

## **Dehydroepiandrosterone (DHEA) - ? a treatment option**

### **DHEA as a therapeutic agent.**

The U.S. Food and Drug Administration removed DHEA from the over-the-counter market in 1985 as there was no support for the health claims that were made for this product. However, as result of the U.S. Dietary Supplement Health and Education Act of 1994, DHEA (5-androsten-3beta-ol-17-one) has become widely and easily available, most commonly being promoted for its “anti-aging” properties. More recently there has been interest in DHEA for the treatment of female sexual dysfunction and low wellbeing. However there are little data to support these uses and safety data for DHEA therapy are clearly lacking.

### **DHEA production in women**

DHEA and its sulphate (DHEAS) are the most abundant sex steroids in women. Daily production rates are approximately 6 to 8mg/day and 3.5-20mg/day for DHEA and DHEAS respectively, and both circulate in micromolar concentrations (1). In contrast, the production of testosterone in premenopausal women is approximately 01. to 0.4 mg/ day and total testosterone circulates in nanomolar concentrations (1) DHEA is produced by the ovaries and adrenals, whereas DHEA sulfate (DHEAS) is a unique secretory product of the adrenal zona reticularis. DHEA is an important precursor for peripheral biosynthesis of both testosterone and estrogen and thus has potentially ubiquitous actions

In descending order of their serum concentrations, the major androgens found in women include dehydroepiandrosterone sulphate (DHEAS), DHEA, androstenedione (A), testosterone (T) and dihydrotestosterone (DHT). Giving T a reference potency of 100, the relative androgenic activities of the other members of the class are DHT, 300, A, 10 and DHEA and DHEAS, 5. Biosynthesis of the androgens takes place both in the adrenal and in the ovary and is modulated by two cytochrome P<sub>450</sub> enzymes, P<sub>450</sub> Scc which catalyses cholesterol side-chain cleavage and P<sub>450</sub> C<sub>17</sub> which catalyses 17-hydroxylation and 17-20 bond cleavage (17/20 lyase), which is required for the production of DHEA from pregnenolone. The further metabolism of DHEA involves 3β-hydroxy steroid dehydrogenase (3β HSD) which catalyses the conversion of DHEA to A. DHEA secretion is acutely stimulated by adrenocorticotrophic hormone (ACTH) . However DHEA-S, which has a long plasma half-life, may not acutely increase following ACTH administration (2). Adrenal androgen and cortisol production are not always linked. Circulating adrenal androgen levels have been observed to be normal or suppressed in acute stress, severe systemic illness, anorexia nervosa and Cushing’s syndrome which are otherwise characterized by elevated cortisol levels. Increased adrenal androgen production may also be seen in association with hyperprolactinemia (3) although the majority of patients with this disorder have normal androgen levels.

Unlike estradiol and testosterone which are highly protein bound, sex hormone binding globulin (SHBG) only weakly binds DHEA , but not DHEAS (4). Thus circulating DHEA is highly metabolically available.

The levels of DHEAS and DHEA fall with increasing age (5;6). We have documented androgens by age in non-health-care-seeking women aged 18 to 75 years (5). We found that the decline in DHEAS with age is such that the mean total levels declines by 77% between the youngest (18-24 years) and oldest group (65-75 years). This may contribute significantly to the decline in total and free testosterone level with age as DHEAS serves as a pre-hormone for about half of ovarian testosterone production (7).

## **DHEA and female sexual function**

Traditionally hormonal action has been understood as endocrine and paracrine and circulating hormone levels have been used as the main indicators of tissue exposure. However intracrinology plays a pivotal role in androgen metabolism, such that the active androgens exert their effects in the same cells in which they are synthesized, without release into the peri-cellular compartment (8). DHEA is the most abundant sex steroid in women and circulating DHEA and its sulfate, provide a large precursor reservoir for the intracellular production of both estrogens and androgens (9-11). DHEA and DHEAS are converted in extra-gonadal target tissues, either by aromatization to estrone, or by 5 $\alpha$ - reduction to testosterone, with the latter being converted to either oestradiol or dihydrotestosterone (DHT) in the same cells (9). Thus androgenic effects vary according to individual variations in the amount and activity of the enzymes 5 $\alpha$ - reductase and aromatase, and individual differences in the androgen receptor response. With substantial testosterone production and metabolism being intracrine, measurement of serum testosterone does not provide a specific measure of testosterone tissue exposure or action.

