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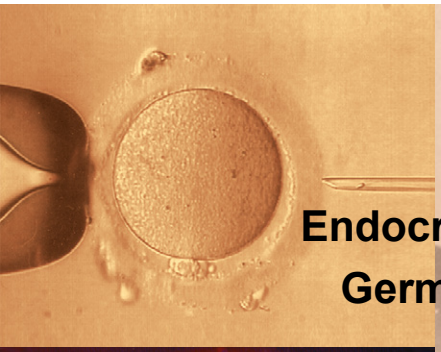

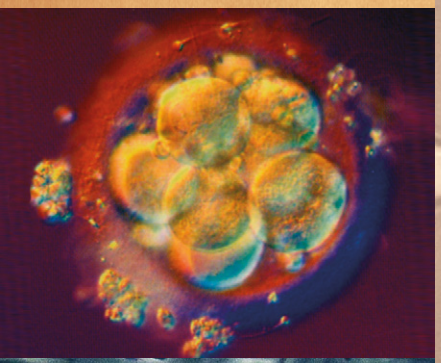

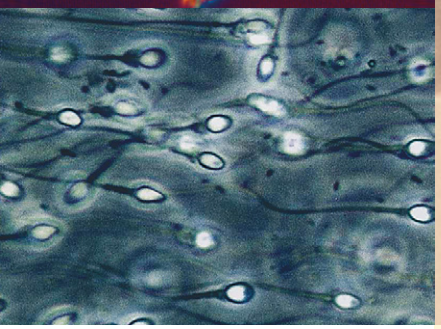

Dehydroepiandrosterone and its Sulfate Joint Statement by the German Society for Gynecological Endocrinology and Reproductive Medicine [DGGEF] and the German Professional Association of Gynecologists [BVF])

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Dehydroepiandrosterone and its Sulfate

Joint Statement by the German Society for Gynecological Endocrinology and Reproductive Medicine (DGGEF) and the German Professional Association of Gynecologists (BVF)

T. Rabe[1] and the study group "Hormone Therapy" (in alphabetical order): H.-J. Ahrendt[2], C. Albring[3], A. Bachmann[4], J. Bitzer[5], U. Blume-Peytavi[6], C. Egarter[7], B. Hinney[8], H. Kentenich[9], K. König[10], G. Merki-Feld[11], E. Merkle[12], A. O. Mueck[13], W. Rossmanith[14] N. Sänger[4]

Dehydroepiandrosterone (DHEA) is the most frequent circulating steroid hormone in humans. It is formed in the reticular zone of the adrenal glands to 90–95% and, to a lower extent in the gonads and the brain where DHEA acts as neuro-steroid. There is an interconversion of DHEA to DHEAS in both directions. DHEAS levels in the blood are approximately 300 times higher in comparison to free DHEA levels. The DHEA peak levels are reached in the early morning hours whereas DHEAS is not subject to a circadian rhythm. Hence, DHEAS is well suitable for analysis in serum. DHEA is a universal precursor for the formation of androgen and estrogen in peripheral tissues. They contain enzyme systems such as 3β-HSDH for the formation of androstenedione, 17β-hydroxysteroid dehydrogenase for the synthesis of testosterone and aromatase for estrogen-synthesis. Maximum levels of DHEA/DHEAS are reached between 20 and 30 years of age. At the age of 70 or older DHEAS levels can be up to 75% lower.

Mode of action: DHEA acts predominantly as steroid precursor in the biosynthesis of androgenic and estrogenic sex steroids. There have been no DHEA/DHEAS receptors identified yet. DHEA and DHEAS bind and activate several receptors including ER-α and ER-β, peroxisome-proliferator activated receptors, PXR (pregnant-X-receptor), AUTO (constitutive androstane receptor) and beyond that membrane receptors as neuro-steroids like NMDA receptors (N-methyl-D-aspartate, glutamate) as positive allosteric modulator of the GABAA receptor and negative allosteric modulator. DHEA/DHEAS has a variety of dose independent effects like immune-modulation, effects on haemostasis, the lipid- and carbohydrate metabolism, bone health and mental health.

Pharmacology: The pharmacokinetic of DHEA depends on gender, dosing (25–50, 100 or 300 mg/day oral, no further increase of DHEA or DHEAS concentrations, respectively), and the route of application (oral, transdermal, vaginal). The oral adsorption is excellent. DHEA is converted in DHEAS by sulphation in the intestines and the liver after oral intake. DHEA and DHEAS were converted in several biologically active metabolites, including androstenedione, testosterone, estrone, estradiol and estriol. The elimination half-life of DHEA is 15–38 minutes; the half-life of DHEAS is 7–22 hours. Clearance of 51–73% of DHEAS and its metabolites is achieved by renal excretion.

Route of administration:

– Oral: Females take initially (10)–25 mg in the morning with dose reduction depending on clinical symptoms and DHEA levels in the blood. Dose adjustment is required for long-term treatments (e.g. 15–25 mg/day for females and 25–50 mg/day in males). Blood levels should be checked regulary and should range from 20 to 30 nmol/l (5.6–8.6 ng/ml).

Supplements:

– Oral: There are several international vendors offering compounds with 10, 20, 50 and 100 mg (off-label in Germany on prescription). Physiological doses of DHEA when taken per oral in healthy men > 40 years of age are between 20–50 mg for males and 10–30 mg for females. US pharmacists recommend 50–200 mg daily despite some studies investigated doses above and below these ranges.

– Transdermal: There is a 10% DHEA cream for transdermal administration available. 3–5 g cream per day are usually applied resulting in 300–500 mg DHEA applied to the skin.

– Intravaginal: According to Cleveland Clinic (http://www.clevelandclinicwellness.com/Features/Pages/DHEA-Suppository.aspx): 25 mg suppository for use at night.

Side effects: Most of unwanted side effects are mild and occur due to the androgenic effect of DHEA. Increased sebum production, increased facial hair and changes in androgenic hair might occur in females. Changes of the voice have not been observed yet.

Advantages and risks:

– No health-advantage detectable: There is no evidence that DHEA treatment can be used to prevent cardiovascular diseases, cognitive disorders, depression or to improve well-being. Most workgroups did not find any positive effects of DHEA on general well-being and physical strength. Small sample sizes and short observational periods may play a role there. So far, there is no evidence that DHEA has positive effects in patients wishing to become pregnant: premature ovarian insufficiency reduced ovarian reserve, poor response to stimulation in the context of ART.

– Potential health-advantages: DHEA substitution might play a role in women with low DHEA levels, e. g. adrenal insufficiency: Beside the substitution with gluco- and mineral corticosteroids, one might consider DHEAS substitution in single cases.

– Anorexia nervosa: DHEA has positive effects on bones, also in women with a lack of estrogen in fertile ages, as for example in patients with anorexia nervosa.

– Vaginal atrophy: Treatment with vaginal DHEA suppositories results in a rapid relief of symptoms of vaginal atrophy with only minimal to no changes in serum steroids. There are no concerns of systemic side effects, as observed in estrogen therapy. However, local administration is required daily. Approved alternative treatment options such as low dose intravaginal estriol treatment or oral administration of novel SERMs (Ospemifen) should be preferred.

– Health hazards: DHEA can be metabolized to testosterone as well as to estrogen. There is increasing evidence on a potential correlation between low DHEA levels and a cardiovascular risk as well as to high DHEA levels and the risk to develop breast cancer. ►

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Precautions:
– Doping: DHEA is a prohibited substance according to the World Anti-Doping Code by the World Anti-Doping Agency.
– Drug-drug interactions: for example tamoxifen – concomitant DHEA administration might lead to tamoxifene-resistance.
– DHEA is commonly used as prescription-free food supplement or anti-ageing drug in the United States. This does not necessarily mean that the product is safe since there are no corresponding long-term studies.
– Informed consent: Patients must be informed thoroughly about potential risks and benefits of DHEA treatment.
– Males: DHEA should not be used by persons suffering from prostate- or testicular cancer.
– All patients: Patients with severe diseases or hormonal disorders should take DHEA only after seeking competent medical advice and surveillance.
Future perspectives:
– Oral DHEA treatment might be indicated in special clinical indications as, in single cases, in patients with adrenal insufficiency, particularly in women.
– Intravaginal application in cases of vaginal atrophy is an interesting therapeutic option in this disorder.
– Positive effects of DHEA treatment on well-being, disturbances of memory, psychosexual disorders and bone-health were observed in studies investigat ing DHEA in other indications.
– Clinical trials with new DHEA metabolits e.g. 7-keto-DHEA are still ongoing. **J Reproduktionsmed Endokrinol_Online 2015; 12 (4): 318–41.**

Key words: DHEA, androgens, supplementation, benefits, side effects, doping, future perspectives

Structure

Dehydroepiandrosterone (DHEA) (or more correctly didehydroepiandrosterone), also known as androstenolone or prasterone as well as 3β-hydroxyandrost-5-en-17-on is an important endogenous steroid hormone [1].

Isomers: The term "dehydroepiandrosterone" is chemically ambiguous since it does not specify the position of lacking hydrogen atoms on the epiandrosterone molecule. DHEA has numerous natural isomers, which might show similar pharmacological effects. 1- and 4-dehydroepiandrosterone are isomers of DHEA. These isomers also belong to the DHEA group since they are dehydroepiandrosterones that lack hydrogen atoms on the epiandrosterone skeletone.

Synthesis

DHEA is the most frequent steroid hormone in humans [2]. 90–95% are synthesized in the adrenal glands (The Merck Index), but also to a lower extent in the gonads and brain [3]. It primarily serves as precursor substance for the biosynthesis of androgens and estrogens [1, 4].

Figure 1 provides an overview of the steroid genesis including the DHEA metabolism. The androgenicity of the various androgens is shown in figure 2. DHEA is formed from cholesterol by two cytochrome P450 enzymes. The enzyme P450 scc converts cholesterol by side chain cleavage to pregnenolone. CYP17A1, another enzyme, converts pregnenolone to 17α-hydroxy-pregnenolone and subsequently to DHEA [5].

Dehydroepiandrosterone sulphate (DHEAS) is the sulphate ester of DHEA. The conversion is catalysed by a sulfotransferase and occurs primarily in the adrenal glands, the liver and the small intestine. The enzyme DHEA sulfotransferase occurs in high concentrations in the adrenal glands but not in the ovaries. In peripheral tissues and the adrenal glands, DHEA and DHEAS can be alternately converted by a sulfohydrolase [6]. Approximately 64–74% of daily-synthesized DHEAS is converted to DHEA whereas only 13% of metabolized DHEA are converted to DHEAS [7–9]. DHEA occurs mainly as DHEAS in the blood. There, the ratio of DHEA:DHEAS is 1:500.

DHEA and DHEAS form the largest pool of hormones in the body: the concentrations are 10-times higher than those of cortisol, 1,000 to 10,000 times higher than those of estrogen and 100 to 1,000 times higher than the concentrations of testosterone [10] (Fig. 3).

The kidneys of young adults secrete approximately 4 mg DHEA and 25 mg DHEAS per day [7].

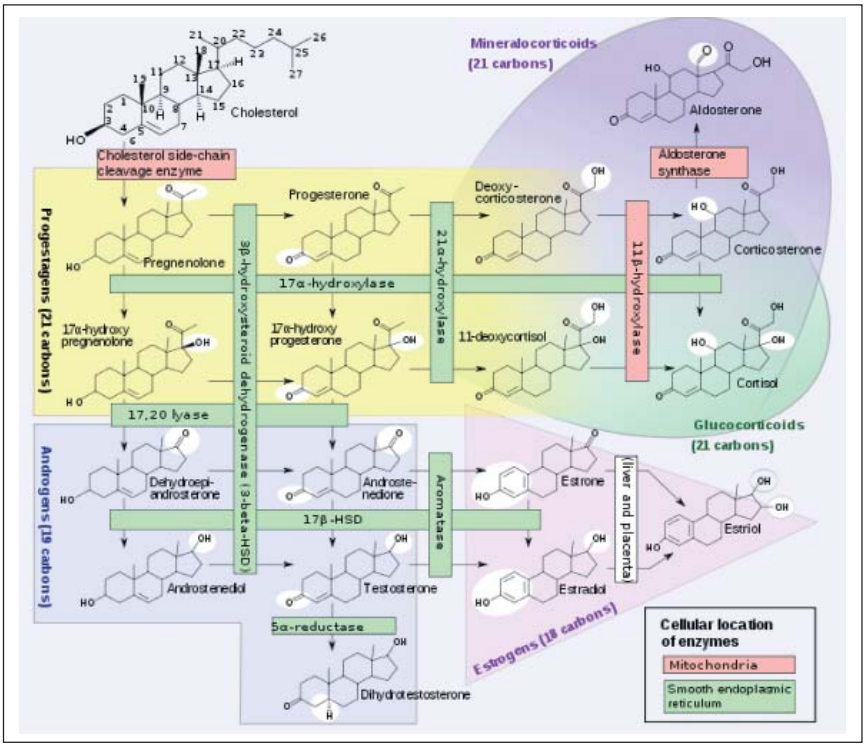

Figure 1. Steroid synthesis (yellow: progestins; blue: androgens). From Wikipedia (http://en.wikipedia.org/wiki/Steroid); GNU-License.

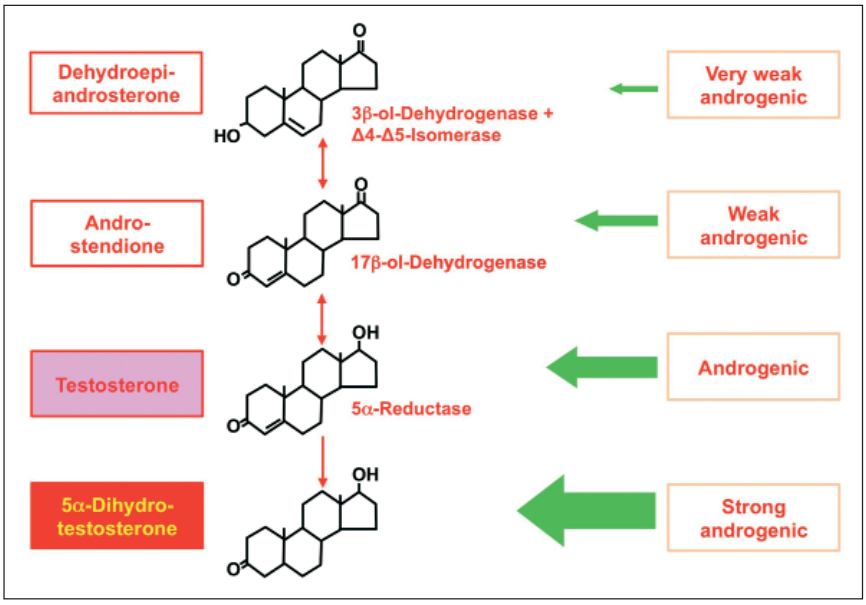

Figure 2. Androgenic potency of various androgens during androgen synthesis. © Thomas Rabe.

Brain: In the human brain, the brain-to-plasma ratio for DHEA and DHEAS is 4–6.5 respectively 8.5, which indicates a neuroendocrine effect of the hormone [7, 11, 12]. For further information on the endocrine effects of DHEA in the brain refer to an overview provided by Starka et al. 2015 [13].

Pregnancy: High amounts of DHEA and DHEAS are synthesized in the adrenal glands of the foetus during pregnancy, acting as a main source for the synthesis of estrogen in the placenta.

Age dependency: The production of DHEA and DHEAS starts in the adrenal glands with the beginning of the adrenarche and increases during adolescence. Peak levels of DHEA, respectively DHEAS synthesis can be found in the age between 20 and 30 years. Thereafter, it decreases by approximately 2% per year. In the age of 80–90 years, the maximum synthesis is only 10–20% of the peak levels in the mid-20s [7, 14–17] (Fig. 3).

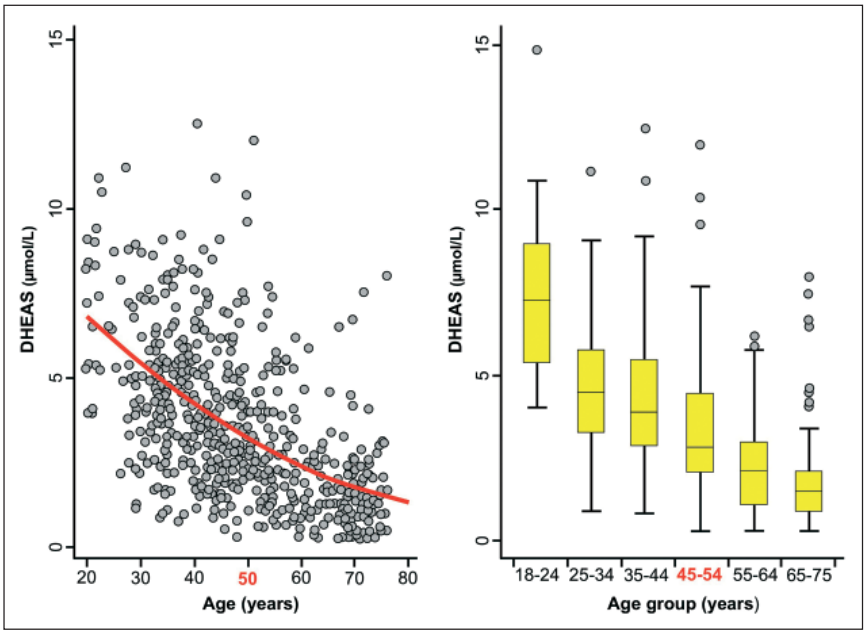

Figure 3. Dehydroepiandrosterone sulfate (DHEAS) in serum by age. Mod. according to [17]. © Thomas Rabe.

Metabolism

DHEA and DHEAS are steroid-precursors of approximately 50% of androgens in men, 75% of active estrogens in premenopausal women und 100% of active estrogens after the menopause [7, 16].

Testosterone-synthesis: DHEA is converted to 4-androstenedione by 3β-hydroxysteroid-dehydrogenase (3βSD) and, in a second step converted to testosterone by 17β-hydroxysteroid-dehydrogenas type 3 (HSD17B3) (Fig. 1) [18, 19].

Testosterone is predominantly formed from DHEA/DHEAS precursors in the ovaries and to a small extent in the adrenal glands of fertile women [20]. The androgen level of bilaterally ovariectomized fertile breast cancer patients is lower compared to women that undergo a natural menopause. Here, the biggest difference is in the levels of free testosterone [21]. The DHEAS increase (5–8%) during the menopause in women after bilateral salpingo-oophorectomy is of adrenal origin [22].

Estrogen-synthesis: The intracellular aromatase enzyme CYP19A1 converts testosterone to 17β-estradiol by a different metabolic pathway. The aromatase may also form estrone from 4-androstenedione which is further processed by 17β-HSD to 17β-estradiol [16, 23]. Reactions mediated by CYP-enzymes are irreversible whereas, dependent on the type, the hydroxysteroid dehydrogenase may also catalyse reverse reactions.

Active steroids are predominantly metabolized to inactive conjugated reduced steroids, which then can be excreted.

