I) REPORTS WITH RESERVED OPINIONS ON DHEA TREATMENT


3. L’Ordre National des Médecins français; communiqué du 10 Avril 2001


II) “NO SIGNIFICANT EFFECT” OF DHEA ON MEMORY- STUDIES:

The studies were of short duration


III) NEED FOR DHEA WITH ADVANCING AGE: There may be a need for DHEA with increasing age as senescence is associated with a decline of the adrenal-DHEA axis

Senescence is associated with a decline in adrenal androgen levels


The anabolic/catabolic hormone balance becomes increasingly inadequate with senescence


Senescence is associated with alterations of the circadian cycle of serum DHEA sulphate:

a reduced amplitude up to a disappearance of the circadian rhythm


IV) BENEFICIAL EFFECTS OF DHEA ON MENTAL AND PHYSICAL HEALTH PARAMETERS, AND AGAINST THE DEVELOPMENT OF AGE-RELATED DISEASES

1) DHEA may improve psychic well-being

Lower quality of life and fatigue: the association with lower DHEA levels


Lower quality of life and fatigue: the improvement with DHEA treatment


Depression: the association with lower DHEA levels


Depression: the improvement with DHEA treatment


Anxiety: the association with lower DHEA levels


35. Goyal RO, Sagar R, Ammini AC, Khurana ML, Alias AG. Negative correlation between negative symptoms of schizophrenia and testosterone levels. Ann NY Acad Sci. 2004 Dec;1032:291-4

Anxiety: the association with lower androstenedione levels


Anxiety: the improvement with DHEA treatment


**Memory loss and Alzheimer's disease: the association with lower DHEA levels**


**Memory loss: the improvement with DHEA treatment**


**Sleep disorder: the improvement with DHEA treatment**

Friess E, Trachsel L, Guldner J, Schier T, Steiger A, Holsboer F. DHEA administration increases rapid eye movement sleep and EEG power in the sigma frequency range. Am J Physiol. 1995 Jan;268(1 Pt 1):E107-13

**Loss of sexual drive, sensitivity and potency: the association with lower DHEA levels**


**Loss of sexual drive, sensitivity and potency: the improvement with DHEA treatment**


2) DHEA may partially protect against age-related diseases

**Hypercholesterolemia: the association with lower DHEA levels**


**Hypercholesterolemia: the improvement with DHEA treatment**


Atherosclerosis: the association with lower DHEA levels


Atherosclerosis: the improvement with DHEA treatment


Arterial hypertension: the association with lower DHEA levels


Arterial hypertension: the improvement with DHEA treatment


77. Bonnet S, Dumas-de-La-Roque E, Begueret H, Marthan R, Fayon M, Dos Santos P, Savineau JP, Baulieu EE. Dehydroepiandrosterone (DHEA) prevents and reverses chronic hypoxic pulmonary hypertension. Proc Natl Acad Sci USA. 2003 Aug 5;100(16):9488-93

Cardiovascular disease: the association with lower DHEA levels


Coronary heart disease and other cardiac diseases: the improvement with DHEA treatment

Cerebrovascular disorders: the association with lower DHEA levels

Stroke: the improvement with DHEA treatment

Obesity: the association with lower DHEA levels

Obesity: the improvement with DHEA treatment
Diabetes: the improvement with DHEA treatment


Diabetes: the association with lower DHEA levels


Rheumatism: the association with lower DHEA levels


Rheumatism: the improvement with DHEA treatment


Osteoporosis: the association with lower DHEA levels


Osteoporosis: the improvement with DHEA treatment


Infections and lower immunity: the association with low DHEA(s) levels


Lower Immunity: the improvement with DHEA treatment


194. Yang JY, Schwartz A, Henderson EE. Inhibition of HIV-1 latency reactivation by dehydroepiandrosterone (DHEA) and an analog of DHEA. AIDS Res Hum Retroviruses. 1993;9(8):747-54


Cancer: the association with lower DHEA levels


Cancer: the improvement with DHEA treatment?


Breast cancer: the improvement with DHEA in presence of estradiol in vitro and in vivo?