Thus, no single androgen measure is predictive of low female sexual function.

There has been considerable conjecture that the age-related decline in DHEA and DHEAS results in loss of libido and wellbeing (12).

The effects of oral DHEA on the sexual function of women have been evaluated in a number of placebo-controlled RCTs with inconsistent findings.

### *Studies of women with adrenal insufficiency*

In a crossover study of 24 women with adrenal insufficiency, sexual thoughts, interest and satisfaction (mental and physical) increased significantly after 4 months of active treatment (50 mg/day) (13). In this study, serum testosterone was increased from below normal to the lower part of the normal range by the therapy. Two other studies of women with Addison's disease found no effect of the same dose of DHEA on cognitive or sexual function, body composition, or bone mineral density. In a parallel group study in 39 women with adrenal failure, treatment with 25 mg DHEA did not produce significant changes in desire, satisfaction or sexual problems (14). A smaller RCT crossover study in Addisonian patients using 50 mg DHEA also failed to show improvements in sexual parameters (although the increments in testosterone levels were lower than expected) (15). Significant improvements in self-esteem, mood, and fatigue were observed (14;15).

### *Studies of otherwise healthy women*

In perimenopausal women without adrenal deficiency a parallel group placebo-controlled RCT did not show improvements in libido in 66 perimenopausal treated with 50 mg/day DHEA for 4 months (16). Whereas an open-label study of DHEA treatment (50 mg/day) in 113 healthy women with diminished desire, arousal and orgasmic capacity showed improvement in desire, arousal, lubrication, orgasm and satisfaction ( $P < 0.05$ ) (17).

In postmenopausal women, high dose DHEA (300mg) resulted in greater subjective mental ( $p < 0.016$ ) and physical ( $p < 0.036$ ) sexual response to an erotic video versus placebo in a small RCT (18). Both therapy and placebo increased vaginal pulse amplitude and vaginal blood volume with no difference between treatments (18). Baulieu et al reported improved libido in women over 60 years treated with DHEA 50mg daily in a RCT, however sexual function assessment did not involve a validated questionnaire and the visual analogue scale used was only understood by 25% of the women (12). Libido was reported as unchanged in women less than 70 years of age and increased in women over 70 years of age with DHEA versus placebo.

In summary there are no strong data to support beneficial effects of exogenous DHEA on sexual function in health or in adrenal insufficiency.

### **DHEA and bone health**

Androgenic steroids have an important physiologic role in the development and maintenance of bone mineralization in women and men, although, the mechanisms of androgen action on bone is still a matter of debate. The skeletal effects of androgens appear to be mediated in part via the estrogen receptor after local aromatization of androgens to estrogen, and mutations in either the estrogen receptor gene or the aromatase gene are associated with osteoporosis (19). Abundant aromatase activity has been reported in fetal osteoblasts and cell lines of osteoblastic origin(20). There is also evidence that androgens act directly on bone. Androgen receptors have been demonstrated in human osteoblast-like cell lines, and androgens have been shown to directly stimulate bone cell proliferation and differentiation. Androgen insufficiency may also be a factor underlying bone loss in young women with premature ovarian failure. Despite adequate standard estrogen-progestin therapy, two-thirds of such women have significantly reduced BMD to levels associated with increased hip fracture risk.

Circulating DHEA and DHEAS are positively correlated with BMD in ageing women (21-23)and the progressive decline in DHEA with increasing age is believed to contribute to senile osteoporosis. It is unlikely that these adrenal pre-androgens directly influence bone metabolism but that their effects are mediated indirectly following conversion to estradiol, A, or testosterone. Suppression of adrenal production of DHEA and DHEAS with chronic glucocorticosteroid therapy may also contribute to the pathogenesis of osteoporosis and osteopenia which are known complications of this therapy in women and men. DHEA or testosterone administration may be effective in preventing and or treating this common and serious side-effect of glucocorticosteroid therapy. Women treated with oral DHEA, have restoration of circulating A, DHT, and testosterone to premenopausal levels, as well as increases in DHEA and DHEAS, with no changes in circulating levels of estrone or estradiol from baseline (24). Similarly, the daily percutaneous administration of 10ml of a 20 percent DHEA solution results in an increase in circulating total testosterone of approximately 50 percent, with no consistent effect on estradiol or estrone (6). Circulating DHEAS, but not estradiol, in postmenopausal women is positively correlated with BMD (23), and daily application of a 10 percent DHEA cream has been reported to increase hip BMD in older women (25). Thus DHEA therapy may prove, in time, to be an alternative to administering testosterone replacement to androgen deficient women.