Laboratory Diagnostics

DHEA occurs mainly as DHEAS in the blood. There the concentrations of DHEAS are approximately 300 times higher than the concentrations of free DHEA. Concentrations of DHEA and DHEAS can be measured in the peripheral blood. There, the concentration of DHEAS is not dependent on the time of sampling whereas DHEA concentrations vary with the time with peak levels in the morning hours. The measurement of DHEAS in the peripheral blood is more reasonable since there is almost no variation.

Normal ranges of DHEAS

(Mayo Clinic; http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/8493)

- 18–29 years of age: 44–332 µg/ml (120–905 µmol/l)
- 30–39 years of age: 31–228 µg/ml (85–621 µmol/l)
- 40–49 years of age: 18–244 µg/ml (49–665 µmol/l
- 50–59 years of age: < 15–200 µg/ml (< 41–545 µmol/l)
- 60 years of age and older: < 15–157 µg/ml (< 41–428 µmol/l)

Increased Levels

Hyperfunction of the adrenal cortex

Since almost the entire DHEA production takes place in the adrenal cortex, the determination of DHEA/DHEAS in the blood is useful for the diagnosis of an excessive adrenal cortex function which might be triggered by an adrenocortical carcinoma or hyperplasia but also by several forms of congenital adrenocortical hyperplasia.

Five- to tenfold higher levels of DHEAS can be detected in patients with congenital adrenocortical hyperplasia (CAH) compared to healthy populations (Mayo Clinic). Slightly increased levels in adults are usually idiopathic. DHEAS levels above 6 µg/ml indicate an androgen secreting adrenocortical tumor. In patients with such tumors, the DHEAS levels are increased in more than 90% of cases. Typically, they are remarkably higher than 6 µg/ml in these cases. This is especially the case in androgen producing adrenocortical carcinomas, which have lost the ability to produce downstream androgens like testosterone. In contrast to these, androgen forming adrenocortical adenomas produce high amounts of testosterone and low levels of DHEAS (Mayo Clinic).

PCOS

Women with PCO-syndrome show frequently elevated levels of DHEAS [24].

Exercise

Frequent exercise increases the DHEA production [25, 26].

Calorie reduction leads to an increase in DHEA levels in primates [27]. Therefore, it was believed in the past that the increase in endogen DHEA induced by caloric restriction might result in an increased life expectancy [28].

Drugs increasing the DHEAS levels: metformin, troglitazone, prolactin (several neuroleptics indirect by inducing hyperprolactinaemia), danazol, calcium channel blockers (e.g. diltiazem, amlodipine) and nicotine (Mayo Clinic)

Decreased Levels

- Adrenal Insufficiency.
- Drugs and hormones that might lower the levels of DHEAS among others are: insulin, oral contraceptives, CNS-active substances that might increase liver enzyme levels (e.g. carbamazepine, clomipramine, imipramime, phenytoin), numerous antilipemics (e.g. statins, cholestyramine), dopaminergic drugs (e.g. levodopa/dopamine, bromocriptine), fish oil and vitamin E (Mayo Clinic).
- Low concentrations of DHEAS are signs of ageing.
- Decreased concentrations of DHEAS can also frequently be found in patients with diabetes, osteoporosis, dementia, erectile dysfunction, vaginal atrophia or colpitis after reduction of the thickness and plasticity of the vaginal skin and tissue, reduced libido and reduced sexual desire (Rochester University 2014; http://www.urmc.rochester.edu/encyclopedia/content.aspx?ContentTypeID=167&ContentID=dhea).

Relevance of DHEAS Determination

Detection of an adrenocortical hyperfunction due to adrenocortical hyperplasia or adrenocortical carcinoma. Diagnosis of adrenocortical insufficiency due to pituitary or peripheral adrenal disorders.

Mechanism of Action

DHEA receptor: A specific DHEA receptor has not been identified yet but there are indications for the existence of a DHEA plasma-membrane receptor in the bovine aorta [29, 30]. The receptor is located on the surface membrane of vascular endothelial cells and binds DHEA but no DHEAS. It is functionally coupled to G-proteins and the NO synthase [29].

Precursor for further effective androgens: DHEA mainly serves as precursor for stronger active androgens like testosterone and 5α-dihydrotestosterone.

Androgen receptor: DHEA is a weak partial antagonist of the androgen receptor. However, due to the low affinity to the androgen receptor it seems highly unlikely that this effect is of any clinical relevance [31, 32].

Estrogen receptor: DHEA can also bind the ERα and ERβ receptors leading to their activation.

ERα: Partial agonist but the concentrations needed for an activation are too high to play a physiological role.

ERβ: A full agonist with a maximum reaction comparable or even higher than estradiol. The DHEA concentration in the circulation and local tissues in humans are sufficient to activate the receptor to the same extent compared to maximum increased but not ovulating inducing concentrations of circulating estradiol. The ERβ receptor activation is doubled when DHEA is combined with estradiol at levels which correspond to the physiological concentrations. Therefore, DHEA was considered to have an important endogenous estrogen effect in the human body [31, 33].

Other steroid receptors: DHEA did not bind or activate progesterone-, glucocorticoid- or mineralocorticoid receptors [31, 34].

Other nucleus receptors: "peroxisome-proliferator-activated receptors", PXR ("pregnant-X-receptor") and CAR ("constitutive androstane receptor").

Membrane Receptors

GABAA-receptors as negative allosteric modulators: Stimulation of the synthesis of GABAA (gamma-aminobutyric acid); DHEA and DHEAS can antagonize the effect of GABA [35]. NMDA (N-methyl-D-aspartate, glutamate) receptors as positive allosteric modulators and transmitters of anti-depressive and cognitive effects as well as effects on memory and stresscoping [7]. (sigma)1-receptor as agonist; the (sigma)-1-receptor binds neurosteroids including DHEA and DHEAS which show antidepressive like effects in animal models [36].

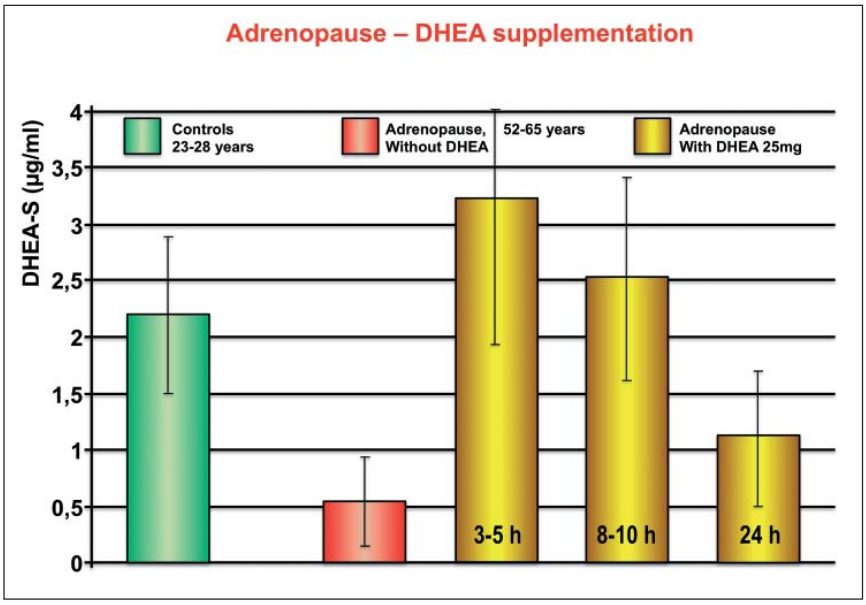

Figure 4. DHEA-S in blood after oral administration of DHEA in women. Mod. according to [56] with kind permission by A. Römmler.

Neurosteroidal effects in the brain: All the above-mentioned effects of DHEA in the brain led to its labelling as being a "neurosteroid". DHEA is also formed partly in brain tissue. It easily passes the blood-brain barrier. DHEA acts, after its transformation to testosterone and dihydrotestosterone or estradiol, via the androgen and estrogen receptors, which are frequently expressed in the brain. This effect is predominantly facilitated by non-genomic mechanisms or indirectly by the efficacy of its metabolites locally formed in the brain.

As a neuroactive hormone, DHEA interacts with other hormones and transmitters (see Membrane receptors) resulting in an obvious influence on several aspects of human moods and influences some facets of human emotions and behaviour [13].

Direct effects on genomic enzymes: Regulation of other proteins by indirect genomic mechanisms, including the enzymes P4502C11 and 11β-HSD1 – of which the latter is important for the biosynthesis of glucocorticoids and cortisol – as well as in the anti-glucocorticoid effect of DHEA and the carrier IGFBP1 [31, 37].

Neuroprotection: A neuroprotective and anti-glucocorticoid activity as well as an influence on immunoreactions has been described. Some authors also reported its regenerative role in degenerative brain diseases [13].

Immunity: DHEA can improve the immunity by activating T- and natural killer cells. DHEA antagonizes the efficacy of cortisol, which represses immunity [38–40].

Interleukin-6 serum levels (a pro-inflammatory cytokine that plays a role in the pathogenesis of osteoporosis, rheumatoid arthritis, atherosclerosis, Alzheimer's disease, Parkinson's disease and of beta-cell tumors) increase significantly with age and correlate with DHEA and DHEAS serum levels ($p < 0.001$) [41].

Growth hormone: DHEA stimulates the formation of the IGF-1 growth hormone [42].

Role in depression and anxiety states: DHEA acts as neurosteroid in the brain (see Membrane receptors).

Stress management – the role of cortisol: The DHEA concentration is inversely correlated to the concentration of cortisol. Cortisol is one of the few hormones that shows increasing concentrations with progressing age. The stress inducing effect of cortisol is well known. Long-term increased cortisol levels have a negative influence on several aspects of body function, as for example the occurrence of insulin resistance and endocrine disorders by interacting with the hypothalamus. Preservation of healthy DHEAS levels and concurrent control of the cortisol concentrations is meaningful in slowing down the physical ageing process with simultaneous stress reduction (Virileplex; http://www.virileplex.com/DHEA.htm).

Sexual activity is increased by elevated DHEA levels as reported in some studies [43].

Quantity of muscle and fat: DHEA increases the quantity of muscle- and reduces the fat tissue mass (especially via the growth hormone and the insulin-like growth factor I, IGF-1) [42].

Lipolytic effects: Stimulation of glucose-6-phosphate dehydrogenase and NADPH, lowering of cholesterol and lipoprotein (a), improvement of the thermogenetic lipolysis [44].

Partially positive effects on the physical and mental condition [45].

For a summary of mechanisms of action of DHEA refer to Wolf [46] and Starka et al [13].

Pharmacology

The metabolism of DHEA is gender-specific, dose dependent and the way of application (oral, transdermal, vaginal):

25 mg/day DHEA – oral [47]

- Study design: Treatment on postmenopausal women for a period of 6 month led to the following changes of hormone levels
- DHEA: Increase of the DHEA concentration
- SHGB: Unchanged
- Free testosterone: Increased
- Estradiol: No significant increase in estrone and estradiol compared to baseline
- Androgens: No significant increase in Cmax and AUC 0–24h levels for androgens and estrogens from day 1 until the 3rd and 6th moth under treatment.

50 mg/day DHEA – oral [48]

- Study design: Daily oral supplementation of 50 mg DHEA for a period of 1 year in a double blind, placebo controlled study in 20 healthy elderly men and women (60–80 years of age) – (DHEAge-Study)
- Half time: The terminal half time of DHEA in the blood appeared to be > 20 hours, at the same amount of

DHEAS in the blood. A result of back hydrosilation of high levels of DHEAS after oral DHEA supplementation, which is a mechanism that results in long-lasting, un-conjugated DHEA and its metabolites.
- The metabolization of DHEAS was significantly increased in women compared to men.
- Accumulation: There was no accumulation of steroids.
- Formation of androgen and estrogen: There were no concerning transformation in androgens or estrogens observed; a slightly increased endogenous estradiol level in aging women might be beneficial. The study demonstrated the safety of daily oral administration of DHEA at 50 mg in elderly patients.

100 mg/day DHEA – oral [42]
- Study design: Healthy, non-obese elderly (50–65 years of age) men (n = 9) and females (n = 10) were randomized in a double blind, placebo controlled crossover study. Sixteen patients completed the study period of one year with a six months period of placebo and six months period of daily oral 100 mg DHEA treatment.
- Basal serum levels of DHEA, DHEAS, androstenedione (A), testosterone (T) and di-hydrotestosterone (DHT) were within or below the normal levels for younger adults.
- DHEA: The DHEA levels of younger adults were reached in both sexes at a daily dose of 100 mg DHEA. The serum DHEAS levels were led back or even slightly exceeded the levels in younger adults.
- Cortisol: The serum cortisol levels remained unchanged. The DS/cortisol ratio was increased to levels occurring during adolescence (10:1).
- Testosterone, 5α-dihydrotestosterone, androstenedione: The levels for each of the hormones increased to a 3–5 fold higher levels compared to baseline in females ($p < 0.001$ for each).
- Insulin-like growth factors: The serum IGF-I level was increased compared to baseline in man (16 ± 6%, $p = 0.04$) and women (31 ± 12%, $p = 0.02$). The serum levels of IFG-BP-1 and IGFBP-3 remained unchanged. The GHBP (growth hormone binding protein) levels decreased in women (28 ± 6%, $p = 0.02$) but not in men.
- Safety parameters: There were no changes in the basal metabolic rate, bone density, urine pyridinoline, "cross-links", fasting insulin, glucose, cortisol or lipids in both sexes.

300 mg/day DHEA – oral [49]
- Doses of 300 mg oral DHEA per day did not result in a further increase of serum DHEA and DHEAS concentrations. Therefore, higher doses have almost no further therapeutic benefit.

Summary [50]
Physiological DHEA substitution in elder people aged 40 years or higher are within the range of 20–50 mg per day for man and 10–30 mg per day for women [7, 51]. These doses are usually sufficient to increase the DHEAS levels to those of young adults aged 20–30 years. Higher doses might be indicated in case of suppressed DHEA and DHEAS levels due to chronic diseases, adrenal insufficiency and during corticosteroid therapy. DHEA is usually taken once a day in the morning hours.

Remark: An assessment of DHEA therapy will be performed at the end of this article.

Pharmacokinetics after oral Administration of DHEA [49, 50, 52–55]
- Adsorption: The adsorption of oral DHEA is excellent.
- Distribution volume: The distribution volume is 17.0 to 38.5 L for DHEA and 8.5–9.3 L for DHEAS.
- Metabolism: oral administered DHEA is metabolized to a sulphate in the liver and bowel.

DHEA and DHEAS are metabolized to active metabolites including androstenedione, testosterone, estrone, estradiol and estriol.

- The elimination half-life of DHEA is 15–38 minutes whereas the half-life of DHEAS is 7–22 hours.
- Excretion: 51–73% of DHEAS and its metabolites are excreted renally.

Medical Compounds
- There are several international vendors offering preparations of 10, 20, 50 and 100 mg.

Recommendations for use
- Oral: DHEA can be obtained on prescription only from the pharmacy or from international online pharmacies.
- Dosing: Females initial: (10)–25 mg in the morning hours with a dose reduction depending on the symptomatology and the blood DHEA level.
- Side effects: DHEA treatment can cause the occurrence of seborrhoea due to its androgen residual effects.

Dose adjustment is necessary for a long-term treatment (e.g. 15–25 mg per day in females and 25–50 mg/day in man). Römmler [56] conducted important studies.

- Depot injection: The combination of estradiol valerate and 200 mg DHEA (tradename Gynodiandepot) is in Germany not available anymore, but can be ordered from international online pharmacies.
- Transdermal: As shown by clinical and biophysical investigations DHEA is topically resorbed and effective [57]. This was supported by investigations of the pan genomic expression profile [58]. Nouveau et al [57] investigated the in vivo effects of topical DHEA (1%) on skin ageing in a pilot study. Two groups of 20 postmenopausal women applied DHEA (1%) or carrier substance on the skin of face and hands for a period of 4 months. Clinical and biophysical signs of skin ageing assessed the efficacy of the treatment. This pilot study demonstrated positive effects on skin ageing which could be rarely observed in topical treatments. For the first time, Calvo et al 2008 [58] investigated the pan genomic profile of the human skin in women receiving topical DHEA treatment. Sixty postmenopausal women participated in this prospective, randomized, double blind and placebo controlled Phase II trial and were randomized in four groups: Twice daily topical application of 0% (placebo), 0.3%, 1% and 2% DHEA cream. Changes in the pangenomic expression profiles were investigated by use of Affymetrix gene chips. Significant changes ($p < 0.05$) were found in 66 DHEA reactive special sets corresponding to 52 well characterised genes und 9 unknown gene sequences. In this study, DHEA induced an anti-

ageing effect on the skin by stimulating the collagen biosynthesis and improved the structural organisation of the dermis by modulation of the keratinocyte metabolism – as demonstrated by several gene expressions.

Diamond et al [59] investigated the effect of DHEA substitution in women of 60–70 years of age (n = 15) who received a percutaneous injection of a 10% DHEA containing cream for a period of 12 months. They found a positive effect of the DHEA treatment without negative effects (including lipids, growth hormone, IGF-1, decrease of fasting glucose and fasting insulin).

Labrie et al [60] investigated the bioavailability of DHEA after oral and percutaneous application. Three groups of 12 postmenopausal women aged 60–70 years received either two capsules 50 mg DHEA orally before breakfast for 14 days or applied 4 g of a 10% DHEA cream/gel daily. The results showed:

- No changes in the estrone (E1) and estradiol (E2) serum levels in all three formulations.
- Increase in androstenedione (4-dion), testosterone, DHAE sulphate (DHEAS), Ei-S, androsterone glucuronide (ADG-T) and 3α-androstanediol-G (3α-diol-G) in all cases.
- The major result of the study by Labrie et al [60] was, that the changes in serum DHEA levels after oral or percutaneous application of DHEA are no reliable parameter for the DHEA effect. Particularly since the DHEA increase is in minimum 100% higher than the increase in the active androgens and estrogens and therefore far above the potential physiological effects.
- Vaginal: Panjari and Davis 2011 [61], Labrie et al 2009 [62, 63] and Berger et al 2008 [64] investigated the vaginal application of DHEA. The authors found positive effects in vaginal dystrophy but discussed the benefits and acceptance of permanent daily local vaginal treatment and whether DHEA might be less expensive than an estrogen treatment.

Clinical use of DHEA

The following aspects are of interest: Is DHEA a serum marker for a specific disease? In which diseases can DHEA treatment lead to an improvement or is it useful for prophylactic reasons? Can ageing be stopped by DHEA? What are the benefits and risks?

Laboratory assessment and Supplementation of DHEA – yes or no?

Among others, the question in whether the decrease in a laboratory parameter – in this context estrogens and androgens – during the ageing process should be increased to the level of young adults, with the exception of diabetes mellitus, for several ageing specific parameters is not finally resolved. A substitution of estrogen is an individual decision. The potential areas for a clinical use of DHEA are discussed in the following sections.

Adrenal insufficiency

Adrenal insufficiency can be caused for example by the failure of the pituitary gland resulting in impaired ACTH secretion or by M. Addison.

Some functions of the adrenal gland also decrease during the normal ageing process, including the DHEA synthesis.

DHEA and Adrenal insufficiency

According to the literature available: All RCT [65–68].

