly been carried out in women. So far no studies have compared the effects of DHEA administration with those of other anabolic steroid hormones in patients with adrenal insufficiency. Side effects of treatment with DHEA were mild and androgen related.

Some studies suggest a favourable effect of DHEA in pharmacological doses in treatment of depression. So far, no consistent beneficial effect of DHEA administration on mood, general well-being and on cognitive function in elderly people has been found. DHEA administration in postmenopausal women needs to be assessed in larger and longer-lasting studies before therapy with DHEA is used for these purposes. Pharmacological therapy with DHEA in autoimmune diseases, such as SLE, may prove to be beneficial for these patients. More and longer-term studies are required to demonstrate the immunomodulatory effects of DHEA administration in patients with SLE. Further, long-term studies would also need to assess if long-term treatment with DHEA in either pharmacological or physiological doses will have any effect on the incidence of cardiovascular or malignant disease.

REFERENCES

1. Labrie F, Van Luu-The, Labrie C et al. Endocrine and intracrine sources of androgens in women: inhibition of breast cancer and other roles of androgens and their precursor dehydroepiandrosterone. Endocrine Reviews 2003;24;152-82.
2. Orentreich N, Brind JL, Vogelman JH, Andres R, Baldwin H. Long-term longitudinal measurements of plasma dehydroepiandrosterone sulfate in normal men. J Clin Endocrinol Metab 1992;75:1002-4.
3. Parker CR, Mixon RL, Brissie RM, Grizzle WE. Aging alters zonation in the adrenal cortex of men. J Clin Endocrinol Metab 1997;82:3898-901.
4. Laughlin GA and Barrett-Connor E; Sexual dimorphism in the influence of advanced aging on adrenal hormone level: the Rancho Bernardo Study. J Clin Endocrinol Metab 2000;85:3561-8.
5. Kalmijn S, Launer LJ, Stolk RP et al, A prospective study on cortisol, dehydroepiandrosterone sulfate, and cognitive function in elderly. J Clin Endocrinol Metab 1998;83:3487-92.
6. Demirgoren S, Majewska MD, Spivak CE, London ED. Receptor binding and electrophysiological effects of dehydroepiandrosteronesulfate, an antagonist of the GABAβ receptor. Neuroscience 1991;45:127-35.
7. Baulieu EE, Robel P. Dehydroepiandrosterone and dehydroepiandrosterone sulfate as neuroactive neurosteroids. J Endocrinol 1996;150:S221-39.
8. Cutler GB, Glenn M, Bush M, Hodgen GD, Graham CE, Loriaux DL. Adrenarche: a survey of rodents, domestic animals, and primates. Endocrinology 1978;103:2112-8.
9. Løvås K, Håvard Loge J, Husebye ES. Subjective health status in Norwegian patients with Addison's disease. Clin Endocrinol 2002;56:581-8.
10. Arlt W, Callies F, Vlijmen JC van et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. N Engl J Med 1999;341:1013-20.
11. Callies F, Fassnacht M, Vlijmen JC van et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency: effects on body composition, serum leptin, bone turnover, and exercise capacity. J Clin Endocrinol Metab 2001;86:1968-72.
12. Hunt PJ, Gurnell EM, Huppert FA et al. Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial. J Clin Endocrinol Metab 2000;85:4650-56.
13. Johannsson G, Burman P, Wiren L et al. Low dose dehydroepiandrosterone affects behavior in hypopituitary androgen-deficient women : a placebo-controlled trial. J Clin Endocrinol Metab 2002;87:2046-52.
14. Løvås K, Gebre-Medhin G, Trovik TS, et al. Replacement of dehydroepiandrosterone in adrenal failure: no benefit for subjective health status and sexuality in a 9-month, randomized, parallel group clinical trial. J Clin Endocrinol Metab 2003;88:1112-18.