Thus DHEA is a potential alternative to the prevention of bone loss and the treatment of osteopenia and osteoporosis. However, prospective data confirming a reduction in fracture rate with such therapy is lacking, and DHEA cannot be recommended for this purpose at present.

### **DHEA therapy and other endpoints**

Sex hormones are implicated in the immune response, with estrogens as enhancers at least of the humoral immunity and androgens as natural immune-suppressors. DHEA has been studied as a potential pharmacological agent in the treatment of the autoimmune disease systemic lupus erythematosus (SLE)(26). Five controlled clinical trials and a number of additional observational studies have been performed investigating the use of DHEA in SLE. The results indicate that 200 mg/day of DHEA over 7 - 12 months may reduce the corticosteroid requirements, the frequency of disease flares, and have a global beneficial effect on SLE disease activity in female patients.

A small RCT (n=58) of DHEA 100mg per day versus placebo did not show any benefit on cognition in individuals with Alzheimer's Disease (27)

Schmidt and others most recently reported on the short term use of DHEA in the management of mid-life onset major/minor depression (28). They conducted a double-blind, randomized, placebo-controlled, crossover trial involving 23 men and 23 women aged 45 to 65 years.. Treatment was with extremely high dose DHEA (90 mg/d for 3 weeks followed by 450 mg/d for 3 weeks) or 6 weeks of placebo. DHEA administration was associated with a significant improvement in the 17-Item Hamilton Depression Rating Scale and the Center for Epidemiologic Studies Depression Scale ratings compared with both baseline ( $P < .01$ ) and 6 weeks of placebo treatment ( $P < .01$ ). A 50% or greater reduction in baseline Hamilton Depression Rating Scale scores was observed in 23 subjects after DHEA and in 13 subjects after placebo treatments. Mean DHEA-S, total and free testosterone levels achieved in women were supraphysiological and urine androgen metabolites were massively increased. Although interesting this study was of extremely high dose therapy and very brief in duration and is insufficient evidence to recommend the use of DHEA for management of depression, particularly with respect to safety.

### **Why may DHEA be an alternative to testosterone therapy ?**

Several studies have demonstrated that exogenous testosterone is effective in the treatment of postmenopausal women presenting with low libido, however the therapeutic range is narrow and efficacy is substantially influenced by factors that alter SHBG levels and thus free testosterone concentrations, such as oral estrogens.

As much of testosterone production in women is intracellular from the adrenal precursors, DHEA supplementation as opposed to testosterone therapy seems a logical alternative approach. Furthermore, DHEA is an important precursor for extragonadal estrogen production, thus it may offer therapeutic benefits in terms of the management of menopausal symptoms.

### **Potential risks of DHEA therapy**

Potential risks of DHEA therapy include direct adverse metabolic effects and effects of the estrogenic and androgenic actions of DHEA metabolites. However there is a striking paucity of papers reporting formal documentation of safety of oral DHEA therapy, with the little data available resulting from extremely small patient numbers.

The side effects acne and hirsutism have been described as being seen relatively frequently in studies employing high dose DHEA (26). Many studies have not used objective measures of acne and hirsutism.

Oral DHEA treatment may result in changes in lipid profile with small reductions in HDL cholesterol and apolipoprotein A1 versus placebo at low doses (25mg/day) (29). Again, there is a lack of data for higher doses and longer durations of therapy.

There is insufficient documentation of the use of DHEA regarding effects on the breast and uterus. Labrie and other have investigated the effects of DHEA on mammary tissue extensively in *in vitro* and rodent models(9). They have consistently reported an inhibitory effect of DHEA on mammary carcinoma development. However this warrants further investigation in women.

Concerns pertaining to the psychiatric effects of DHEA therapy have been as severe psychiatric symptoms have been reported in a subset of users in the community (30).

## **Conclusion**

**Although circumstantial evidence might suggest potential benefits of DHEA therapy, until large randomized controlled trials using validated scales and hard safety endpoints have been conducted, the prescription of DHEA therapy for treatment of any specific symptoms cannot be recommended.**

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