Therapeutic recommendations by the German Society for Endocrinology

(http://www.endokrinologie.net/krankheiten-nebenniereninsuffizienz.php)

Cortisol deficiency: Treatment with hydrocortisone or a comparable substance (Remark: The DHEAS level in healthy people is 10 times higher than the cortisol level).

Aldosterone deficiency: Fludrocortison

DHEA deficiency: will not necessarily be substituted. Some women benefit from DHEA supplementation, especially when there is a high level of suffering caused by strong dryness of the skin, loss of the libido or fatigue. 24 female patients with adrenal insufficiency received every morning by random 50 mg DHEA or placebo for a period of four months followed by a washout period of one month in a double blind study. DHEA improved the well-being scores for depression and anxiety remarkably. In addition, the sexual interest as well as the satisfaction of mental and physical aspects of sexuality improved [65]. In adolescents with central adrenal insufficiency, the application of 25 mg oral DHEA per day is of advantage: It leads to an increase in pubic hair growth and to an improvement of psychic well-being [69]. Srinivasan et al 2009 [70] did not observe any benefit of DHEA (50 mg/day oral) versus placebo on the lipid levels in 33 Caucasian women with adrenal insufficiency (mean +SD, age 50.3 +15.2 years, BMI 26.6 ± 4.4 kg/m²) in a double blind, randomized, placebo controlled crossover study.

In a review of the available literature, Alkatib et al 2009 [71] concluded that a routine use of DHEA in women suffering from adrenal sufficiency should not be supported.

Treatment of peri- and postmenopausal Symptoms

DHEA and Hot Flushes

In a small prospective study, Barton et al 2006 [72] treated 22 postmenopausal patients with 50 mg/day oral DHEA for a period of four weeks. The mean number of hot flushes decreased by 50% compared to the baseline. There were no adverse effects observed. The quality of life in terms of hot flushes improved statistically significant under DHEA treatment. Larger placebo controlled studies, investigating DHEA are demanded.

DHEA in Women after Menopause

The use of DHEA in postmenopausal women with normal renal function was assessed by Davis et al 2011 [73] and Goel and Capploa 2011 [74]. Despite the fact, that cross-sectional studies showed a coherence of DHEA levels and sexual function, well-being and cognitive function in postmenopausal women, placebo controlled RCTs failed to verify this. Moreover, there were also no positive effects on lipid- or carbohydrate metabolism observed [73]. Data from randomized studies investigating DHEA in postmenopausal women with normal adrenal function did not justify the use of DHEA in those women [73]. Goel and Cappola 2011 [74] also criticised the use of DHEA in postmenopausal women in a review article. By the daily oral intake of DHEA, serum concentrations comparable to those of young 20-year-old females

were reached. Several observational studies demonstrated that low DHEA levels were associated with an increased risk of cardiovascular events in females. However, interventional studies failed to show an improvement of atherosclerotic or cardiovascular risk factors but a decrease in HDL cholesterol. Concomitant to other therapies, DHEA slightly improved the BMD and memory function in women with slight weakness of memory but did not show any additional benefit in women with normal memory. Intravaginal but not oral application of DHEA led to an improvement of symptoms of vaginal atrophy and the sexual function in postmenopausal women.

Based on these data, there is no rationale for the use of DHEA in healthy, postmenopausal women. In areas, where potential benefits are considered, as well as for the verification of the safety profile, long-term studies are needed.

DHEA in Combination with Estrogen Substitution

In a 12 months period study, 10 mg DHEA were combined with an estradiol patch (50 µg/day). Here, androgen levels, comparable to those of young women, were reached and a positive effect on the estrogenization was observed. The impact of DHEA on well-being and sexual function was not assessed [75]. DHEA in combination with a selective estrogen receptor modulator.

See: US governmental trial (http://clinicaltrials.gov): DHEA and acolbifene for vasomotor symptoms.

Well-being, Mood and DHEA

Women in the climactic period frequently report fatigue, a reduced well-being and loss of libido [76, 77]. The major reason for vasomotor symptoms is the deficiency of estrogen during the premenopausal transition phase. In this period of life, the decrease in estrogen production occurs to a higher extent than the decrease of androgen formation.

Therapeutic Options

The following summary is based on the review by Panjari and Davis 2010 [78].

Testosterone: Some studies demonstrated an improvement of the well-being under testosterone treatment [79–81], whereas other studies failed to verify this [82].

DHEA: One might assume in theory that DHEA has a positive effect on well-being comparable to testosterone since DHEA is metabolized to testosterone and estrogen. However, data on DHEA administration and the effect on the well-being during the perimenopause are controversial [78].

According to the literature available: Six RCTs investigated the effect of DHEA on the well-being and the mood [45, 83–87].

DHEA in supra-physiological doses: The first studies had methodological weaknesses because sample sizes were too small, doses of DHEA were supra-physiological, and treatment periods were too short. There are two studies which indicate that supra-physiological doses of DHEA lead to a lift of the mood [85, 87].

Up tp 2009, none of the up to then current studies could demonstrate an advantage of DHEA treatment on well-being [88–90].

The prospective, randomized, placebo controlled pilot study by Dayal et al 2009 [91] showed no improvement of the health related quality of life by DHEA. A randomized study with 57 elderly women (age > 60 years) who received 50 mg/day oral DHEA for a period of 24 months did not show an improvement in the quality of life [90]. In another randomized study, also investigating 50 mg/day oral DHEA, was also no positive effect regarding mood, quality of life, sensation of physical and mental health as well as life satisfaction observed [88]. Panjari et al [89] also failed to show an improvement of well-being by 50 mg DHEA.

Intravaginal treatment with DHEA: Despite the promising positive effect on the sexual function intravaginal application of DHEA did not lead to an improved well-being [63].

DHEA and Well-being – Summary

- Data on the efficacy of a DHEA treatment on the well-being in the climacteric period are controversial [78].
- Women with very low DHEA/DHEAS levels, e.g. due to adrenal insufficiency, anorexia nervosa or even postmenopausal status might gain therapeutic benefit – However, the efficacy of alternative treatments must be taken into account.

Cognitive Function and DHEA

In the year 2006, there were 26.6 million people diagnosed with Alzheimer's disease worldwide. According to projections, one out of 85 men will have been diagnosed with Alzheimer's disease in the year 2050 [92]. Four out of five studies generated data on elderly women in adequate parallel-group comparisons [93]. Barnhart et al [84] investigated perimenopausal women who stated to have a lowered well-being and conducted three tests to examine the memory function. There were no differences in memory function observed between DHEA and placebo after a three-month treatment period.

Wolf et al [94] investigated 75 healthy subjects (37 females and 38 males aged between 59 and 81 years) to analyze the effect of DHEA on stress induced impairment of memory and found positive, clinically relevant effects.

Dayal et al [91]: 50 postmenopausal women were randomized to receive the following daily treatments over a period of 12 weeks (1) DHEA 50 mg, (2) conjugates equine estrogen (CEE) 0.625 mg (3) DHEA 50 mg + CEE 0.625 mg or (4) placebo. Beside other results, there was no effect on the health related quality of life detected.

Nair [90] investigated in a two-year, placebo controlled, randomized, double blind study the effect of DHEA versus placebo in 87 elderly man with a low DHEA- and free testosterone level as well as in 57 elderly women with low DHEA levels. The dosing in men was 75 mg/day DHEA, respectively placebo. Women received a testosterone patch (5 mg/day) or placebo. DHEA neither had a positive effect on the body composition, physical strength, the insulin sensitivity nor on the quality of life.

Von Mühlen [95] also demonstrated that a DHEA treatment for a one-year period has no advantage for memory function in 225 heathy elderly.

Several controversial studies investigated the effect of DHEA on the cognitive

function, including patients with Alzheimer's disease. Yamada et al [96] described positive effects on the memory in Alzheimer's disease patients. A small case control study investigated the effect of 25 mg DHEA daily in 17 patients between 65 and 90 years old with impaired memory and cognitive function vs placebo. A potential positive effect of DHEA on the memory and activities of the daily life was shown.

No positive effects on cognitive function was observed by Kritz-Silverstein et al [97]. The authors investigated the effect of DHEA (50 mg/day) compared to placebo on the cognitive function and quality of life in healthy, elderly adults (110 man, 115 women) (aged 55–85 years) in a double blind, randomized, controlled clinical study over a one-year period.

DHEA and Memory – Summary

- Positive memories of the past often become more important due to increasing isolation of an ageing population. The thoughts of elderly are increasingly in the past.
- Memory and cognitive functions are dependent on genetic risk factors and on environmental- and mental training. Social isolation and drugs, excessive alcohol consumption, anti-depressants, sleeping pills as well as several drugs, taken against age related diseases, impaired memory function.
- The few data available from controlled studies do not support the use of DHEA for the improvement of memory in middle-aged or old women without pre-existent dementia. The data on safety are insufficient [93].
- In patients with dementia, the data available are not sufficient to judge on improvement of memory or other aspects of cognitive functions by DHEA. In addition, there has been no proven efficacy yet on studies on DHEA treatment in female patients with Alzheimer's disease [98].
- Facing the growing public enthusiasm for DHEA supplementation, in particular in the US, and the theoretical possibility of a long-term neuro-protective effect of DHEA, there is a need for clinical trials with treatment durations of more than one year. Adequate sample sizes are required to get sufficient statistical power and cognitive functions should be assessed in all studies [93].

DHEA and Depression

Since DHEA plays a role in several receptor-mediated reactions in the CNS, there are assumptions concerning positive effects on the central mechanisms of depression. However, results of studies on this topic are controversial.

DHEA is a poor indicator for depression according to a study by Kurita et al [99]. In this study, serum levels of adrenal androgens in male and female patients with major depressions (major depressive disorders [MDD]) were investigated. In total 90 patients, all of them receiving antidepressant treatment were included in the study. Baseline serum levels of DHEA and DHEAS were determined. The levels were compared to those of 128 healthy subjects in the beginning. The correlation of obtained serum hormone levels with the depression score according to the Hamilton rating scale for depression (HAM-D), stratified by gender was performed in a second step. There were different DHEAS serum levels detected between males and females, but DHEA, respectively DHEAS appeared to be a bad indicator for the determination of the severity of the depression.

A correlation between increased DHEAS levels and symptoms of depression during the perimenopause was shown in the PENN Ovarian ageing study [100].

A population-based study on 436 Afro-Americans and Caucasian premenopausal women aged between 35 and 47 years revealed no correlation between DHEAS levels and the diagnosis of a major depression. However, DHEAS levels correlated with symptoms of depression during the perimenopause. This indicates that DHEA might trigger symptoms of depression in perimenpausal women.

DHEA and Depression – Summary

Worldwide, approximately 500 million people suffer from neurotic-, stress dependent- and psychiatric disorders [101]. Depression is globally recognized as a major disease in all populations. Approximately 350 million people are currently affected by depressions (WHO 2012; http://www.who.int/mental_health/management/depression/who_paper_depression_wfmh_2012.pdf). The incidence in women is 50% higher than in men (WHO 2008; http://whqlibdoc.who.int/publications/2010/9789241548069_eng.pdf). There are at least three levels of depressions: subdued mood, depression as a symptom and clinical depression (NAMS 2014; http://www.menopause.org/for-women/menopauseflashes/depression-menopause).

Depressive disorders belong to the so-called affective disorders (manic episodes, bipolar affective disorders, depressive episodes, recurrent depressive disorders, persisting affective disorders). The classification is based on the ICD-10 and the US-American diagnostic manual (DSM). According to ICD-10 and DSM depressions can be distinguished from mood changes [102].

Currently, in Germany there are approximately 5% of the population aged 18–65 years suffering from depression requiring treatment (approximately 3.1 million people). Moreover, approximately 4 million people suffer from depressive episodes. The number of people who develop depression during their lifetime is even higher (Deutsche Depressionshilfe; www.deutsche-depressionshilfe.de). DHEA and DHEAS are formed in the brain tissue and act as neurosteroids. However, the neurosteroid allopregnanolone is a more potent ligand. The few studies available did not show a correlation between serum DHEAS levels and the diagnosis of a major depression. Some data suggest that DHEAS substitution could lead to a deterioration of depressive disorders.

Cardiovascular Diseases and Mortality

More than 23 million people will die from cardiovascular diseases (CHD) per year until 2030 (WHO 2011, http://whqlibdoc.who.int/publications/2011/9789241564373_eng.pdf and WHO 2014, http://www.who.int/cardiovascular_diseases/en/).

DHEA/DHEAS as Biomarker for Coronary Heart Disease (CHD)

A study on men aged 50 years or higher, published in 1986, revealed that there is no correlation between DHEAS levels and deaths of any cause. DHEAS levels are inversely proportional to deaths due to cardiovascular disease [103]. In a re-

view article, analysing four case-control- and eight cohort studies, Thijs et al 2003 [104] found that the data available were sufficient to conclude that low levels of DHEAS among men are associated with an increased risk of cardiovascular disease but that the data were insufficient to determine whether DHEA supplementation lowers this risk. However, these findings could not be verified by Arnlöv et al [105]. They found no correlation between DHEA levels and the risk of cardiovascular disease or deaths in 2,084 middle-aged men without a risk for CHD at the start of the study. Serum testosterone and DHEAS did not correlate statistically significant with the CHD results. In this population-based study increased serum estradiol levels correlated with a lowered risk of CHD in elderly men.

DHEAS Substitution and CVD

DHEA improves the oxidative balance and lowers the tissue levels of pentosidine – a marker for advance glycation end-products – in patients with diabetes [106].

DHEA and CVD – Myocardial Infarction

Increased risk for myocardial infarction: Page et al [107] investigated the correlation between DHEA and DHEAS serum levels and the observed risk for myocardial infarction in females in a retrospective case-control study, including participants from the Nurses' Health Study cohort. A weak positive correlation between serum DHEA-/DHEAS levels and the risk for myocardial infarction was found, predominantly in postmenopausal women.

Perfusion parameters and arteriosclerosis Weiss et al [108] investigated whether oral application of DHEA in elderly decreases the carotid augmentation index (AI) and the carotid pulse wave velocity (PWV) as markers for the vascular wall stability (arterial stiffness). The AI could be measured in 92 and the PWI in 51 women, aged 65–75 years, who received 50 mg DHEA oral in a double blind, randomized study. The results showed that DHEA substitution in elderly improved the arterial flexibility index. Arterial flexibility decreases with age and is an independent risk factor for CHD. So far, there is evidence that supplementation of DHEA had a positive effect on vascular ageing and results in a decreased risk for CHD.

Cardiovascular Mortality and DHEA

In 1996, it was assumed that the majority of studies would show an inverse correlation between DHEA/DHEAS levels and cardiovascular morbidity and mortality in men but not in women [109]. Later on, this optimistic assumption could not be supported by additional clinical studies. A five-year epidemiologic cohort study revealed no statistically significant correlation between DHEA/DHEAS serum levels and the development of arteriosclerosis in men or women [110]. Ohlsson et al [111] summarized available data on DHEA and cardiovascular mortality as follows:

– Elderly men: Although the publications appear inconsistent, the authors conclude that several population based studies show a correlation between low DHEA/DHEAS levels and the risk for mortality at least in elderly men. The currently available data rather indicate a correlation with cardiovascular mortality than with cancer mortality.
– Elderly women: There is no association.

However, there are biologically plausible mechanisms for the effect of DHEA/DHEAS on the development of cardiovascular disease. Nevertheless, there is strong evidence that any disease lowers DHEA/DHEAS levels. However, the pathomechanism and consequences are not fully understood yet [111].

DHEA and cardiovascular diseases – Summary

Worldwide, cardiovascular disease, including arterial hypertension, myocardial infarction, stroke and venous thromboembolism increasewith age. More than 23 million people will die from cardiovascular disease in the year 2030 worldwide (WHO 2014, http://www.who.int/cardiovascular_diseases/en/). Most of the cardiovascular diseases depend on avoidable risk factors. Changes in blood lipids and carbohydrate metabolism are increasing due to an unhealthy lifestyle.

Estrogens: A primary and secondary prevention of cardiovascular diseases by an estrogen therapy during peri- and postmenopause is controversial but might be possible when the estrogen treatment starts very early.

DHEA: There are several studies investigating the effect of DHEA on the lipid- and carbohydrate metabolism, cardiovascular disease and cardiovascular mortality. However, a statement cannot be made due to the limited sample sizes and potential biases of the study designs.

Changes in Metabolism

DHEA is an indirect parameter of cardiovascular health; its effect on the lipid- and carbohydrate metabolism and haemostasis will be discussed here.

Interpreting clinical laboratory results as predictors for certain diseases is sometimes misleading, since the changes, which can be detected in ill patients might have a different meaning in healthy people. There are several partly synergistic, partly antagonistic or neutral parameters in the lipid- and carbohydrate metabolism and haemostasis, which have no predictive value. Further studies are of importance for the evaluation of the complex interaction of these parameters.

Lipid Metabolism

Cardiovascular disease is the leading cause of death and invalidity with restrictions in the quality of life worldwide. Increased LDL- and cholesterol levels are major factors for cardiovascular diseases. At least one third of all cardiovascular diseases are correlated with the following five risk factors in the so called developed countries: smoking, excessive alcohol consumption, increased blood pressure, increased serum cholesterol levels and obesity. Here, increased cholesterol is correlated to 56% of all cases of coronary heart disease and 18% of all cases of ischemic stroke [112].

The following analysis is based on a review by Panjari and Davis [78]:

– DHEA has anti-atherogenic effects as shown in animal models [113–115].
– Exogenous DHEA is supposed to influence the cardiovascular risk mainly by its effect on the lipid metabolism.
– The cardio-protective effect occurs predominantly in men. This indicates that the effect is based on the conversion to estrogens and androgens [103, 117].

– However, Cheng et al [115] could show, that the possibly anti-androgenic effect of DHEA is not based on the conversion to estrogens and androgens but on its own bioactivity.
– DHEA substitution: several studies describe the effects of DHEA on lipids: A slight decrease of HDL cholesterol was shown by Mortola and Yen [118], Morales et al [45], Nair et al [90], Labrie et al [16], Casson et al [119], Srinivasa et al [70], Barnhart et al [84], Johannson et al [67], Dhatariya et al [120], Dayal et al 2005 [91] and Arlt et al 1999 [65] with concurrent decrease of total cholesterol [16, 65, 70, 118, 121].

However, not all studies demonstrated significant changes in the lipid pattern [68, 89, 122–124], but the interpretation of changes in the lipid pattern and the relevance of total cholesterol and HDL cholesterol observed in these studies is controversial [70, 113].

Current Studies on the impact of DHEA on Lipid Metabolism

A three month treatment with 100 mg DHEA (oral) showed a potentially favourable lipid profile compared to placebo treatment [125]. The group of Bednarel-Tupikowka et al [126] demonstrated varying correlations of serum lipids (increase of triglycerides and HDL cholesterol) and endogenous DHEA levels in 40 postmenopausal female patients. A decrease of triglyceride level under treatment with 50 mg DHEA (oral) was found in a larger double blind, randomized study in postmenopausal women with pathological glucose tolerance at baseline [127]. A three month treatment period with DHEAS (100 mg oral per day) showed an improvement of metabolic parameters compared to placebo in a randomized, placebo controlled, double blind study in 61 postmenopausal female patients with metabolic syndrome [128].

