Dehydroepiandrosterone replacement for patients with adrenal insufficiency

Dehydroepiandrosterone (DHEA) and its sulphate ester, dehydroepiandrosterone sulphate (DHEA-S), are two steroids that are made and released in substantial quantities from the adrenal glands of human beings. Although first identified in the 1930s, the exact physiological role of these steroids is still not fully understood and the benefits of replacing them in deficiency states have only recently been studied.

Circulating DHEA/DHEA-S concentrations show characteristic changes with age. DHEA/DHEA-S are the principal steroids released by the human fetal adrenal gland and concentrations fall during infancy as the fetal zone of the adrenal involutes. However, concentrations of DHEA/DHEA-S rise again in mid-childhood as the zona reticularis matures (“adrenarche”), and reach a peak at 20–30 years of age. At this time, DHEA-S concentrations are approximately 20 times greater than those of cortisol because of increased secretion and decreased clearance of DHEA-S, and conversion of DHEA to DHEA-S in the adrenal and liver. Thereafter, a steady decline in DHEA/DHEA-S occurs with age, such that by age 70 circulating concentrations are only 20–30% of the peak concentrations of young adulthood. Thus, normal elderly individuals might be deemed “deficient” in DHEA/DHEA-S.

DHEA may exert its physiological effects through various mechanisms (figure). For example, many tissues are able to convert DHEA-S back to DHEA, which in turn can act as a precursor for the synthesis of androgens and oestrogens. This local formation of sex steroids appears to involve large numbers to detect differences. A recent systematic review concluded that there is insufficient evidence yet to support the use of DHEA in this population.

Penelope Hunt and colleagues reported the effects of DHEA replacement in patients with Addison’s disease (primary adrenal insufficiency) who were on standard glucocorticoid replacement and mineralocorticoid replacement as necessary. These patients are generally young, have severe DHEA/DHEA-S deficiency at an age when DHEA/DHEA-S would normally be high, and have few of the confounding variables associated with ageing. In this randomised, double-blind, placebo-controlled cross-over study, 39 patients with Addison’s disease (24 women, median age 40 years [range 25–69]) received either 50 mg micronised oral DHEA daily or placebo for 12 weeks, followed by a 4-week washout period, and then the alternative preparation for 12 weeks. During DHEA treatment, DHEA-S concentrations increased in both sexes from subnormal to within the young adult physiological range. In women, total testosterone increased from subnormal concentrations into the low-normal range. Total testosterone concentrations at baseline were normal in all the men, since testicular Leydig-cell function is intact in these patients.

A significant improvement in self-esteem and mood, and a decrease in fatigue (especially in the evenings), were reported during DHEA treatment in both sexes. This observation in men, independent of changes in circulating total testosterone, may be evidence that DHEA/DHEA-S have a direct central action, although detailed analysis of outcome by sex was not provided.
No significant changes were seen in the many other measures of wellbeing and cognitive function over this 12-week period, and no improvement in sexual function was reported. This latter finding contrasts with the improved sexual function after 4 months of DHEA treatment (50 mg) reported by Arlt and co-workers, in a study of women with primary and secondary adrenal insufficiency.

Although treatment with 50 mg DHEA daily increased DHEA/DHEA-S concentrations into the age-related normal range, and increased total testosterone into the low-normal range for women, mild facial acne was reported in a substantial proportion of women (8/24 on DHEA vs 3/24 on placebo). Androgenic skin changes were also reported by Arlt and colleagues in 19 of 24 women, and many of these changes were mild and transient. A mild reversible rise in serum aminotransferase concentrations occurred in three women, but no changes in hepatic enzymes were found by Hunt and co-workers. Potentially, other side-effects could result from long-term use, either due to the direct action of DHEA/DHEA-S or indirectly from exposure to androgens and oestrogens, and patients should be monitored carefully for evidence of breast and prostate cancer.

Taken together, these two recent studies suggest that short-term oral DHEA replacement may improve certain neuropsychological features in patients with adrenal insufficiency in whom endogenous DHEA/DHEA-S concentrations are much lower than in age-matched controls. In Addison’s disease, the goal of DHEA therapy is to restore a normal physiological state, whereas in the elderly the goal of DHEA therapy would be to raise concentrations to those of a younger population. However, in both groups long-term, double-blind, placebo-controlled trials with sufficient patients and DHEA treatment can be properly assessed.

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