15. Gebre-Medhin G, Husebye ES, Mallmin H et al. Oral dehydroepiandrosterone (DHEA) replacement therapy in women with Addison's disease. Clin Endocrinol 2000;52:775-80.
16. Morales AJ, Nolan JJ, Nelson JC, Yen SSC. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. J Clin Endocrinol Metab 1994;78:1360-67.
17. Morales AJ, Haubrich RH, Hwang JY, Asakura H, Yen SSC. The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition, and muscle strength in age-advanced men and women. Clin Endocrinol 1998;49:421-32.
18. Arlt W, Callies F, Koehler I et al. Dehydroepiandrosterone supplementation in healthy men with an age-related decline of dehydroepiandrosterone secretion. J Clin Endocrinol Metab 2001,86:4686-92.
19. Wolkowitz OM, Reus VI, Keebler A, Nelson N, Friedland M, Brizendine L, Roberts E. Double-blind treatment of major depression with dehydroepiandrosterone. Am J Psychiatry 1999;156:646-49.
20. Schmidt PJ, Daly RC, Bloch M, et al. Dehydroepiandrosterone monotherapy in midlife-onset major and minor depression, Arch Gen Psychiatry. 2005; 62 (2):154-62.
21. Wolkowitz OM, Epel ES, Reus VI. Stress hormone-related psychopathology: pathophysiological treatment implications. World J Biol Psychiatry 2001;115-43.
22. Huppert FA, Niekerk van JK. Dehydroepiandrosterone (DHEA) supplementation for cognitive function. Cochrane Review; The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley and Sons, Ltd.
23. Wolf OT, Neumann E, Hellhammer DH et al. Effects of a two-week physiological dehydroepiandrosterone substitution on cognitive performance and well-being in healthy elderly women and men. J Clin Endocrinol Metab 1997;82:2363-67.
24. Wolf OT, Kudielka BM, Hellhammer DH, Hellhammer J, Kirschbaum C. Opposing effects of DHEA replacement in elderly subjects on declarative memory and attention after exposure to a laboratory stressor. Psychoneuroendocrinology 1998;23:617-29.
25. Barnhart KT, Freeman E, Grisso JA et al. The effect of dehydroepiandrosterone supplementation to symptomatic perimenopausal women on serum endocrine profiles, lipid parameters, and health-related quality of life. J Clin Endocrinol Metab 1999;84:3896-902.
26. Wolf OT, Naumann E, Hellhammer DH, Kirschbaum C. Effects of dehydroepiandrosterone (DHEA) replacement in elderly men on event related potentials (ERPs), memory and well-being. J of Gerontology 1998;53(5):M385-90.
27. Flynn MA, Weaver-Osterholtz D, Sharpe-Timms KL, Allen S, Krause G. Dehydroepiandrosterone replacement in aging humans. J Clin Endocrinol Metab 1999;84:1527-33.
28. Genazzani AD, Stomati M, Bernardi F, Pieri M, Rovati L, Genazzani AR. Long-term low-dose dehydroepiandrosterone oral supplementation in early and late postmenopausal women modulates endocrine parameters and synthesis of neuroactive steroids. Fertility and Sterility 2003;80:1495-1501.
29. Vn Vollenhoven RF, Park JL, Genovese MC, West JP, McGuire JL. A double-blind, placebo-controlled, clinical trial of dehydroepiandrosterone in severe systemic lupus erythematosus. Lupus 1999;8:181-87.
30. Hartkamp A, Geenen R, Godaert GL, Bijl M, Bijlsma JW, Derksen RH. The effect of dehydroepiandrosterone on lumbar spine bone mineral density in patients with quiescent lupus erythematosus. Arthritis Rheum 2004;50:3591-95.
31. Chang DM, Lan JL, Luo SF. DHEA in the treatment of women with mild-to-moderate systemic lupus erythematosus: a multi-center randomised, double-blind, placebo controlled trial. Arthritis Rheum 2002:46;2924-27.