DHEA and lipids – Summary

The interpretation of the predictive impact of lipid changes on the development of cardiovascular diseases resulted in different evaluations in the recent years. For example, the anti-atherogenic effect of HDL should rather be based on its functionality (particle size, quantity) than on its plasma concentration [13, 70]. This would in return outweigh the negative impact of the DHEA induced decrease in HDL cholesterol. The data available show that the effect of DHEA on the plasma lipid profile, respectively glycoproteins, is moderate and not of clinical significance [78].

Carbohydrate Metabolism

Excessive food intake and lack of exercise are important risk factors for cardiovascular disease and result in a global increase in obesity and type-2 diabetic patients.

The following analysis is based on a review by Panjari and Davis [78]:

DHEA as metabolic marker: Low DHEA serum levels, as they occur during ageing, are correlated with an disorder in the glucose tolerance, an increased insulin resistance and an increased risk for the development of diabetes mellitus [10, 129, 130]. Exogenous supplementation of DHEA in women after menopause (see review by Panjari and Davis [78]) resulted in the following changes of the carbohydrate metabolism:

– Increase in insulin sensitivity after treatment with DHEA [120, 122, 131]
– Decreased insulin sensitivity [118]
– No changes [45, 89, 90, 119, 123, 124, 132, 133]
– The results are inconsistent and therefore, the correlation between DHEA and the carbohydrate metabolism requires further investigations.
– Panjari et al [89] showed no correlation between DHEA and the carbohydrate- and lipid metabolism in a placebo controlled, double blind, randomized study in postmenopausal women (n = 93) with decreased libido investigating the sexual improvement, lipid- and carbohydrate profile and endometrial safety of 50 mg DHEA/day (oral). DHEA showed no effect on the lipid metabolism and insulin resistance. The endometrial perfusion pattern showed no significant differences in DHEA treated- and placebo treated patients. There were also no significant changes in the endometrial safety observed.
– Glucose tolerance was improved by 50 mg DHEA/day compared to placebo in a large randomized double blind study in women with pre-existing pathological glucose tolerance. For further details of the study see also the chapter on lipid metabolism [127].

Haemostasis

Several factors might influence an increased haemostasis, which can result in a restriction or interruption of blood flow. An embolus might result in thromboembolism, cardiac infarction, stroke and other damages to body organs that can also result in death (American Heart Association, http://www.heart.org/HEARTORG/Conditions/More/Understand-Your-Risk-for-Excessive-Blood-Clotting_UCM_448771_Article.jsp). In 60–80% of patients with thromboembolism, pre-existing genetic factors are the cause for the embolism. Up to 10% of the population have constitutional haemostasis-disorders that might lead to embolism or thromboembolism according to multimodal models [134]. An unphysiologically high dose of 100–300 mg DHEA per day results in an inhibition of thromboxane A2 in activated thrombocytes, to a decrease of the plasminogen inhibitor type I in the plasma and the plasminogen activator in tissues as well as in an increase of the insulin-like growth factor I, of cyclic guanosine monophosphate and the nitrogen monoxide synthesis (either directly or by an increase of IGF-1) in humans [51, 135–137].

These effects on the metabolism indicate that in clinically not relevant supraphysiological doses DHEA,might improve microcirculation. It might also have a positive effect on risk factors for cardiovascular disease by regulation of factors like aggregation of thrombocytes and prevention of ischemia.

DHEA and Haemostasis – Summary

In physiological concentrations DHEA does not appear to influence haemostasis.

DHEA and Lupus erythematosus

DHEA might play a positive role in immunomodulation due to functional activation of T-cells with an increase of CD8+ and CD56+ cell (natural killer cells), increased cytotoxic activity [40, 45, 51, 138) and an inhibition of the pro-inflammatory cytokine interleukin-6 [41]. Lupus erythematosus is an autoimmune disease. There are several studies investigating the effect of DHEA on the symptoms due to its impact on the immune system. An exogenous application of DHEA for the treatment

of SLE initially showed promising results.

Patients with SLE were treated with 200 mg DHEA/day for a period of three months in a randomized, double blind study. There were several clinical effects observed, however, the antibody titres remained unchanged [137, 139, 140]. Overmann et al [141] investigated whether low levels of DHEA/DHEAS play a role in SLE-induced fatigue and compared:
1) DHEAS levels and fatigue in 60 female patients with SLE of low activity (31 used prednisolone, 29 did not) compared to 60 age-adjusted healthy female subjects and
2) Fatigue-levels of female SLE-patients with low or normal DHEAS levels.

Since the authors showed, that the DHEA treatment did not result in a decrease in fatigue symptoms, low DHEA(S) levels alone cannot explain fatigue in SLE patients. Treatment with 200 mg DHEA per day in 13 premenopausal patients with SLE and pre-clinical signs of arteriosclerosis did not result in an improvement of symptoms [142].

DHEA and Lupus erythematosus – Summary

There are several signs that DHEA treatment has a short-term benefit in patients with systemic Lupus erythematosus but there is almost no evidence for the efficacy and safety of a long-term treatment [143].

Physical Strength

Muscle Development

Several studies revealed a positive effect of DHEA on muscle development in higher ages of life.

Nair [90] investigated 57 females and 87 males with low DHEAS levels for 24 months in a placebo controlled, randomized double blind study. Neither DHEA- nor a low dose testosterone-substitution showed a pathophysiologically relevant advantage on body composition, physical capability, insulin resistance or the quality of life in elderly participants. DHEA improved the gain of muscular mass and strength due to heavy weight training in elderly [144]. There was no change in BMI in a placebo controlled study with 50 mg DHEA over a six-month treatment period observed [145]. A study by Igwebuike et al [123] showed a positive effect on the body composition due to combined endurance- and weight training.As shown by a placebo controlled, randomized pilot study, DHEA supplementation increased the serum androgen level in postmenopausal women without considerable effects on muscle cross-section area, strength, muscle function or health related quality of life [91].

Physical Strength and DHEA – Summary

- Physical strength is of importance for the mobility and coordination of movements and therefore enables auto-mobility without assistance in the elderly.
- The available data on the effects of DHEA on strength in elderly people are insufficient [146].
- In a placebo controlled study among middle-aged men, there was no statistically significant effect of DHEA on body mass, strength or testosterone levels observed [147]. In addition, a large study with 100 participants showed no effect of DHEA on strength in a group of elderly [148].
- There is a single small study supporting the thesis that DHEA results in an increase of free (but not total) testosterone [149].
- DHEA did not show a significant effect on strengths in postmenopausal women as shown in a randomized, placebo controlled study, investigating the effect of a combined program endurance- and weight training [123, 150].

DHEA and Athletes

Hahner and Allolio [151] provided the following statement on the restriction of the use of DHEA by athletes:

- Oral intake of DHEA results in a dose dependent increase if circulating androgens that might reach supra-physiological concentrations in women. The World Anti-Doping Agency (WADA) listed DHEA as prohibited substance.
- However, there is no evidence of performance-enhancing effects of DHEA yet. Randomized studies in elderly patients with age dependent decrease of DHEA levels revealed only limited or no evidence for an improvement of physical performance after long-term intake (50 mg/day). Smaller short-term studies in healthy male athletes investigating higher doses were completely negative. Therefore, the supposed performance-enhancing activity of DHEA is more myth than reality.
- Due to the lack of studies in female athletes, a potentially performance-enhancing effect of high-dose DHEA cannot be ruled out in this population. Adverse effects, like hirsutism, acne and alopecia must be taken into account then.

Osteoporosis

It is estimated that currently 200 million people suffer from osteoporosis worldwide. Approximately 30% of all women in the U.S. and Europe have osteoporosis after menopause at least. In minimum, 40% of these women and 30% of men will suffer from one or more bone fractures during their lifetime. The over ageing society worldwide is considered to be the main reason for osteoporosis in postmenopausal women (International Osteoporosis Foundation 2014, http://www.iofbonehealth.org/epidemiology). Due to its conversion into testosterone and its partial estrogenic-activity, it is supposed that DHEA might be beneficial in women with osteoporosis. However, this has not been verified yet.

Von Muhlen [95] treated healthy elderly adults with 50 mg DHEA per day for a period of one year. He reported a moderate effect on BMD and bone resorption. This effect could not be shown in men. An improved BMD in the hip joint region in elderly and in the vertebral column in elderly women was observed after one year DHEA (50 mg/day) treatment in a randomized, double blind, controlled study [152]. A minor loss of bone quantity in the area of the femoral neck and the lumbar column was observed after DHEA treatment Ghebre et al [153].

The group of Papierska et al [154] was able to show a beneficial role of DHEA substitution in the treatment of steroid-induced osteoporosis. Bloch et al [155] reported a positive effect of DHEA (100 mg/day) on the mood and BMI compared to placebo in a double blind, randomized study over a six-month treatment period in outpatient patients with anorexia nervosa. DiVasta et al [156] found a positive effect on the surrogate

parameters for bone stability and not on bone density only in a randomized, placebo controlled study in young women.

DHEA and Osteoporosis – Summary
Estrogens: A primary or secondary prevention of osteoporosis and bone fractures in peri- and postmenopause is possible by estrogentherapy as a second line treatment.

DHEA: DHEA treatment might be beneficial in distinct groups (e. g. women with estrogen-deficiency, patients with anorexia nervosa) or in the treatment of steroid-induced osteoporosis.

Sexuality

There are several forms of sexual dysfunction in women. Among others, there is lack of sexual urge, impairment of sexual arousal, inability to achieve an orgasm or pain during sexual activities. Sexual dysfunction can be a lifetime problem or occur de novo later in life after a period of normal sexual function (UpToDate 2014, http://www.uptodate.com/contents/sexual-dysfunction-in-women-management).

The prevalence of sexual dysfunction in women shows a high variance of 9–43% as shown in a few population-based studies (review by Nijland et al [157]). The analysis of 25 double blind, randomized and controlled studies (up to the year 2005) that investigated the effect of pharmaceutical intervention on female sexual function showed that approximately 40% of women in the U.S. stated to have sexual dysfunctions. 12% of the women rated the sexual dysfunction as incriminating [158].

Incriminating sexual dysfunctions (defined as stated to have a sexual dysfunction as well as a personal burden due to the sexual dysfunction) were reported in 12% of those polled and occurred more frequently in women aged 45–64 years (14.8%) compared to younger women (10.8%) or elderly (8.9%) [158]. The sexual function in women has remarkably subsided with the age of 60 years. A minority of these women experience the decreased sexual function as significantly incriminating. The burden due to sexual dysfunctions is often associated with depression and problems in the relationship [159].

In case the lack of sexual desire is caused by personal problems, it is referred to as hypoactive sexual desire disorder (HSDD) which occurs in 7–26% of women living in a residential community [160]. It occurs more frequent in postmenopausal women with impaired health status and decreased health related quality of life [161]. Women who experienced surgical menopause also have an increased risk for developing HSDD. HSDD is put in association with a lowered satisfaction in sexual relationships and a negative emotional self-picture [162].

Factors of relationship were more important for a lack of sexual desire than age or menopausal status whereas physiological and psychological factors were more important than relationship factors in case of insufficient genital arousal and the ability to experience an orgasm [163]. Normal sexual function during peri- and postmenopause depend also on distinct anatomical premises (e.g. no vaginal dryness, infections, pain during sexual intercourse) and a general well-being with absence of stress factors. The female libido is to be considered a multifactorial complex, including erotic fantasies, sexual arousal and the ability to experience an orgasm in association with the sexual partner. An emotional relationship is the prerequisite for the latter factor.

The interrelation between age dependent DHEA- and testosterone serum levels and sexuality as well as the clinical relevance of DHEA substitution on sexuality is discussed in the following section.

Pathophysiological Changes during Peri- and Postmenopause and Female Sexuality

Knowledge about the importance of sex hormones, estrogens and androgens, in the context of the normal sexual function in women are limited and object of further investigations. The shift of steroid hormones during postmenopause is summarized by the workgroup of Panjari and Davis [78].

– Estrogen deficiency: In a majority of women, lack of estrogen results in vasomotor symptoms and vaginal atrophy during the peri-menopause. Cognitive changes and mood changes due to hot flushes, attacks of sweating and sleep disorders might occur in some women [164]. This results in a negative impact on the quality of life and has impact on the sexual function in many cases. The decreased formation of estrogen in the ovaries results in changes in the vaginal milieu in postmenopausal women [165]. A vaginal atrophy can result in dyspareunia, which again has a negative impact on the sexual function [166].

Female sexual function decreases with the naturally occurring menopause. This decrease is also caused by decreased levels of estrogens and androgens in the blood [164].

– Androgens: Testosterone is formed in the ovaries and, to a lower extent, in the adrenal glands from its precursor DHEA/DHEAS in fertile women [20]. The cyclic increases in androgens do not occur after the menopause anymore [167] and androgens are only formed in the adrenal glands [168], which becomes the major source for DHEA/S and testosterone. By aromatization in the subcutaneous fat tissue, estrogen can be formed from the steroid precursors DHEA and DHEAS.

DHEA as neuro-steroid in the brain: Besides its function as precursor for the steroid synthesis, DHEA also serves as neuro-steroid in the brain and might therefore have a positive impact on sexuality [169].

Androgen-Serum Levels and Sexuality

Androgens play a role in the normal sexual function in women. Serum androgen-levels decrease with increasing age [170]. Thus, it could be biologically plausible that the female sexual function decreases due to this drop of androgen levels. A naturally occurring menopause does not result in a sudden drop of serum androgen concentrations but elderly women have lower levels of androgen compared to younger ones [171].

– Testosterone: Observational studies revealed that sexual dysfunctions increase with age [158, 172]. A cross-sectional study in 1,423 Australian women who provided information on their sexual function revealed no significant correlation between low tes-

tosterone levels (free or total) and androstenedione with the sexual function [173].
– DHEAS: There is a coherence between low DHEAS levels in serum and low sexual function, although women with low DHEAS levels stated not to have a lowered sexual function. There are indications that a testosterone substitution is highly effective in treatment of lowered sexual function [79, 80–82, 174, 175]. However, since it was not possible to proof that DHEAS serum levels (or testosterone) are predictive markers for a lowered sexual function and considering the fact that it was also not possible to define a serum androgen level that characterizes a female androgen deficiency; DHEA treatment to improve sexual function cannot be recommended. This has to be proven in well-designed clinical studies before giving any recommendations.

Therapeutic Approach

Despite indications that impaired sexuality in ageing societies is an issue of clinical relevance, there are only limited therapeutic options:
– Estrogens: Estrogens play an important role in normal female sexuality. An estrogen therapy can improve the sexual function by alleviating from postmenopausal vaginal atrophy and vasomotor symptoms [176–179].
– Testosterone: There is a direct correlation between transdermal testosterone supplementation and several parameters of female sexuality. A developed and marketed testosterone patch (trade name: Intrinsa) was taken off market. A low dose testosterone gel, micronized testosterone in liposomal formulation for women, 3 mg/puff in a 100 g dispenser can be used off-label in Germany. One puff is applied daily on the calf. The testosterone level is checked (IGEL) after six and 12 weeks with subsequent dose adjustment [Schwenkhagen and Schauding 2013, personal communication]. A combined androgen-/estrogen substitution was approved from health authorities in the U.S.A.

DHEA Substitution and Sexuality

Animal experiments – DHEA in rats: Intravaginal treatment with DHEA in rats results in a strong stimulation of formation of intravaginal nerve fibres. This might be an explanation for the positive effects of intravaginal DHEA supplementation on sexual dysfunction in women after the menopause [180]. Nine randomized studies, investigating the impact of oral DHEA treatment on the improvement of female sexual function in healthy, post-menopausal women were analysed in a meta-analysis by Panjari and Davis [78], Baulieu et al [181], Mortola and Yen [118], Morales et al [45], Wolf et al [83], Hackbert and Heiman [182], Schmidt et al [87], Donna [88] and Panjari et al [89].

Some of the studies showed positive effects of DHEA on the female sexual function [87, 181, 182]. However, this could not be confirmed by other studies [45, 83, 88, 89, 118]. In two of the three studies which showed a therapeutic benefit, DHEA was applied in supra-physiological doses with a short treatment duration [87, 182]. A third study in elderly women applied a non-validated investigation on sexual function which was correctly interpreted by 25% of the subjects only [181].

The first studies that failed to show a positive effect of DHEA were unrepresentative due to limited sample sizes [45, 118], the short therapy [83, 118], the use of non-validated investigations [83, 118] and treatment with un-physiologically high doses of DHEA ([118] according to [78]).

Some studies are described in more detail in the following section:
– DHEAge-study: A double blind, placebo controlled study over a 12 months period with a daily application of 50 mg DHEA in 208 healthy males and females (age 60–79 years) resulted in an increase in the libido and an improvement of the numerous parameters of complexion in elderly women [181].
– DHEA at doses of at least 100 mg per day can be effective for treatment of women with decreased sexual desire (HSDD) [155].
– Three different treatment schemes (10 mg DHEA daily per oral, a hormone replacement therapy or treatment with Tibolon) improved the sexual function significantly and resulted in increased frequencies of sexual intercourses in women in early menopause compared to women, treated with vitamin D [183].
– Intravaginal DHEA for a period of twelve weeks was investigated in a randomized study in post-menopausal women with vaginal atrophy [62, 184]. The treatment resulted in an improvement of the vaginal atrophy with a minimum change of serum steroids which were within normal ranges for post-menopausal women [62, 63]. Positive effects of intravaginal DHEA treatment on four partial aspects of female sexuality, namely lust, arousal, orgasm and pain during sexual activity were reported [184]. Unfortunately, the number of women in the different treatment arms was low and the authors missed to report how many women completed the different treatment arms.

DHEA and Sexuality – Summary
– Sexuality in elderly is generally under-estimated.
– Sexual desire is individually different, due to high mortality in men and lack of potential partners.
– In case an elderly woman is requesting medical assistance due to sexual problems, low-risk therapies shall be offered.
– General well-being: Estrogen-substitution (in case of uterus preservation in combination with gestagen) or Tibolon in patients with vasomotor symptoms.
– Vaginal health: Treatment of vaginal atrophy, vaginal dryness and dyspareunia by oral (in case of uterus preservation in combination with gestagen if indicated) or local estrogen administration, Tibolon or oral administration of a new SERMS – Ospemifen – "see vaginal health".
– Testosterone improved sexual thoughts, desire, arousal and the capability to experience an orgasm in women in a dose dependent manner.
– DHEA: The efficacy in treatment of limited sexual function in women is not sufficiently proven since no change in total testosterone levels only limited increases in free testosterone were observed. It cannot be excluded that DHEA might show activity by its effects on estrogen in the genital area or as neurosteroid in the CNS. However, there is a lack of large-scale randomized studies investigating these objectives.

Vaginal Atrophy

Vaginal atrophy and dryness are common symptoms of estrogen deficiency during the menopause. Frequent results are dyspareunia and sexual function disorders [166]. More than 50% of post-menopausal women suffer from vaginal dryness and frequent vaginal infections. Those urogenital disorders result in a decreased frequency of all forms of sexual behaviour.