3) DHEA may help to live longer

Longevity: the association with DHEA levels


IV) DHEA TREATMENT OF DHEA DEFICIENCY

1) DHEA medications

**Oral DHEA**


**Sublingual/buccal DHEA**


**Transdermal DHEA**


2) DHEA treatment may be justified for treatment in Addison’s disease next to glucocorticoids and fludrocortisone

increased fatigue. Female patients reported reduced physical function, which might be due to adrenal androgen depletion. ... markedly reduced subjective health status and working ability in many others. Thus, there might be potential for further refinement of replacement therapy)


V) DHEA TREATMENT: SAFETY

DHEA treatment: relatively safe, minimal side effects


1) Can DHEA treatment suppress the production of hormones by the adrenal glands?

A treatment with DHEA at physiological doses does not or poorly inhibit the hypothalamic-pituitary-adrenal axis


2) Can DHEA increase the risk of PROSTATE CANCER?

Fear: DHEA could promote or aggravate hormone dependent cancers, because of its transformation into sex hormones. The effect could be more important in treatment of long duration or at high doses.

Facts: In humans, studies show no significant effect of DHEA on prostate cancer. In most animal studies a protective effect of DHEA on prostate cancer is observed. The more the DHEA dose is increased, the more potent DHEA's anti-cancer effect is.

Arguments against DHEA use


Studies that show that DHEA may protect the human prostate against cancer

Lower serum DHEA and DHEA sulfate levels have been found in men with prostate cancer


Lower prostate tissue levels of DHEA and androstenedione are found in recurrent prostate cancer compared to the levels in benign prostate hypertrophy


The serum DHEA sulfate is inversely related with the serum PSA: a high DHEAs is related to a low PSA

With age, the serum DHEA sulfate progressively declines, while the incidence of human prostate cancer gradually and almost exponentially increases.


DHEA treatment reduces the development of transplants of human prostate cancer in animals


DHEA treatment inhibits prostate cancer promoted by testosterone and estradiol in rats


DHEA treatment reduces the frequency and severity of carcinogen (MNU, N-methyl-N-nitrosourea)-induced prostate cancer from -33 to -60 %, whatever the moment of administration of the carcinogen (one week before, or 20 or 40 weeks after)


DHEA treatment of rats predisposed to develop endocrine testicular Leydig cell tumors inhibits tumor development


No effect of DHEA on the prostate: Studies that show that the effect of DHEA on human prostate cancer is neutral

Healthy men have a level of DHEA (sulfate) equal to that of men with benign prostate hyperplasia or prostate cancer, even adjusted to age


The level of DHEA in the prostate is 6-7 times that in the plasma, but the level in benign hypertrophic prostates does not differ from that in normal prostates


The serum DHEA sulfate level does not influence the PSA, no significant association

The prostate of men with normal adrenal glands but with no testicular function throughout life (hypogonadotropic hypogonadism or prepubertal castration) is at autopsy atrophic, while that of men with normal adrenal glands and normal testes is enlarged and shows some degree of benign prostatic hyperplasia.


DHEA treatment does not increase PSA, nor at a physiologic (50 mg/day; Reiter et al.), nor at a supraphysiologic dose (100 mg/day; Wallace et al., Sun et al.)


DHEA treatment at physiologic dose (50 mg/day) does not increase the prostate volume, nor the urinary residual volume.


DHEA treatment in vitro has no influence on the growth of prostate stromal cells.


Arguments against DHEA use

DHEA administered to castrated rats stimulated the development of an implanted prostate cancer. (critic: but to obtain an adverse effect rats must first be castrated. Castrated rats have a lower risk of implanted prostate cancer development. DHEA administration normalized the risk of prostate cancer and brought it up to the level of non castrated rats, not above)

Anecdotal report


3) Can DHEA increase the risk of BREAST CANCER?

Fear: DHEA could promote or aggravate hormone dependent cancers such as breast cancer, because of its transformation into sex hormones. The effect could be more important in treatment of long duration or at high doses.

