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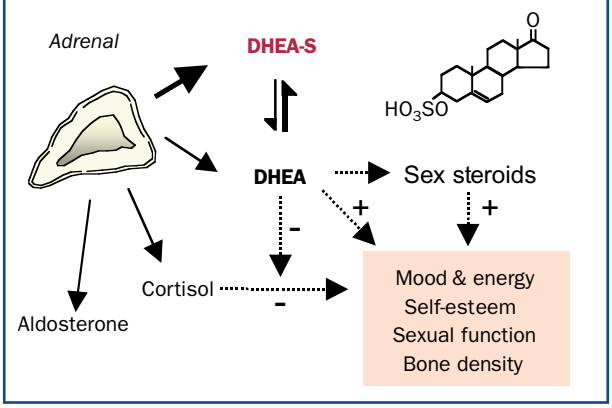
Dehydroepiandrosterone replacement for patients with adrenal insufficiency

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.[1] 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.[2] 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.[2] 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.[1,3] This local formation of sex steroids may explain part of the effects of DHEA/DHEA-S on brain, liver, and bone. DHEA/DHEA-S may also be centrally acting neurosteroids.[4] DHEA may be synthesised de novo in the brain, and animal studies have shown that DHEA is concentrated in the hippocampus and can modulate the receptor activities of γ-aminobutyric acid and N-methyl-D-aspartate. In addition, DHEA/DHEA-S have powerful antiglucocorticoid effects[5] and a decline in circulating

DHEA: metabolism and putative benefits



DHEA/DHEA-S concentrations may result in a state of relative glucocorticoid excess with associated neuropsychological sequelae, such as impaired memory, cognition, and mood.[6,7]

Because of these findings, several studies have assessed the effects of oral DHEA supplementation in the normal elderly population. Improvements have been reported in psychological wellbeing, as have beneficial changes in lean body mass, bone turnover, concentrations of circulating insulin-like growth factor-1, and skin features associated with ageing.[8,9] Consequently, DHEA has been hailed by some as an "antidote for ageing", and its use as a "dietary supplement" is widespread in some communities. However, since certain baseline measures, such as memory and concentrations of DHEA/DHEA-S, vary greatly between individuals, studies in the elderly need 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.[10]

Penelope Hunt and colleagues[11] 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,[12] 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* 4/24 on placebo). Androgenic skin changes were also reported by Arlt and colleagues[12] in 19 of 24 women, but most of these changes were mild and transient. A mild reversible rise in serum aminotransferase concentrations occurred in three women,[12] but no changes in hepatic enzymes were found by Hunt and co-workers.[11] 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 individuals to obtain adequate power are essential before the benefits and risks of DHEA treatment can be properly assessed.

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Diversity of congenital disorders of glycosylation

Almost all proteins that are secreted or membrane bound, as well as many others, have carbohydrate side-chains (glycans) that are essential for their normal activity. N–linked glycans have a branched structure with many variations. The synthesis of oligosaccharides, their transfer to the nascent polypeptide chain, and subsequent modification to produce the mature glycans require a complex pathway of at least 40 steps. Defects of this pathway (congenital disorders of glycosylation, CDG) were first identified by studying changes in transferrin, which normally has two glycans with four sialic acid residues. Any change in the number of residues can be detected in the pattern of isoelectric focusing (IEF). This investigation is now supplemented by analysis of other proteins, enzymology, and molecular genetic studies. Two main CDG groups are recognised. Type 1 (CDG Ia–e) concerns the synthesis and transfer of the carbohydrate chain. The commonest is caused by deficiency of phosphomannomutase.[1] In type II, defects in the processing of the carbohydrate chains have been found, and three causes have been identified so far. There remain many patients with CDG of unknown cause, CDG-x.

The disorders of glycosylation are remarkable for their clinical diversity (even within each disorder), a point that has been emphasised by P de Lonlay and her colleagues in their analysis of 26 cases.[2] The patients with type Ia were divided into two groups—those with primarily neurological disease and those with multivisceral disease—but there is considerable overlap. In both groups the commonest neurological features are neonatal hypotonia, squint, ataxia, and psychomotor retardation. The younger patients may have other features, such as facial dysmorphism, inverted nipples, and unusual distribution of fat. After the age of 1 year areflexia and retinopathy are common, and in older patients kyphosis, fixed flexion deformities, and, in females, absent puberty (gonadotropins are glycosylated). In patients with multivisceral disease failure to thrive is common and may be accompanied by diarrhoea, pericarditis, liver disease, or proximal tubulopathy. Mortality is high among these patients. However, there is great variability in the phenotype, even among siblings. At a later age, the neurological abnormalities become more evident, with a variable degree of mental retardation, non-progressive cerebellar ataxia, peripheral neuropathy, retinitis pigmentosa, seizures, and stroke-like episodes being described.

CDG-Ic mainly causes a neurological disorder similar to, albeit milder than, CDG-Ia, but without the dysmorphic features, cerebellar hypoplasia, or polyneuropathy.[3]