Further urogenital disorders correlated with increasing age in women are irritations and sensation of pressure, fluor and infections, vulvo-vaginal pruritus, postcoital bleedings, pollacisuria, urinary incontinence and recurring urinary tract infections [185].

Therapeutic Options

- Estrogens: Oral, vaginal: estradiol or estriol. Efficacy and long-term safety of low dowse estradiol and estriol are well established. Local vaginal estrogen therapy requires an application for 2–3 times per week instead of daily hormone administration.
- SERM: A new SERM (Ospemifen, 60 mg/day, oral) was approved for treatment of dyspareunia by the FDA in the USA. The marketing authorization holder expects an approval in Europe as therapeutic option for the treatment of vaginal dryness in postmenopausal women within this year.
- DHEA: DHEA is absorbed and locally metabolized in androgens and estrogens if applied vaginally. There is a rapid onset of relief of all symptoms of vaginal atrophy. This therapeutic approach is free of concerns of systemic side effects compared to an estrogen treatment. Intra-vaginal treatment with DHEA represents a new physiologic form of a local androgen-therapy.

Animal Experiments in Rats

Berger et al [64] investigated the efficacy of an intravaginal administration of DHEA in daily doses of 0.33, 0.66 or 1 mg for a treatment period of two weeks in ovarectomized rats. They showed that a local vaginal therapy with DHAE has a positive effect on the vaginal epithelia without significant systemic side effects.

Clinical Studies

Intravaginal administration of DHEA for the treatment of symptoms caused by vaginal atrophy were investigated by Labrie et al [62, 63] in the context of a prospective, randomized, double blind, placebo controlled phase III study in 216 post-menopausal women. Depending on the treatment arm, DHEA was applied as vaginal-ovular (1.3 ml) (0, 0.25, 0.5 and 1.0%) daily for a period of twelve weeks. The treatment resulted in an improvement of vaginal atrophy with a minimum change of serum steroids, which were within normal ranges for post-menopausal women.

Panjari and Davis [61] speculate that vaginal application of DHEA in postmenopausal women can be justified for the treatment of vaginal atrophy. However, large-scale, randomized, placebo controlled studies are required. In this context, the effect of vaginal DHEA on the female sexual function in women without vaginal atrophy shall be investigated. By assessing potential advantages of a vaginal DHEA treatment compared to an estrogen therapy it must be taken into account that daily, topic intravaginal application of an ovulum or a cream is required.

DHEA and Vaginal Atrophy – Summary

- Prevalence: More than 50% of postmenopausal women suffer from vaginal dryness and frequently occurring inflammations of the vagina.
- Treatment options are estrogens (estriol, estradiol) as well as the recently marketed SERM Ospemifen (60 mg/day oral) which already received marketing approval for treatment of dyspareunia in the USA. The European approval for the treatment of vaginal dryness is pending.
- DHEA: The intra-vaginal application of DHEA in post-menopausal women with vaginal atrophy is a promising approach for the treatment of vaginal atrophy and the impaired sexual function resulting thereof. Further effects of DHEA on lust, arousal, orgasm and pain during sexual activity, as well as the above mentioned effect on vaginal atrophy requires further investigation in large-scale, placebo controlled, randomized clinical studies.

Hormonal Contraception with DHEA Additives

Androgen restored contraception (ARC) was a novel concept for a combined oral contraceptive (COC) invented by Pantarhei Bioscience, a Dutch pharma company. The first clinical studies started ten years ago. The ARC "triple hormone" concept, combining an estrogen (E), a gestagen (P) and an androgen (A) in a COC was patented for oral contraception by Pantarhei Bioscience. Moreover, Pantarhei licenced in a patent held by Bio-Sante, USA, covering the general use of E, P and A in combinations.

Drop of Testosterone Levels due to combined Hormonal Contraceptives

The concept is based on the fact that the use of combined oral contraceptives (COC) results in a decrease in androgen levels, particularly testosterone (T) by inhibition of androgen synthesis in the ovaries. According to the literature, testosterone levels drop for up to 50%. However, the large-scale, prospective studies conducted by Pantarhei showed that the decrease in testosterone levels was much more severe. Foidart from Belgium conducted a phase II study investigating the safety and endocrinology in 99 first time users in cooperation with Pantarhei Bioscience. The study revealed a significant mean decrease from 1.5 to 0.5 mmol/l of total testosterone and from 20 to 2 pmol/l of free testosterone after three cycles of COC. This study was published in 2010 at the COGI conference in Berlin.

Since the naturally occurring human androgen DHEA is metabolized partly to testosterone, the testosterone levels can be restored by concomitant administration of DHEA during COC.

Clinical Studies

The studies conducted by Pantarhei showed, that a daily dose of 59 mg DHEA normalizes the testosterone levels without exceeding the maximum testosterone levels of women who do not take COC. Besides the normalization of the testosterone level, adding DHEA to the pill resulted in a significant clinical improvement of the mood and sexual function in non-selected COC-users [Coelingh Bennik, personal communication, 2011].

- Phase II study: The first results of a clinical phase II study, investigating the ARC concept with focus on sexual function and safety were reported in May 2011 during the 11th congress of

the European Society of Contraception in Den Haag/The Netherlands. This crossover study investigated two treatment cycles of 5 months each and compared an oral contraceptive alone or in combination with 50 mg DHEA daily in 82 women. The study was conducted by van Lunsen and Laan from the department of sexual sciences of the Academic Medical Centre in Amsterdam, The Netherlands in close collaboration with Bennink and Zimmerman from Pantarhei Bioscience. The sexual excitability, genital sensation and lubrication was significantly improved in OC-users without specific sexual dysfunctions. The frequency of sexual activities was doubled and the rejection of sexual activity by the partners was significantly reduced. The Lüttich-study showed a significant improvement of mood as assessed by the use of validated questionnaires during the six-month DHEA treatment period [Coelingh Bennink, personal communication 2011].

- Studies in women with severe mood-changes or sexual dysfunction: There was no effect observed in two small, so-called "n = 1 studies" in women with severe mood-changes or sexual dysfunction. The addition of DHEA to COC caused no side effects and had no influence on the frequency of hirsutism during the 10, respectively 12 months treatment periods in the studies of Amsterdam and Lüttich. The incidence of acne was equal compared to the incidence in non-users [Coelingh Bennink, personal communication 2011].
- According to the Bayer business report 2008 (http://www.bayer.com/en/gb-2008-en.pdfx), Bayer Healthcare conducted a safety and efficacy Phase II study, investigating oral dehydroepiandrosterone (100 mg) concomitant to oral contraceptives in women with reduced libido. Purpose of the study was to investigate the efficacy of the study medication on the libido of women which apply oral contraceptives and who have experienced libido reductions as side effect of contraception. However, the results of the study are not published.
- Heijboer et al [186] investigated the methods of testosterone measurement under oral hormonal contraception, which cause a decrease of free testosterone and pointed out the advantages and disadvantages of the different methods.

DHEA and Contraception – Summary

- DHEA is a weak androgen, produced in the adrenal glands. As steroid-precursor, it facilitates the synthesis of the stronger androgen-acting testosterone and the synthesis of estrogen by aromatization.
- The doses of DHEA applied in studies that investigated the combination with a contraceptive compared to the off-label use of DHEA was relatively high. In most countries, DHEA supplements are sold OTC for use in post menopause (10–25 mg/day)
- A preclinical study of a COC and concomitant DHEA administration (100 mg/day) has already been performed (Bayer Health-Care, http://clinicaltrials.gov/ct2/show/NCT00566384.The applied dose of 100 mg per day in fertile women and is un-physiologically high potential and unwanted long-term effects cannot be ruled out according to the authors.
- Women with spontaneous menstruation cycles produce testosterone in a cycle dependent manner whereas the testosterone production in women under hormonal contraception (COC) is suppressed.
- The normalization of testosterone production under COC treatment by 50 mg DHEA per day significantly improves the mood and sexual function.
- The question of an increased risk for developing breast cancer is not finally solved, especially since some studies reported an increased, some studies no change and some studies a decreased risk.
- The dose of 50 mg DHEA per day is higher compared to doses tested in HRT studies (10–25 mg/day) but does not seem to result in clinically relevant side effects according to the literature.
- Since the restoration of testosterone levels by DHEA, which were suppressed by COC in selected users did not result in obvious complaints, ARC developed a first-choice concept for healthy women but not for women with severe psychological and sexual disorders as shown in studies conducted by Bayer Healthcare and Pantarhei [Coelingh Bennink, personal communication 2012].

Anti-ageing Effects

Estrogen- and androgen levels decrease with increasing age in post-menopausal women [187].

DHEA and DHEAS drop continuously with increasing age [16, 23], so that the DHEA production is decreased by 60% with the menopause [188]. In the 8th or 9th decade of life, only 10–20% of the maximum amount of DHEA as produced in the age of 20–30 years are produced only Baulieu [7], Migeon et al [188], Orentreich et al [14], Labrie et al [16], Davidson et al [17] (Fig. 4).

The decrease of DHEA as major source of androgens in women results in a decrease of total androgen levels. Limited well-being, menopausal complaints and loss of libido are consequences thereof [189]. Impaired insulin resistance, obesity and cardiovascular disease might occur additionally [181].

A "female androgen insufficiency syndrome" due to low androgen levels and a worsening of mood, general well-being as well as motivation was described by Bachmann et al [190] without reporting a clear definition of boundary values of androgens used for diagnosis.

A rapid decline of DHEA- (DHEAS, respectively) concentrations in the blood occurs during the normal ageing process, potentially resulting in clinical symptoms of adrenopause [46, 191, 192]:

- Chronic fatigue, loss of physical and mental capabilities
- Immuno-defects
- Insufficient stress resistance
- Gain of weight (in particular visceral- and subcutaneous fat tissue)
- Dryness of skin, decrease of body hair, skin atrophy
- Muscle atrophy
- Arthrosis and osteoporosis
- Sweating, sleep disorders and a tendency to develop depression in men

Animal experiments showed positive effects of DHEA against the development of diabetes, atherosclerosis, osteoporosis, cancer and the decrease of immune function [193]. Pugh et al [194] investigated the incidence of the most common carcinoma (plasma-cell tumor) which was higher in calorie-restricted held mice (66%) compared to mice held un-

der normal diet (41%). Treatment with DHEA did not result in an in- or decrease of the cancer incidence or a prolongation of life [194]. However, the low doses of DHEA in laboratory animals and the clear role of DHEA in humans raise doubts on the results of the animal studies.

In very old, healthy people of both sexes aged 90–106 years, DHEAS seems to clearly influence the activities as observed by the workgroup of Ravaglia et al [195].

DHEA and Anti-ageing – Summary
- A lack of estrogens and androgens occurs during natural ageing in the postmenopause.
- There is not sufficient evidence for the efficacy of DHEA as anti-ageing drug.

Wound Healing

Animal experiments demonstrated that exogenous DHEAS has positive effects in wound healing disturbances. The data indicate that DHEAS could be used for prophylaxis of impaired wound healing. Additional clinical studies are demanded [196].

Reproductive Medicine

Since the year 2000, attempts of additional treatment of women with distinct forms of infertility with gonadotropins and DHEA are undertaken in the context of reproductive medicine [197]. DHEA administration in "poor responders" was described by Arlt [198]. Elder studies showed an improved quantity and quality of oocytes with a decrease of aneuploidy and rates of spontaneous abortions [199].

Some questions on DHEA treatment of women wishing to become pregnant with special indication are discussed in the following. Here, three questions are of special interest:
1. Is DHEA a surveillance marker of human fertility and the monitoring of the menstrual cycle in the context of ovarian hyper-stimulation by ART?
2. Can ART results be influenced by DHEA?
3. What is the influence of DHEA in the course of premature ovarian failure (POF)?

Mode of action: DHEA is a precursor of the androgen- and estrogen synthesis. Both groups of steroids have a role in the maturation of follicles, the ovulation and the luteal phase. DHEA is converted to androstenedione and estrone, the source of testosterone and estradiol, in the follicle [200].

DHEA in Patients wishing to become pregnant

DHEA is a predictive serum marker in IVF-patients: There are only limited data, which only show a predictive value for testosterone but not for DHEA.

Definition
Patients showing limited response to gonadotropin stimulation in the context of assisted reproduction.

Meta-Analysis
Diminished ovarian reserve: Narkwichean et al [201] investigated the effect of DHEA in women with diminished ovarian reserve in a meta-analysis. Of 22 studies, only three could be taken into consideration for the analysis. There was no significant difference in the rate of clinical pregnancy and the frequency of abortions in women that were pre-treated with DHEA compared to not pre-treated women (RR 1.87, 95.%-CI: 0.96–3.64 and RR 0.59, 95-%-CI: 0.21–1.65, respectively). The quantity of oocytes obtained (WMD -1.88, 95-%-CI: –2.08–1.67; $p < 0.001$) was significantly lower in the DHEA group. In total, there were only 200 IVF cycles, which was not sufficient to show a positive effect of DHEA in the context of controlled stimulation during IVF. Randomized, controlled studies are needed to obtain useful results on the efficacy of DHEA in poor responder patients with diminished ovarian reserve.

Mode of action of DHEA in ART
The improvement of IVF treatment results is not due to recruitment of more pre-antral or small antral follicles or due to a change of AMH and inhibin B levels; The potential mechanism is a reduction of atresia of very small antral follicles and an increased AFC [201]. This is also supported by in vivo investigations on follicular genesis in sheep [202], where an increased rate of follicles in antral stage were found after DHEA administration.

Premature ovarian insufficiency (POI)
Treatment with DHEA (30 mg/day for a period of 3 months) resulted in a significant decrease of thyroperoxidase antibodies (median 85.0 IU/ml, range 41–600 IU/ml vs median 51.0 IU/ml, Range 20–589 IU/ml) in POI patients (n = 67) with increased thyroid antibodies due to Hashimoto's thyroiditis. Thyroglobulin antibodies remained unchanged [203].

Mamas and Mamas [204] investigated the biochemical changes due to DHEA administration in five women aged 35–40 years with premature ovarian insufficiency. AMH, inhibin B and AFC were not measured. The mean FSH-level was 45 mU/ml in this group. A drop of FSH and an increase of estradiol was observed in many cases.

In this short summary, only few studies on DHEA and reproduction were identified. Therefore, the use of DHEA in patients wishing to become pregnant, especially in women who poorly respond to IVF stimulation, women with downscaled ovarian reserve (DOR), patients with premature ovarian ageing and insufficiency is not justified.

Although some authors observed favourable effects in their studies, available data on the efficacy of DHEA in ART do not justify its usage.

DHEA and Drug-Drug Interactions

Interaction is possible with several drugs.

Tamoxifene: DHEA should not be used in combination with tamoxifene since it triggers tamoxifene-resistance [205].

Oral Contraceptives: DHEA in combination with oral contraceptives does not influence the pharmacokinetic properties of EE and drospirenone. Therefore, it is unlikely that the contraceptive efficacy might be impaired [206].

Hormone replacement therapy: Concomitant intake of DHEA in patients undergoing HRT might result in increased rates of side effects of estrogen.

Patient information: The patient shall inform the treating physician about all food supplements, herbs, homeopathic drugs etc. she is taking [205].

Side Effects

As DHEA is a hormone precursor, there are sporadic reports on potential side effects of DHEA which might be caused by DHEA-metabolites [207, 208].

Very low doses of DHEA (10–50 mg/day)
Römmler [56] reported a very good tolerability in dose ranges of 10–25 mg/day in women and 25–50 mg/day in men; it is of importance to assure the purity of the drug.

Low doses of DHEA (50 mg/day)
51 patients (30 females, 21 males) with panhypopituitarism were observed in a double blind, placebo controlled long-term study. They received treatment with 50 mg DHEA/day concomitant to a GH-therapy for a period of twelve months. The results revealed that the rate and intensity of side effects were low in females. No were observed in men [209]. Another randomized, double blind placebo controlled study (DHEA n = 29; control n = 27; elderly females and males) over a period of ten months revealed no severe adverse events of DHEA treatment (50 mg/day) [144]. Other studies reported acne, cardiac arrhythmia, hepatic problems, alopecia and oily skin as side effects. An influenced blood glucose regulation was also reported [205].

Average doses of DHEA (100 mg/day)
There are no data available.

Higher doses of DHEA (200 mg/day)
Mild androgenetic adverse reactions were reported at a daily dose of 200 mg DHEA for a treatment period of 24 weeks [210].

High doses of DHEA (up to 400 mg/day)
Another study investigating DHEA in doses of up to 400 mg/day for a period of 8 weeks revealed only few adverse reactions [211].

However, aggressiveness, fractiousness, sleep disorders, hirsutism as well as increased growth of body and facial hair might occur in females due to treatment with high doses of oral DHEA [205].

- Mortality: [50, 109]
- Results of clinical studies on this topic are ambiguous with the majority of data indicating a reverse correlation between DHEA/DHEAS concentrations and cardiovascular mortality in men but not in women [111].
- Long-term side effects are unknown: DHEA is naturally formed in the human body; long-term side effects of exogenous administration are largely unknown [205, 207].

Health Concerns

Cardiovascular Diseases

Some studies indicate that DHEA substitution might increase the risk for cardiac diseases, diabetes and stroke [207] since, for example, DHEA lowers the HDL-cholesterol concentration [205].

Cancer

Endometrial Safety
Cutaneous application of DHEA (10% DHEA cream) for a period of twelve months in postmenopausal women showed an estrogenic effect on the vagina without effects on the atrophic endometrium [212]. No increase in thickness of the endometrium was observed in a study investigating oral DHEA at doses of 25 mg/day for a period of six months [213] and 50 mg/day for a period of twelve months [214]. No significant changes of the endometrium compared to placebo were observed in a randomized, double blind, placebo controlled study in post-menopausal women (n = 93) receiving 50 mg DHEA per day [89]. The frequencies of breakthrough bleedings were not different also.

Breast Cancer
Some workgroups assume that DHEA substitution increases the risk for developing breast cancer since this is a hormone sensitive type of tumor [207].

Cell lines: Some studies proofed that DHEA has anti-proliferative as well as pro-apoptotic effects on cancer cell lines [216–218]. The clinical relevance of these findings is unknown.

Insulin like growth factor: As shown in a pooled analysis, the insulin like growth factor (IGF-1) correlates positively with the risk for breast cancer in pre- and postmenopausal women [56, 218, 219], found an increase of IGF-1 under DHEA administration.

DHEA: Higher levels of DHEA and other sex steroids are remarkably correlated with an increased breast cancer risk in peri- and postmenopausal women [21, 220, 221].

Testosterone: The role of testosterone in the pathogenesis of breast cancer is controversial (http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/riskfactors/breast-cancer-risk-factors) [21, 222, 223].

DHEA: An older epidemiologic study revealed no consistent correlation between DHEA and the risk to develop breast cancer in the pre-menopause. In contrast to postmenopausal breast cancer, a preventive effect of DHEA on the development of breast cancer in premenopausal women is assumed. This hypothesis is deemed doubtful due to the limited sample sizes and should be verified in further studies [224].