Fact: In premenopausal women high levels of DHEA are associated with a low risk of breast cancer. Two studies in HRT untreated postmenopausal women show the opposite, namely that a high level of DHEA sulfate is associated with an increased risk of breast cancer. This confirms the finding that DHEA inhibits the proliferation of breast cancer cells in vitro in the presence of oestradiol, but stimulates it in the absence of oestradiol. Postmenopausal women should therefore get female hormone replacement when they receive corrective DHEA therapy.
In the majority of animal studies a protective effect of DHEA on breast cancer is observed. The higher the dose of DHEA, the greater the anti-cancer effect.

**Arguments FOR DHEA use:** DHEA may protect premenopausal women and HRT treated postmenopausal women against breast cancer

### HUMAN STUDIES

#### Studies with associations between low levels of DHEA sulfate and an increased risk of breast cancer


#### Studies with associations between low urinary levels of DHEA metabolites and an increased risk of breast cancer


#### Studies with an association between low urinary levels of DHEA metabolites and aggravation/progression of breast cancer


#### Studies where the DHEA and DHEA sulfate levels are significantly lower inside the breast cancer tumours compared to healthy breast tissues of control patients


#### Studies where low levels of DHEA sulfate were found in female patients with advanced cancer (with metastases) compared to the level found in women with loco-regional cancer


#### With age the level of DHEA sulfate gradually declines, while at the same time the incidence of breast cancer quickly increases, phenomena that plead against the implication of DHEA in the genesis of breast cancer, and rather for the implication of DHEA deficiency as a factor in favor of breast cancer


#### A low serum level of DHEA has been observed in other cancers in women: ovarian cancer, metastasized ovarian cancer, the adult type of acute T cell leukemia, metastasized cancer


**ANIMAL STUDIES:**

DHEA potently reduces the incidence and development of breast cancer in rats that keep their ovaries (The effect is proportional to the dose (the cancer incidence can be up to less than 10 % of normal mice not treated with DHEA!!)


24. Ratko TA, Detrisac CJ, Mehta RG, Kellof GJ, Moon RC. Inhibition of rat mammary gland chemical carcinogenesis by dietary dehydroepiandrosterone or a fluorinated analogue of dehydroepiandrosterone. Cancer Res. 1991;51(2):481-6


**DHEA reduces the incidence and development of breast cancer in mice that keep their ovaries**


**The levels of DHEA that protect rodents against breast cancer are the same than the physiological levels found in premenopausal women**


**DHEA protection is possible on condition that the ovaries remain**


**DHEA treatment may facilitate the development of breast cancer induced by carcinogens at the condition that the ovaries are previously removed, and thus major estrogen deficiency is created.** These data should incite MD’s not to prescribe DHEA to postmenopausal women without addition of female hormone replacement.

**DHEA treatment protects animals from breast cancer caused by intensive radiation**


**DHEA treatment significantly prevents spontaneous breast cancer development in mice predisposed to breast cancer**

38. Labrie F, Luu-The V, Labrie C, Simard J. DHEA and its transformation into androgens and estrogens in peripheral target tissues: intracrinology. Front Neuroendocrinol 2001 Jul;22(3):185-212 (Labrie, one of the top-researchers in DHEA suggests after several years of research in animals and humans that DHEA is free of breast and uterine cancer risk)

**DHEA treatment can significantly inhibit the development of human breast cancer transplants in mice**


**DHEA treatment can be beneficial for many other cancers, in animals: uterin, prostate, testicular, pancreas, thyroid, liver (at low doses)**


No effect of DHEA on the breast cancer risk in premenopausal women and HRT treated postmenopausal women

Studies with no significant association between DHEA levels and breast cancer


Studies with no significant associations between the urinary levels of DHEA metabolites and the risk of breast cancers


Arguments contra DHEA use in untreated postmenopausal women: DHEA may increase the risk in postmenopausal women without HRT

Two studies with report of an association between high levels of DHEA and an increased risk of breast cancer in (HRT) untreated postmenopausal women


Apparently, women need to have all their deficiencies corrected, including female hormones in order to benefit from the breast cancer protective actions of DHEA


In vitro and in vivo studies where DHEA treatment inhibited the proliferation of breast cancer (cells) in presence of estradiol in vitro, but if estrogens are withdrawn (estrogen deficiency) DHEA stimulated the proliferation of the breast cancer cells