Androgen metabolism in the breast: Women produce two third of the androgen levels that can be found in men, especially by converting DHEA to androgens in the peripheral tissues. The importance of androgens for several physiologic functions in women, including the breast is broadly underestimated [187]. The mammary gland has all enzymes required for the conversion of DHEA and DHEAS in androgens and estrogens, whereas androgens are f predominantly ormed in the breast [187]. Early clinical studies showed positive effects of androgens on breast cancer comparable to the observations of other hormone therapies. A higher number of preclinical and clinical data indicate that the proliferation of normal breast tissue and breast cancer tissue depend on the equilibrium between the stimulating effect of estrogen and the inhibitory effect of androgens [187].

A clinical observational study investigated the correlation between physiological DHEA levels and the development of breast cancer for a period of 15 years. There was no correlation observed [103].

Ovarian Cancer
A positive effect of high DHEA levels and the occurrence of ovarian carcinomas was described in a study by Helzlsouer et al [26]. However, the results could not be confirmed later on. The

study had severe methodological weaknesses.

Prostate Cancer

Some workgroups assume that DHEA treatment increases the risk to develop a prostate carcinoma [207]. Enlargement of the prostate gland might occur in men with benign prostate hyperplasia under DHEA treatment [205]. For further information, refer to specialized literature.

Precautionary Measures

The following recommendations are particularly valid in the USA:

DHEA should not be used in the following circumstances: pregnancy and lactation period, hormone-dependent diseases, hepatic problems, diabetes mellitus, depressions or mood disorders, PCOS syndrome or increased cholesterol levels [226]. Medical consultation is required before administration.

Legal Aspects

USA

DHEA is sold legally as food supplement in the USA. It is termed "old dietary ingredient" and was offered for sale before 1994 already. DHEA and DHEAS are open to the public and sold over the counter as food supplement [227]. The use of DHEA during competitions is prohibited. In particular, DHEA is excluded from the "Anabolic Steroid Control Act" from 1990 and 2004 [228].

Germany

- Available by prescription in pharmacies only
- Potentially free procurement from foreign online-pharmacies
- Administration in Germany, as so called "off-label use" by prescription is financially not covered by health insurances.

Sport and Athletics – Doping

DHEA is a prohibited substance according to the World Anti-Doping Code by the World Anti-Doping Agency, that is responsible for doping controls during Olympic Games and other competitions (refer to the summary by Collomp et al [229].

Clincal Studies

Refer to http://clinicaltrials.gov/ct2/results?term=DHEA&Search=Search; 154 studies were registered on April 14, 2014.

Most of the registered studies focus on:

- Response on ovarian stimulation in the context of assisted reproduction
- Treatment of premature ovarian insufficiency (POI)
- Women with adrenal gland insufficiency
- Vasomotor symptoms (hot flushes) in postmenopausal women
- Vaginal atrophy
- Reduced sexual desire (hypoactive sexual desire disorder)
- Women after breast cancer
- Anorexia nervosa
- Systemic Lupus erythematosus
- Wound healing
- Depression (major depressive disorder)
- Schizophrenic patients
- Polycystic ovarian syndrome (PCOS)
- Contraception and libido
- Epilepsy
- DHEA and SERM (acolbifene): Vasomotor symptoms (hot flushes)

There is a single study on the use of 7-keto-DHEA treatment to improve mental health in American veterans with post-traumatic stress disorders (PTSD).

Summary

- Several reviews deal with the clinical relevance of DHEA [13, 74, 90, 230–235]. DHEA is the most frequent circulating steroid hormone in humans. 90–95% of DHEA is formed in the reticular zone of the adrenal glands. To a lower extent it is also produced in the gonads and the brain where DHEA acts as neurosteroid.
- DHEAS levels in the blood are approximately 300-times higher in comparison to free DHEA levels. The DHEA peak levels are reached in the early morning hours whereas DHEAS is not subject to a circadian rhythm. Hence, DHEAS is well suitable for analysis in serum.
- DHEA is a universal precursor for the formation of androgen and estrogen in peripheral tissues that hold enzyme systems like 3β-HSDH for the formation of androstendione, 17β-hydroxysteroid dehydrogenase for the synthesis of testosterone and aromatase for estrogen-synthesis.
- DHEA/DHEAS levels reach their maximum between 20–30 years of age and are about 75% lower in elderly, aged 70 years or older.
- Mode of action:
  - DHEA acts predominantly as steroid precursor in the biosynthesis of androgenic and estrogenic sex steroids.
  - There have been no DHEA/DHEAS receptors identified yet.
  - DHEA and DHEAS bind and activate several receptors including ER-α and ER-β, peroxisome-proliferator activated receptors, PXR (pregnant-X-receptor), AUTO (constitutive androstane receptor) and beyond that membrane receptors as neuro-steroids like NMDA receptors (N-methyl-D-aspartate, glutamate) as positive allosteric modulator of the GABA-A receptor and negative allosteric modulator. For DHEA effects on the brain refer to Starka et al [13].
  - DHEA/DHEAS has a variety of dose independent effects like immune-modulation, effects on haemostasis, the lipid- and carbohydrate metabolism, bone health and mental health.

Pharmacology

Pharmacokinetic of DHEA

- Depending on gender
- Dose dependent 25 mg/day oral [47], 50 mg/day oral [48], 100 mg/day oral [42], 300 mg/day oral [49]. No further increase in DHEA or DHEAS concentrations, respectively.
- Dependent on the route of application (oral, transdermal, vaginal)
- Pharmacokinetic after oral intake [49, 53–55, 237] can be summarized as followed [50]:
  - Adsorption: The oral adsorption is excellent.
  - Distribution volume: The distribution volume is 17.0–38.5 l for DHEA and 8.5–9.3 l for DHEAS.
  - Metabolism: DHEA is converted in DHEAS by sulphation in the intestines and the liver after oral intake. DHEA and DHEAS can be converted into several biologically active metabolites, including androstenedione, testosterone, estrone, estradiol and estriol.
  - The elimination half-life of DHEA is 15–38 minutes; the half-life of DHEAS is 7–22 hours.
  - Excretion: 51–73% of DHEAS and its metabolites are renal secreted.

Risk Factors

- **Androgens:** Oral administration of DHEA can result in a dose dependent increase in circulating androgens whereby supra-physiological plasma levels of androgens were reached by supra-physiological doses of DHEA (> 50 mg/day, oral). The results differ between different studies.
- **Estrogens:** Oral administration of DHEA can result in a dose dependent increase of circulating estrogen.
- **Insulin-like growth factor:** Oral administration of DHEA leads to an increase in IGF levels in serum [42]. In investigations by Khorram et al [40] intake of 50 mg DHEA/day (oral) led to an increase of 20% of serum IGF-1 ($p < 0.01$) with concomitant decreasing propensity of IGFBP-1 and an increase of 32% of the ratio IGF-1/IGFBP-1 ($p < 0.01$).
- **Caution:** IGF-1 plays an important role in the pathogenesis of breast-, colon- and prostate cancer.

Medical Compounds

- **Oral:** There are several international vendors offering compounds with 10, 20, 50 and 100 mg (off-label in Germany on prescription). Physiological doses of DHEA when taken orally are between 20–50 mg for in healthy men > 40 years males and 10–30 mg for females [7, 51]. US pharmacists recommend 50–200 mg daily (cvs pharmacy; http://health.cvs.com/GetContent.aspx?token=f75979d3-9c7c-4b16-af56-3e122a3f19e3&chunkiid=21678#ref71), despite some studies investigated doses above and below these ranges.
- **Transdermal:** There is a 10% DHEA cream for transdermal administration available. 3–5 g cream per day are usually applied resulting in 300–500 mg DHEA applied to the skin
- **DHEA-control:** regular control examinations are required during DHEA treatment. The blood levels should be in the range of 20–30 nmol/l (5.6–8.6 ng/ml) (http://www.endmemo.com/medical/unitconvert/Dehydroepiandrosterone.php)
- **Intravaginal:** Refer to Cleveland Clinic (http://www.clevelandclinicwellness.com/Features/Pages/DHEA-Suppository.aspx) – 25 mg suppository for use at night.

Availability

In the United States DHEA and DHEAS are available as over the counter food supplement [227], in Germany DHEA and DHEAS in oral formulations can be obtained on prescription only.

Route of Administration

Oral

- Dosing: females initial: (10)–25 mg in the morning with dose reduction depending on clinical symptoms and DHEA levels in the blood.
- Side effects: DHEA might cause seborrhoea due to its residual androgenic effects.
- Dose adjustment is required for long-term treatments (e.g. 15–25 mg/day for females and 25–50 mg/day in males). For important studies, refer to Römmler [56].

Transdermal

- Refer to the SMPC of the individual medical compounds

Intravaginal

- Refer to the SMPC of the individual medical compounds

Adverse effects

- Most of the unwanted effects are mild and occur due to the androgenic effect of DHEA. Increased sebum production, increased facial hair and changes in pubic hair might occur in females. Changes of the voice have not been observed yet.

Clincal Advantages and Risks

See reviews by Nair et al [90], Raven and Hinson [231], Allolio et al [232], Traish et al [233], Goel and Cappola [74], Fouany and Sharara [234], Samaras et al [235] and Starka et al [13].

No health-advantage detectable

There is no evidence that DHEA treatment can be used to prevent cardiovascular diseases, cognitive disorders, depressions or for the improvement of well-being. Most workgroups did not find any positive effects of DHEA on general well-being and physical strength. Small sample sizes and short observational periods may play a role there.Until now, there is no evidence that DHEA has positive effects in patients wishing to become pregnant: premature ovarian insufficiency reduced ovarian reserve, poor response to stimulation in the context of ART.

Potential Health-Advantages

DHEA substitution might play a role in women with low DHEA levels.

Adrenal Insufficiency

Beside the substitution with gluco- and mineral corticosteroids, one might consider DHEAS substitution in single cases. Refer to the recommendations by the German Society of Endocrinology.

DHEA might be beneficial in postmenopausal women undergoing long-term glucocorticoid therapy.

DHEA has positive effects on bones, also in women with a lack of estrogen in fertile ages, as for example in patients with anorexia nervosa.

Vaginal Atrophy

Local intravaginal treatment with DHEA results in a rapid relief of symptoms of vaginal atrophy due to the local androgen and estrogen formation with only minimal or no changes in serum steroids. The concentrations are in the same range as in post-menopause. There are no concerns about systemic side effects, as observed in estrogen therapy. However, daily local administration is required. Alternative treatment options, such as low dose intravaginal estriol treatment or oral administration of novel SERMs (Ospemifen) should be taken into consideration, particularly since these drugs received approval in this indication.

Health Hazards

DHEA can be metabolized to testosterone as well as estrogen. There are increasing signs of a potential correlation between low DHEA levels and a cardiovascular risk as well as high DHEA levels and the risk to develop breast cancer.

Precautions

- Doping: DHEA is a prohibited substance according to the World Anti-Doping Code by the World Anti-Doping Agency, which conducts doping tests during the Olympic Games and other competitions.
- Drug-drug interactions: For example tamoxifene – concomitant DHEA administration might lead to tamoxifene-resistance.

- DHEA is commonly used as prescription-free food supplement or anti-ageing drug in the United States. This does not necessarily mean that the product is safe since there are no corresponding long-term studies.
- Patients must thoroughly be informed about potential risks and benefits of DHEA treatment.
- Males: DHEA should not be used by persons suffering from prostate- or testicular cancer.
- All patients: Patients who suffer from a severe disease or hormonal disorders should take DHEA only after having had competent medical advice and surveillance.

Future Perspectives

- Oral DHEA treatment might be indicated in distinct clinical indications as, in single cases, in patients with adrenal insufficiency, especially in women.
- Intravaginal application in cases of vaginal atrophy is an interesting therapeutic option in this disorder.
- Positive effects of DHEA treatment on well-being, disturbances of memory, psychosexual disorders and bone-health were observed in studies investigating DHEA in other indications.

Distinct forms of follicle maturation disorders in the context of fertility treatment must be verified in larger, carefully designed, placebo controlled, double blind, randomized clinical trials.

Drug safety must also be an objective in this context, as for all other steroid hormones.

The interest of the pharmaceutical industries in such studies is limited since there is only a low probability that a product can be patented.

- 7-keto-DHEA cannot be converted to testosterone or estrogen. This is especially of advantage in women (particularly in the post menopause) who do not want to experience testosterone related side effects like increased facial hair or acne as observed on higher doses of DHEA treatment. 7-keto-DHEA is two and a half times more potent (on milligram basis) than DHEA: a daily dose of 12.5 mg is equivalent to 25 mg DHEA. 7-keto-DHEA can be effective in low doses of 5–10 mg per day and can be applied under medical surveillance (Vireplex).

Research has shown a correlation between low DHEA levels and decreasing immunoreactions. Hence, effects of DHEA on diseases like Lupus erythematosus and HIV should be subject of clinical studies.

Conclusions on DHEA

Mayo Clinic (USA)

The Mayo Clinic in Rochester (USA) posted a recommendation on DHEA on their current website that relied on a review by Nair et al [90]: *"Neither DHEA nor low dose testosterone substitution therapy in elderly have physiological relevant positive effects on body composition, physical capability, insulin sensitivity or quality of life."*

Panjari and Davis [78]: *"In summary, we believe that the therapeutic application of DHEA cannot be recommended for the majority of postmenopausal women. […] Up to date, there are no convincing evidences from metabolism studies that oral DHEA treatment can be recommended in anti-ageing therapy"*.

Altogether, interpretation of data in the literature is tough due to insufficient sample sizes, short study durations and different study designs. The authors ask for more controlled and randomized studies also. Positive effects of intravaginal DHEA application in vaginal atrophy as potential indication is currently under discussion.

Further Remarks

Long-term side effects are not known. Even though the agent is freely available as food supplement in foreign countries (as for example the USA), this does not mean that it is safe from drug safety perspectives. Patients who decide to take DHEA supplements should consider the following dosing recommendations: 10–25 mg/day in females and up to 40 mg/day in males.

2011 State of California Decrees Strong Warning Labels on DHEA and Pregnenolone (extract) (http://www.leginfo.ca.gov/cgi-bin/displaycode?section=hsc&group=110001-111000&file=110423-110423.8): *"Not for use by individuals under the age of 18 years. Do not use if pregnant or nursing. Consult a physician or licensed qualified healthcare professional before using this product if you have, or have a family history of, breast cancer, prostate cancer, prostate enlargement, heart disease, low "good" cholesterol (HDL), or if you are using any other dietary supplement, prescription drug, or over the-counter drug. Do not exceed recommended serving. Exceeding recommended serving may cause serious adverse health effects. Possible side effects include acne, hair loss, hair growth on the face (in women), aggressiveness, irritability, and increased levels of estrogen. Discontinue use and call a physician or licensed qualified healthcare professional immediately if you experience rapid heartbeat, dizziness, blurred vision, or other similar symptoms. Keep out of reach of children. […] Do not use DHEA if you are at risk for or have been diagnosed as having any type of hormonal cancer, such as prostate or breast cancer."*

Internetlinks

Comment on this statement: https://www.lef.org/magazine/mag2011/jul2011_State-of-California-Decrees-Strong-Warning-Labels-on-DHEA-and-Pregnenolone_01.html

American Cancer Society: http://www.cancer.org/treatment/treatmentsandsideeffects/complementaryandalternativemedicine/pharmacologicalandbiologicaltreatment/dhea

Conflict of Interest

No conflict of interest: C. Albring, A. Bachmann, U. Blume-Peytavi, C. Egarter, B. Hinney, K. König, N. Sänger, T. Rabe, W. Rossmanith.

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References:

1. Mo Q, Lu SF, Simon NG. Dehydroepiandrosterone and its metabolites: differential effects on androgen receptor trafficking and transcriptional activity. J Steroid Biochem Mol Biol 2006; . 99: 50–8.

2. William F, Ganong MD. Review of Medical Physiology. 22nd ed, McGraw Hill, New York, 2005; 362.

3. Schulman RA, Dean, C. Solve It With Supplements. Rondale Inc., New York, 2007; 100.

4. Thomas S. Concise Encyclopedia Biology. Walter de Gruyter, Berlin, 1996; 49.

5. Granner DK. The Diversity of the Endocrine System. In: Murray et al. Harper's Illustrated Biochemistry. 26th ed., Lange Medical Books/McGraw-Hill/New York, 2003, 434–55.

6. Kroboth PD, Salek FS, Pittenger AL, et al. DHEA and DHEAS: a review. J Clin Pharmacol 1999; 39: 327–48.

7. Beaulieu EE. Dehydroepiandrosterone (DHEA): fountain of youth? J Clin Endocrinol Metab 1996; 81: 3147–51.

8. Bird CH, Masters V, Clark AF. Dehydroepiandrosterone sulfate: kinetics of metabolism in normal young men and women. Clin Invest Med 1984; 7: 119–22.

9. Poortman J, Andriesse R, Agema A, et al. Adrenal androgen secretion and metabolism in post-menopausal women. In: Genazzani AR, Thijssen JH, Siiteri PK (eds). Adrenal androgens. Raven, New York, 1980; 219–40.

10. Labrie F, Luu-The V, Bélanger A, Lin SX, Simard J, et al. Is dehydroepiandrosterone a hormone? J Endocrinol 2005; 187: 169–96.

11. Robel P, Baulieu EE. Dehydroepiandrosterone (DHEA) is a neuroactive neurosteroid. Ann N Y Acad Sci 1995; 774: 82–110.

12. Lacroix C, Fiet J, Benais JP, et al. Simultaneous radioimmunoassay of progesterone, androst-4-enedione, pregnenolone, dehydroepiandrosterone and 17-hydroxy-progesterone in specific regions of the human brain. J Steroid Biochem 1987; 28: 317–25.

13. Stárka L, Dušková M, Hill M. Dehydroepiandrosterone: a neuroactive steroid. J Steroid Biochem Mol Biol 2015; 145: 254–60.

14. Orentreich N, Brind JL, Vogelman JH, et al. Longterm longitudinal measurements of plasma dehydroepiandrosterone sulfate in normal men. J Clin Endocrinol Metab 1992; 75: 1002–4.

15. Migeon CJ, Keller AR, Lawrence B, et al. Dehydroepiandrosterone and androsterone levels in human plasma. Effect of age and sex, day-to-day and diurnal vari-ations. J Clin Endocrinol Metab 1957; 17: 1051–62.

16. Labrie F, Belanger A, Cusan L, et al. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. J Clin Endocrinol Metab 1997; 82: 2396–402.

17. Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. J Clin Endocrinol Metab 2005; 90: 3847–53.

18. Auchus RJ. Overview of dehydroepiandrosterone biosynthesis. Semin Reprod Med 2004; 22: 281–8.

19. Payne AH, Hales DB. Overview of steroidogenic enzymes in the pathway from cholesterol to active steroid hormones. Endocrine Rev 2004; 25: 947–70.

20. Labrie F. Intracrinology. Mol Cell Endocrinol 1991; 78: C113–C118.

21. Endogenous Hormones and Breast Cancer Collaborative Group. Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies. Br J Cancer 2011; 105: 709–22.

22. Lasley BL, Crawford SL, Laughlin GA, Santoro N, McConnell DS, et al. Circulating dehydroepiandrosterone sulfate levels in women who underwent bilateral salpingo-oophorectomy during the menopausal transition. Menopause 2011; 18: 494–8.

23. Labrie F. Extragonadal synthesis of sex steroids: intracrinology. Ann Endocrinol (Paris) 2003; 64: 95–107.

24. Banaszewska B, Spaczyñski RZ, Pelesz M, Pawelczyk L. Incidence of elevated LH/FSH ratioin polycystic ovary syndrome women with normo- and hy-perinsulinemia. Rocz Akad Med Bialymst 2003; 48: 131–4.

25. Filaire E, Duché P, Lac G. Effects of amount of training on the saliva concentrations of cortisol, dehydroepiandrosterone and on the dehydroepiandros-terone: Cortisol concentration ratio in women over 16 weeks of training. Eur J Appl Physiol Occup Physiol 1998; 78: 466–71.

26. Copeland JL, Consitt LA, Tremblay MS. Hormonal responses to endurance and resistance exercise in females aged 19–69 years. J Gerontol A Biol Sci Med Sci 2002; 57: B158–B165.

27. Mattison JA, Lane MA, Roth G, Ingram DK. Calorie restriction in rhesus monkeys. Experimental Gerontology 2003; 38: 35–46.

28. Roberts E. The importance of dehydroepiandrosterone sulfate in the blood of primates: a longer and healthier life? Biochem Pharmacol 1999; 57: 329–46.

29. Liu D, Dillon JS. Dehydroepiandrosterone activates endothelial cell nitric-oxide synthase by a specific plasma membrane receptor coupled to Galpha (i2,3). J Biol Chem 2002; 277: 21379–88.

30. Liu D, Dillon JS. Dehydroepiandrosterone stimulates nitric oxide release in vascular endothelial cells: evidence for a cell surface receptor. Steroids 2004; 69: 279–89.

31. Chen F, Knecht K, Birzin E, et al. Direct agonist/antagonist functions of dehydroepiandrosterone. Endocrinology 2005; 146: 4568–76.

32. Gao W, Bohl CE, Dalton JT. Chemistry and structural biology of androgen receptor. Chem Rev 2005; 105: 3352–70.

33. Webb SJ, Geoghegan TE, Prough RA, Miller KK. The biological actions of dehydroepiandrosterone involves multiple receptors. Drug Metab Rev 2006; 38: 89–116.

34. Lindschau C, Kirsch T, Klinge U, Kolkhof P, Peters I, Fiebeler A. Dehydroepiandrosterone-induced phosphorylation and translocation of Fo-xO1 depend on the mineralocorticoid receptor. Hypertension 2011; 58: 471–8.

35. Sousa A, Ticku MK. Interactions of the neurosteroid dehydroepiandrosterone sulfate with the GABA(A) receptor complex reveals that it may act via the picroto-xin site. J Pharmacol Exp Ther 1997; 282: 827.

36. Takebayashi M, Hayashi T, Su TP. A perspective on the new mechanism of antidepressants: neuritogenesis through sigma-1 receptors. Pharmacopsychiatry 2004; 37 (Suppl 3): S208.

37. Kalimi M, Shafagoj Y, Loria R, Padgett D, Regelson W. Anti-glucocorticoid effects of dehydroepiandrosterone (DHEA). Mol Cell Biochem 1994; 131: 99–104.

38. Loria RM, Padgett DA, Huynh PN. Regulation of the immune response by dehydroepiandrosterone and its metabolites. J Endocrinol 1996; 150: 209–20.

39. Suzuki T, Suzuki N, Daynes RA, Engleman EG. Dehydroepiandrosterone enhances IL-2 production and cytotoxic effector function of human T cells. Clin Immunol Immunopathol 1991; 61: 202–11.

40. Khorram O, Vu L, Yen SS. Activation of immune function by dehydroepiandrosterone (DHEA) in age-advanced men. J Gerontol A Biol Sci Med Sci 1997; 52: M1–M7.

41. Straub RH, Konecna L, Hrach S, et al. Serum dehydroepiandrosterone (DHEA) and DHEA sulfate are negatively correlated with serum interleukin-6 (IL-6), and DHEA inhibits IL-6 secretion from mononuclear cells in man in vitro: possible link between endocrinosenescence and immunosenescence. J Clin Endocrinol Metab 1998; 83: 2012–7.

42. Morales A, Haubrich RH, Hwang JY, et al. The effect of six month treatment with a 100 mg dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. J Clin Endocrinol 1998; 49: 421–32.

43. Arlt W, Haas J, Callies F, et al. Biotransformation of oral dehydroepiandrosterone in elderly men: significant increase in circulating estrogens. J Clin Endocrinol Metab 1999; 84: 2170–6.

44. Yen SCC, Morales AJ, Khorram O. Replacement of DHEA in aging men and women: potential remedial effects. In: Bellino FL, Daynes RA, Hornsby PJ, Lavrin DH, Nestler JE (eds). Dehydroepiandrosterone (DHEA) and aging. New York Academy of Science, New York, 1995; 128–42.

45. Morales A, Nolan JJ, Nelson JC, et al. Effects of replacement dose of dehydroepiandrosterone in men and women of advanced age. J Clin Endocrinol Metab 1994; 78: 1360–7.

46. Wolf AS. Altern und Hormone. Der Gynäkologe 2002; 35: 381–400.

47. Stanczyk FZ, Slater CC, Ramos DE, Azen C, Cherala G, et al. Pharmacokinetics of dehydroepiandrosterone and its metabolites after long-term oral dehydroepiandrosterone treatment in postmenopausal women. Menopause 2009; 16: 272–8.

48. Legrain S, Massien C, Lahlou N, Roger M, Debuire B, et al. Dehydroepiandrosterone replacement administration: pharmacokinetic and pharmacodynamic studies in healthy elderly subjects. J Clin Endocrinol Metab 2000; 85: 3208–17.

49. Tummala S, Svec F. Correlation between the administered dose of DHEA and serum levels of DHEA and DHEAS in human volunteers: analysis of published data. Clin Biochem 1999; 32: 355–61.

50. Peppin J. DHEA: dehydroepiandrosterone. Am J Health Syst Pharm 2000; 57: 2048–50.

51. DHEA monograph. AltMedDex vol. 104. Englewood, CO. MicroMedex; 2000.

52. Longcope C. Dehydroepiandrosterone metabolism. J Endocrinol 1996; 150 (Suppl): S125–S127.

53. Bird CE, Murphy J, Boroomand K, et al. Dehydroepiandrosterone: kinetics of metabolism in normal men and women. J Clin Endocrinol Metab 1976; 47: 818–22.

54. Zumoff BV, Bradlow HL. Sex difference in the metabolism of dehydroepiandrosterone sulfate. J Clin Endocrinol Metab 1980; 51: 334–6.

55. Buster JE, Casson PR, Straughn AB, et al. Postmenopausal steroid replacement with micronized dehydroepiandrosterone: preliminary oral bioavailability and dose proportionality studies. Am J Obstet Gynecol 1992; 166: 1168–70.

56. Römmler A. Die Adrenopause: Individuelle Substitution mit DHEA (Dehydroepiandrosteron). Lifestyle- & Anti-Aging-Medizin, Interdisziplinäre Zeitschrift 2002; 1: 15–25.

57. Nouveau S, Bastien P, Baldo F, de Lacharriere O. Effects of topical DHEA on aging skin: a pilot study. Maturitas 2008; 59: 174–81.

58. Calvo E, Luu-The V, Morissette J, Martel C, Labrie C, et al. Pangenomic changes induced by DHEA in the skin of postmenopausal women. J Steroid Biochem Mol Biol 2008; 112: 186–93.

59. Diamond P, Cusan L, Gomez JL, Bélanger A, Labrie F. Metabolic effects of 12-month percutaneous dehydroepiandrosterone replacement therapy in postme-nopausal women. J Endocrinol 1996; 150 (Suppl): S43–S50.

60. Labrie F, Bélanger A, Labrie C, Candas B, Cusan L, Gomez JL. Bioavailability and metabolism of oral and percutaneous dehydroepiandrosterone in postmeno-pausal women. J Steroid Biochem Mol Biol 2007; 107: 57–69.

61. Panjari M, Davis SR. Vaginal DHEA to treat menopause related atrophy: a review of the evidence. Maturitas 2011; 70: 22–5.

62. Labrie F, Archer D, Bouchard C, Fortier M, Cusan L, et al. Intravaginal dehydroepiandrosterone (Prasterone), a physiological and highly efficient treatment of vaginal atrophy. Menopause 2009; 16: 907–22.

63. Labrie F, Archer D, Bouchard C, Fortier M, Cusan L, et al. Serum steroid levels during 12-week intravaginal dehydroepiandrosterone administration. Menopause 2009; 16: 897–906.

64. Berger L, El-Alfy M, Labrie F. Effects of intravaginal dehydroepiandrosterone on vaginal histomorphology, sex steroid receptor expression and cell proliferation in the rat. J Steroid Biochem Mol Biol 2008; 109: 67–80.

65. Arlt W, Callies F, Van Vlijmen JC, Koehler I, Reincke M, et al. Dehydroepiandrosterone re-placement in women with adrenal insufficiency. N Eng J Med 1999; 341: 1013–20.

66. Hunt P, Gurnell E, Huppert F. Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial. J Clin Endocrinol Metab 2000; 85: 4650–6.

67. Johannsson G, Burman P, Wiren L, Engstrom BE, Nilsson AG, et al. Low dose dehydroepiandrosterone affects behavior in hypopituitary androgen-deficient women: a placebo-controlled trial. J Clin Endocrinol Metab 2002; 87: 2046–52.

68. Lovas K, Gebre-Medhin G, Trovik T, Fougner K, Uhlving S, 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: 1112–8.

69. Binder G, Weber S, Ehrismann M, Zaiser N, Meisner C, et al. Effects of dehydroepiandrosterone therapy on pubic hair growth and psychological well-being in adolescent girls and young women with central adrenal insufficiency: a double-blind, randomized, placebo controlled phase III trial. J Clin Endocrinol Metab 2009; 94: 1182–90.

70. Srinivasan M, Irving BA, Dhatariya K, Klaus KA, Hartman SJ, et al. Effect of dehydroepiandrosterone replacement on lipoprotein profile in hypoadrenal women. J Clin Endocrinol Metab 2009; 94: 761–4.

71. Alkatib AA, Cosma M, Elamin MB, et al. A systematic review and meta- analysis of randomized placebo-controlled trials of DHEA treatment effects on quality of life in women with adrenal insufficiency. J Clin Endocrinol Metab 2009; 94: 3676–81.

72. Barton DL, Loprinzi C, Atherton PJ, Kottschade L, Collins M, et al. Dehydroepiandrosterone for the treatment of hot flashes: a pilot study. Support Cancer Ther 2006; 3: 91–7.

73. Davis SR, Panjari M, Stanczyk FZ. Clinical review: DHEA replacement for postmenopausal women. J Clin Endocrinol Metab 2011; 96: 1642–53.

74. Goel RM, Cappola AR. Dehydroepiandrosterone sulfate and postmenopausal women. Curr Opin Endocrinol Diabetes Obes 2011; 18: 171–6.

75. Pluchino N, Ninni F, Stomati M, et al. One-year therapy with 10 mg/day DHEA alone or in combination with HRT in post-

menopausal women, effects on hor- monal milieu. Maturitas 2008; 59: 293–303.

76. Davis SR. Androgen replacement in women: a commentary. J Clin Endocrinol Metab 1999; 84:1886–91.

77. Oldenhave A, Jaszmann LJ, Haspels AA, Everaerd WT. Impact of climacteric on well-being. A survey based on 5213 women 39 to 60 years old. Am J Obstet Gynecol 1993; 168: 772–80.

78. Panjari M, Davis SR. DHEA for postmenopausal women: a review of the evidence. Maturitas 2010; 66: 172–9.

79. Goldstat R, Briganti E, Tran J, Wolfe R, Davis S. Transdermal testosterone improves mood, well being and sexual function in premenopausal women. Menopause 2003; 10: 390–8.

80. Shifren JL, Braunstein G, Simon J, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N Eng J Med 2000; 343: 682.

81. Davis SR, Moreau M, Kroll R, et al. Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med 2008; 359: 2005–17.

82. Braunstein GD, Sundwall DA, Katz M, et al. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. Arch Intern Med 2005; 165: 1582–9.

83. Wolf OT, Neumann O, Hellhammer DH, Geiben AC, Strasburger CJ, 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: 2363–7.

84. Barnhart KT, Freeman E, Grisso JA, Rader DJ, Sammel M, et al. The effect of dehydroepiandrosterone supplementation to sympto-matic perimenopausal women on serum endocrine profiles, lipid parameters, and healthrelated quality of life. J Clin Endocrinol Metab 1999; 84: 3896–902.

85. Bloch M, Schmidt PJ, Danaceau MA, Adams LF, Rubinow DR. Dehydroepiandrosterone treatment of midlife dysthymia. Biol Psychiatry 1999; 45: 1533–41.

86. Wolkowitz OM, Reus VI, Keebler A, Nelson N, Friedland M, et al. Double-blind treatment of major depression with dehydroepiandrosterone. Am J Psychiatry 1999; 156: 646–9.

87. Schmidt PJ, Daly RC, Bloch M, Smith MJ, Danaceau MA, et al. Dehydroepiandrosterone monotherapy in midlife-onset major and minor depression. Arch Gen Psychiatry 2005; 62: 154–62.

88. Donna KS. Effects of dehydroepiandrosterone supplementation on cognitive function and quality of life: the DHEA and well-ness (DAWN) trial. J Am Geriat Soc 2008; 56: 1292–8.

89. Panjari M, Bell RJ, Jane F, et al. A randomized trial of oral DHEA treatment for sexual function, wellbeing, and menopausal symptoms in postmenopausal women with low libido. J Sex Med 2009; 6: 2579–90.

90. Nair KS, Rizza RA, O'Brien P, et al. DHEA in elderly women and DHEA or testosterone in elderly men. N Engl J Med 2006; 355: 1647–59.

91. Dayal M, Sammel MD, Zhao J, Hummel AC, Vandenbourne K, Barnhart KT. Supplementation with DHEA: effect on muscle size, strength, quality of life, and lipids. J Womens Health (Larchmt) 2005; 14: 391–400.

92. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi MH. Forecasting the global burden of Alzheimer's disease. Alzheimer's and Dementia. 2007; http://works.bepress.com/cgi/viewcontent.cgi?article=1022&context=rbrookmeyer.

93. Grimley Evans J, Malouf R, Huppert FAH, Van Niekerk JK. Dehydroepiandrosterone (DHEA) supplementation for cognitive function in healthy elderly people. Cochrane Database Syst Rev 2006; 4: CD006221.

94. 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.

95. von Mühlen D, Laughlin GA, Kritz-Silverstein D, Barrett-Connor E. The Dehydroepiandrosterone And WellNess (DAWN) study: research design and methods. Contemp Clin Trials 2007; 28: 153–68.

96. Yamada S, Akishita M, Fukai S, Ogawa S, Yamaguchi K, Matsuyama J, et al. Effects of dehydroepiandrosterone supplementation on cognitive function and activities of daily living in older women with mild to moderate cognitive impairment. Geriatr Gerontol Int 2010; 10: 280–7.

97. Kritz-Silverstein D, von Mühlen D, Laughlin GA, Bettencourt R. Effects of dehydroepiandrosterone supplementation on cognitive function and quality of life: the DHEA and Well-Ness (DAWN) Trial. J Am Geriatr Soc 2008; 56: 1292–8.

98. Fuller SJ, Tan RS, Martins RN. Androgens in the etiology of Alzheimer's disease in aging men and possible therapeutic interventions. JAD 2007; 12: 129–42.

99. Kurita H, Maeshima H, Kida S, Matsuzaka H, Shimano T, et al. Serum dehydroepiandrosterone (DHEA) and DHEA-sulfate (S) levels in medicated patients with major depressive disorder compared with controls. J Affect Disord 2013; 146: 205–12.

100. Morrison MF, Freeman EW, Lin H, Sammel MD. Higher DHEA-S (dehydroepiandrosterone sulfate) levels are associated with depressive symptoms during the menopausal transition: results from the PENN Ovarian Aging Study. Arch Womens Ment Health 2011; 14: 375–82.

101. Tawar S, Bhatia SS, Ilankumaran M. Mental health, are we at risk? Indian J Community Med 2014; 39: 43–6.

102. Robert-Koch-Institut. Depressive Erkrankungen. Gesundheitsberichterstattung des Bundes, Heft 51, Berlin, 2010.

103. Barrett-Connor E, Khaw KT, Yen SS. A prospective study of dehydroepiandrosterone sulfate, mortality, and cardiovascular disease. N Engl J Med 1986; 315: 1519–24.

104. Thijs L, Fagard R, Forette F, Nawrot T, Staessen JA. Are low dehydroepiandrosterone sulphate levels predictive for cardiovascular diseases? A review of prospective and retrospective studies. Acta Cardiol 2003; 58: 403–10.

105. Arnlöv J, Pencina, MJ, Amin S, et al. Endogenous sex hormones and cardiovascular disease incidence in men. Ann Intern Med 2006; 145: 176–84.

106. Boggs W. DHEA Restores Oxidative Balance in Type 2 Diabetes. Medscape. http://www.medscape.com/viewarticle/567316. Retrieved on 2007-12-14.

107. Page JH, Ma J, Rexrode KM, Rifai N, Manson JE, Hankinson SE. Plasma dehydroepiandrosterone and risk of myocardial infarction in women. Clin Chem 2008; 54: 1190–6.

108. Weiss EP, Villareal DT, Ehsani AA, Fontana L, Holloszy JO. Dehydroepiandrosterone replacement therapy in older adults improves indices of arterial stiffness. Aging Cell 2012; 11: 876–84.

109. Alexandersen P, Haarbo J, Christiansen C. The relationship of natural androgens to coronary heart disease in males: a review. Atherosclerosis 1996; 125: 1–13.

110. Kiechl S, Willeit J, Bonora E, et al. No association between dehydroepiandrosterone sulfate and development of atherosclerosis in a prospective population study (Bruneck study). Arterioscler Thromb Vasc Biol 2000; 20: 1094–100.

111. Ohlsson C, Vandenput L, Tivesten A. DHEA and mortality: What is the nature of the association? J Steroid Biochem Mol Biol 2015; 145: 248–53.

112. Ray KK. Lipids and cardiovascular disease: re-thinking targets. Br J Cardiol 2012;19 (Suppl 1): s1–s16.

113. Wu FCW, von Eckardstein A. Androgens and coronary artery disease. Endocr Rev 2003; 24: 183–217.

114. Williams JR. The effects of dehydroepiandrosterone on carcinogenesis, obesity, the immune system, and aging. Lipids 2000; 35: 325–31.

115. Cheng HH, Hu XJ, Ruan QR. Dehydroepiandrosterone antiatherogenesis effect is not via its conversion to estrogen. Acta Pharmacol Sin 2009; 30: 42–53.

116. Barrett-Connor E, Khaw KT, Yen SS. A prospective study of dehy- droepiandrosterone sulfate, mortality, and cardiovascular disease. N Eng J Med 1986; 315: 1519–24.

117. Barrett-Connor E, Goodman-Gruen D. Dehydroepiandrosterone sulfate does not predict cardiovascular death in postmenopausal women. The Rancho Bernardo Study. Circulation 1995; 91: 1757.

118. Mortola JF, Yen SS. The effects of oral dehydroepiandrosterone on endocrine - metabolic parameters in postmenopausal women. J Clin Endocrinol Metab 1990; 71: 696–704.

119. Casson PR, Santoro N, Elkind-Hirsch K, et al. Postmenopausal dehydroepiandrosterone administration increases free insulin-like growth factor-I and decreases high-density lipoprotein: a six-month trial. Fertil Steril 1998; 70: 107.

120. Dhatariya K, Bigelow ML, Nair KS. Effect of dehydroepiandrosterone replacement on insulin sensitivity and lipids in hypoadrenal women. Diabetes 2005; 54: 765–9.

121. Allolio B, Callies F, Arlt W. Dehydroepiandrosterone substitution in women. J Endocrinol Invest 1999; 22: 29–31.

122. Villareal D, Holloszy J, Kohrt W. Effects of DHEA replacement on bone mineral density and body composition in elderly women and men. Clin Endocrinol 2000; 53: 561–8.

123. Igwebuike A, Irving BA, Bigelow ML, Short KR, McConnell JP, Nair KS. Lack of dehydroepiandrosterone effect on a combined endurance and resistance exercise program in postmenopausal women. J Clin Endocrinol Metab 2008; 93: 534–8.

124. van Thiel SW, Romijn JA, Pereira AM, et al. Effects of dehydroepiandrostene- dione, superimposed on growth hormone substitution, on quality of life and insulin-like growth factor I in patients with secondary adrenal insufficiency: a randomized, placebo-controlled, cross-over trial. J Clin Endocrinol Metab 2005; 90: 3295–303.

125. Gómez-Santos C, Larqué E, Granero E, Hernández-Morante JJ, Garaulet M. Dehydroepiandrosterone-sulphate replacement improves the human plasma fatty acid profile in plasma of obese women. Steroids 2011; 76: 1425–32.

126. Bednarek-Tupikowska G, Tworowska-Bardzińska U, Tupikowski K, Bohdanowicz-Pawlak A, Szymczak J, Kubicka E, Skoczyñska A, Milewicz A. The correlations between endogenous dehydroepiandrosterone sulfate and some atherosclerosis risk factors in premenopausal women. Med Sci Monit 2008; 14: CR37–41.

127. Weiss EP, Villareal DT, Fontana L, Han DH, Holloszy JO. Dehydroepiandrosterone (DHEA) replacement decreases insulin resistance and lowers inflammatory cytokines in aging humans. Aging 2011; 3: 533–42.

128. Gómez-Santos C1, Hernández-Morante JJ, Tébar FJ, Granero E, Garaulet M. Differential effect of oral dehydroepiandrosterone-sulphate on metabolic syndrome features in pre- and postmenopausal obese women. Clin Endocrinol (Oxf) 2012; 77: 548–54.

129. Livingstone C, Collison M. Sex steroids and insulin resistance. Clin Sci (Lond) 2002; 102: 151–66.

130. Wellman M, Shane-McWhorter L, Orlando, Jennings JP. The role of dehy- droepiandrosterone in diabetes mellitus. Pharmacotherapy 1999; 19: 582–91.

131. Lasco A, Frisina N, Morabito N, et al. Metabolic effects of dehydroepiandrosterone replacement therapy in postmenopausal women. Eur J Endocrinol 2001; 145: 457–61.

132. 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.

133. Callies F, Fassnacht M, van Vlijmen JC, 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.

134. DeLoughery TG. Coagulation abnormalities and cardiovascular disease. Curr Opin Lipidol 1999; 10: 443–8.

135. Jakubowicz D, Beer N, Rengifo R. Effect of dehydroepiandrosterone on cyclic guanosine monophosphate in men of advancing age. Ann N Y Acad Sci 1995; 774: 312–5.

136. Jesse RL, Loesser K, Eich DM, et al. Dehydroepiandrosterone inhibits human platelet aggregation in vitro and in vivo. Ann N Y Acad Sci 1995; 774: 281–90.

137. Beer N, Jakubowicz D, Matt DW, et al. Dehydroepiandrosterone reduces plasma plasminogen activator inhibitor type 1 and tissue plasminogen activator antigen in men. Am J Med Sci 1996; 311: 205–10.

138. Casson PR, Andersen RN, Herrod HG, et al. Oral dehydroepiandrosterone in physiological doses modulates immune function in postmenopausal women. Am J Obstet Gynecol 1993; 169: 1536–9.

139. Van Vollenhoven RF, Engleman EG, McGuire JL. Dehydroepiandrosterone in systemic lupus erythematosus. Arthritis Rheum 1995; 38: 1826–31.

140. Van Vollenhoven RF. Dehydroepiandrosterone in systemic lupus erythematosus. Rheum Dis Clin North Am 2000; 26: 349–62.

141. Overman CL, Hartkamp A, Bossema ER, Bijl M, Godaert GL, et al. Fatigue in patients with systemic lupus erythematosus: the role of dehydroepiandrosterone sulphate. Lupus 2012; 21: 1515–21.

142. Marder W, Somers EC, Kaplan MJ, Anderson MR, Lewis EE, McCune WJ. Effects of prasterone (dehydroepiandrosterone) on markers of cardiovascular risk and bone turnover in premenopausal women with systemic lupus erythematosus: a pilot study. Lupus 2010; 19: 1229–36.

143. Crosbie D, Black C, McIntyre L, Royle PL, Thomas S. Dehydroepiandrosterone for systemic lupus erythematosus. Cochrane Database Syst Rev 2007; 4: CD005114.

144. Villareal DT, Holloszy JO. DHEA enhances effects of weight training on muscle mass and strength in elderly women and men. Am J Physiol Endocrinol Metab 2006; 291: E1003–8.

145. Kenny AM, Boxer RS, Kleppinger A, Brindisi J, Feinn R, Burleson JA. Dehydroepiandrosterone combined with exercise improves muscle strength and physical function in frail older women. J Am Geriatr Soc 2010; 58: 1707–14.

146. Baker WL, Karan S, Kenny AM. Effect of dehydroepiandrosterone on muscle strength and physical function in older adults: a systematic review. J Am Geriatr Soc 2011; 59: 997–1002.

147. Wallace MB, Lim J, Cutler A, Bucci L. Effects of dehydroepiandrosterone vs androstenedione supplementation in men. Med Sci Sports Exerc 1999; 31: 1788–92.

148. Muller M, van den Beld AW, van der Schouw YT, Grobbee DE, Lamberts SW. Effects of dehydroepiandrosterone and atamestane supplementation on frailty in elderly men. J Clin Endocrinol Metab 2006; 91: 3988–91.

149. Liu TC, Lin CH, Huang CY, Ivy JL, Kuo CH. Effect of acute DHEA administration on free testosterone in middle-aged and young men following high-intensity interval training. Eur J Appl Physiol 2013; 113: 1783–92.

150. Brainum J. DHEA Fountain of Youth or Washout. Iron Man Magazine 2009. http://www.ironmanmagazine.com/dhea-fountain-of-youth-or-washout.

151. Hahner S, Allolio B. Dehydroepiandrosterone to enhance physical performance: myth and reality. Endocrinol Metab Clin North Am 2010; 39: 127–39.

152. Jankowski CM, Gozansky WS, Schwartz RS, Dahl DJ, Kittelson JM, et al. Effects of dehydroepiandrosterone replacement therapy on bone mineral density in older adults: a randomized, controlled trial. J Clin Endocrinol Metab 2006; 91: 2986–93.

153. Ghebre MA, Hart DJ, Hakim AJ, Kato BS, Thompson V, et al. Association between DHEAS and bone loss in postmenopausal women: a 15-year longitudinal population-based study. Calcif Tissue Int 2011; 89: 295–302.

154. Papierska L, Rabijewski M, Kasperlik-Zauska A, Zgliczynski W. Effect of DHEA supplementation on serum IGF-1, osteocalcin, and bone mineral density in postmenopausal, glucocorticoid-treated women. Adv Med Sci 2012; 57: 51–7.

155. Bloch M, Ish-Shalom S, Greenman Y, Klein E, Latzer Y. Dehydroepiandrosterone treatment effects on weight, bone density, bone metabolism and mood in women suffering from anorexia nervosa-a pilot study. Psychiatry Res 2012; 200: 544– 9.

156. DiVasta AD, Feldman HA, Beck TJ, LeBoff MS, Gordon CM. Does hormone replacement normalize bone geometry in adolescents with anorexia nervosa? J Bone Miner Res 2014; 29: 151–7.

157. Nijland E, Davis S, Laan E, Schultz WW. Female sexual satisfaction and pharmaceutical intervention: a critical review of the drug intervention studies in female sexual dysfunction. J Sex Med 2006; 3: 763–77.

158. Shifren JL, Monz BU, Russo PA, et al. Sexual problems and distress in United States women: prevalence and correlates. Obstet Gynecol 2008; 112: 970.

159. Dennerstein L, Guthrie JR, Hayes RD, DeRogatis LR, Lehert P. Sexual function, dysfunction, and sexual distress in a prospective, population-based sample of mid-aged, Australian-born women. J Sex Med 2008; 5: 2291–9.

160. Leiblum S, Koochaki P, Rodenberg C, Barton I, Rosen R. Hypoactive sexual desire disorder in postmenopausal women: US results from the women's international study of health and sexuality (WISHeS). Menopause 2006; 13: 46–56.

161. Biddle AK1, West SL, D'Aloisio AA, Wheeler SB, Borisov NN, Thorp J. Hypoactive sexual desire disorder in postmenopausal women: quality of life and health burden. Value Health 2009; 12: 763–72.

162. Dennerstein L, Koochaki P, Barton I, Graziottin A. Hypoactive sexual desire disorder in menopausal women: a survey of Western European women. J Sex Med 2006; 3: 212–22.

163. Hayes RD, Dennerstein L, Bennett CM, Sidat M, Gurrin LC, Fairley CK. Risk factors for female sexual dysfunction in the general population: exploring factors associated with low sexual function and sexual distress. J Sex Med 2008; 5: 1681–93.

164. Dennerstein L, Randolph J, Taffe J, Dudley E, Burger H. Hormones, mood, sexuality, and the menopausal transition. Fertil Steril 2002;77(Suppl. 4): S42–S48.

165. Fernandes T, Costa-Paiva LH, Pinto-Neto AM. Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on sexual function in postmenopausal women: a randomized controlled trial. J Sex Med 2014; 11: 1262–70.

166. Avis NE, Brockwell S, Randolph Jr JF, et al. Longitudinal changes in sexual functioning as women transition through menopause: results from the Study of Women's Health Across the Nation. Menopause 2009; 16: 442–52.

167. Mushayandebvu T, Castracane DV, Gimpel T, Adel T, Santoro N. Evidence for diminished midcycle ovarian androgen production in older reproductive aged women. Fertil Steril 1996; 65: 721.

168. Lasley BL, Crawford SL, Laughlin GA, Santoro N, McConnell DS, Crandall C, Greendale GA, Polotsky AJ, Vuga M. Circulating dehydroepiandrosterone sulfate levels in women who underwent bilateral salpingo-oophorectomy during the menopausal transition. Menopause 2011; 18: 494–8.

169. Friess E, Schiffelholz T, Steckler T, Steiger A. Dehydroepiandrosterone – a neurosteroid. Eur J Clin Invest 2000; 30 (Suppl 3): 46–50.

170. Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. J Clin Endocrinol Metab 2005; 90: 3847–53.

171. Zumoff B, Strain GW, Miller LK, Rosner W. Twentyfour-hour mean plasma testosterone concentration declines with age in normal premenopausal women. J Clin Endocrinol Metab 1995; 80: 1429–30.

172. Hayes RD, Dennerstein L, Bennett CM, Koochaki PE, Leiblum SR, Graziottin A. Relationship between hypoactive sexual desire disorder and aging. Fertil Steril 2007; 87: 107–12.

173. Davis SR, Davison SL, Donath S, Bell RJ. Circulating androgen levels and self-reported sexual function in women. JAMA 2005; 294: 91–6.

174. Davis SR, van der Mooren MJ, van Lunsen RHW, et al. The efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. Menopause 2006; 13: 387–96.

175. Buster JE, Kingsberg SA, Aguirre O, et al. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. Obstet Gynecol 2005; 105: 944.

176. Nappi RE, Polatti F. The use of estrogen therapy in women's sexual functioning (CME). J Sex Med 2009; 6: 603–16.

177. Bachmann GA, Leiblum SR. The impact of hormones on menopausal sexuality: a literature review. Menopause 2004; 11: 120–30.

178. Alexander JL, Kotz K, Dennerstein L, Kutner SJ, Wallen K, Notelovitz M. The effects of postmenopausal hormone therapies on female sexual functioning: a review of double-blind, randomized controlled trials. Menopause 2004; 11: 749–65.

179. Modelska K, Cummings S. Female sexual dysfunction in postmenopausal women: systematic review of placebo-controlled trials. Am J Obstet Gynecol 2003; 188: 286–93.

180. Pelletier G, Ouellet J, Martel C, Labrie F. Effects of ovariectomy and dehydroepiandrosterone (DHEA) on vaginal wall thickness and innervation. J Sex Med 2012; 9: 2525–33.

181. Beaulieu E, Thomas G, Legrain S, et al. Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: contribution of the DHEAge study to a sociobiomedical issue. Proc Nat Acad Natl Sci 2000; 97: 4279–84.

182. Hackbert L, Heiman J. Acute dehydroepiandrosterone (DHEA) effects on sex- ual arousal in postmenopausal women. J Womens Health Gend Based Med 2002; 11: 155.

183. Genazzani AR, Stomati M, Valentino V, Pluchino N, Pot E, et al. Effect of 1-year, low-dose DHEA therapy on climacteric symptoms and female sexuality. Climacteric 2011; 14: 661–8.

184. Labrie F, Archer D, Bouchard C, et al. Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. Menopause 2009; 16: 923–31.

185. Bachmann G. Urogenital ageing: an old problem newly recognized. Maturitas 1995; 22 (Suppl): S1–S5.

186. Heijboer AC, Zimmerman Y, de Boer T, Coelingh Bennink H, Blankenstein MA. Peculiar observations in measuring testosterone in wom1208. Medline Plus. DHEA. Drugs and Supplements Information. National Library of Medicine. Retrieved February 18, 2010.

209. Brooke AM, Kalingag LA, Miraki-Moud F, Camacho-Hübner C, Maher KT, et al. Dehydroepiandrosterone improves psychological well-being in male and female hypopituitary patients on maintenance growth hormone replacement. J Clin Endocrinol Metab 2006; 91: 3773–9.

210. Chang DM, Lan JL, Lin HY, Luo SF. Dehydroepiandrosterone treatment of women with mild-to-moderate systemic lupus erythematosus: a multicenter randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002; 46: 2924–7.

211. Rabkin JG, McElhiney MC, Rabkin R, McGrath PJ, Ferrando SJ. Placebo-controlled trial of dehydroepiandrosterone (DHEA) for treatment of nonmajor depression in patients with HIV/AIDS. Am J Psychiatry 2006; 163: 59–66.

212. Labrie F, Diamond P, Cusan L, Gomez JL, Belanger A, Candas B. Effect of 12-month dehydroepiandrosterone replacement therapy on bone, vagina, and endometrium in postmenopausal women. J Clin Endocrinol Metab 1997; 82: 3498–505.

213. 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. Fertil Steril 2003; 80: 1495–501.

214. Stomati M, Monteleone P, Casarosa E, et al. Sixmonth oral dehydroepiandrosterone supplementation in early and late postmenopause. Gynecol Endocrinol 2000; 14: 342–63.

215. Yang NC, Jeng KC, Ho WM, Hu ML. ATP depletion is an important factor in DHEA-induced growth inhibition and apoptosis in BV-2 cells. Life Sci 2002; 70: 1979–88.

216. Schulz S, Klann RC, Schönfeld S, Nyce JW. Mechanisms of cell growth inhibition and cell cycle arrest in human colonic adenocarcinoma cells by dehydroepiandrosterone: role of isoprenoid biosynthesis. Cancer Res 1992; 52: 1372–6.

217. Loria RM. Immune up-regulation and tumor apoptosis by androstene steroids. Steroids 2002; 67: 953–66.

218. The Endogenous Hormones and Breast Cancer Collaborative Group. Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. Lancet Oncol 2010; 11: 530–42.

219. Arlt W, Callies F, Allolio B. DHEA replacement in women with adrenal insufficiency--pharmacokinetics, bioconversion and clinical effects on wellbeing, sexuality and cognition. Endocr Res 2000; 26: 505–11.

220. Tworoger SS, Missmer SA, Eliassen AH, et al. The association of plasma DHEA and DHEA sulfate with breast cancer risk in predominantly premenopausal women. Cancer Epidemiol Biomarkers Prev 2006; 15: 967–71.

221. Key T, Appleby P, Barnes I, Reeves G, Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst 2002; 94: 606–16.

222. Davis SR. Androgen therapy in women, beyond libido. Climacteric 2013; 16 (Suppl 1): 18–24.

223. Boni C, Pagano M, Panebianco M, Bologna A, Sierra NM, et al. Therapeutic activity of testoterone in metastatic breast cancer. Anticancer Res 2014; 34: 1287–90.

224. Helzlsouer KJ, Gordon GB, Alberg A, Bush TL, Comstock GW. Relationship of prediagnostic serum levels ofHDEA and DS to the risk of developing premenopausal breast cancer. Cancer Res 1992; 52: 1–4.

225. Helzlsouer KJ, Alberg AJ, Gordon GB, et al. Serum gonadotropins and steroid hormones and the development of ovarian cancer. JAMA 1995; 274: 1926–30.

226. DHEA: Side effects and safety. WebMD. Retrieved July 24, 2012.

227. Calfee R, Fadale P. Popular ergogenic drugs and supplements in young athletes. Pediatrics 2006; 117: e577–e889.

228. Drug Scheduling Actions – 2005. Drug Enforcement Administration.

229. Collomp K, Buisson C, Lasne F, Collomp R. DHEA, Physical Exercise And Doping. J Steroid Biochem Mol Biol 2015; 145: 206–12.

230. Weksler ME. Hormone replacement for men. BMJ 1996; 312: 859–60.

231. Raven PW, Hinson JP. Dehydroepiandrosterone (DHEA) and the menopause: an update. Menopause Int 2007; 13: 75–8.

232. Allolio B, Arlt W, Hahner S. DHEA: why, when, and how much – DHEA replacement in adrenal insufficiency. Ann Endocrinol 2007; 68: 268–73.

233. Traish AM, Kang HP, Saad F, Guay AT. Dehydroepiandrosterone (DHEA) – a precursor steroid or an active hormone in human physiology. J Sex Med 2011; 8: 2960–82.

234. Fouany MR, Sharara FI. Is there a role for DHEA supplementation in women with diminished ovarian reserve? J Assist Reprod Genet 2013; 30: 1239–44.

235. Samaras N, Samaras D, Frangos E, Forster A, Philippe J. A review of age-related dehydroepiandrosterone decline and its association with well-known geriatric syndromes: is treatment beneficial? Rejuvenation Res 2013; 16: 285–94.

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