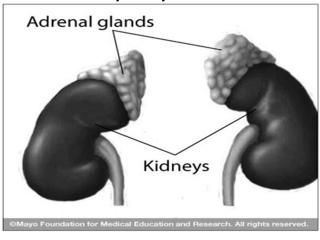
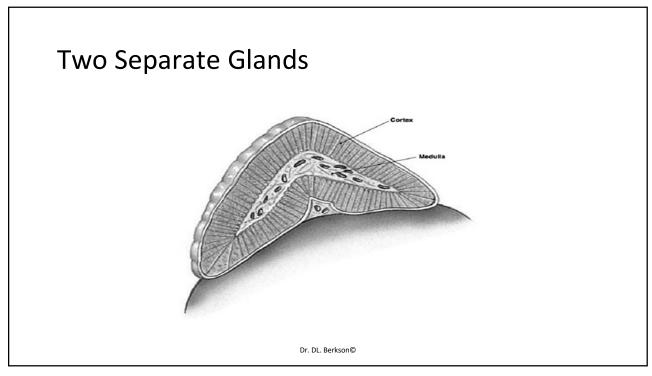


Encased in Ribbon of Fat – Very Vulnerable to EDCs which is why Receptor Detox is great with Cytozyme AD



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Adrenal Hormones

- Two organs really
 - 1. Cortex (80%)
 - 2. Medulla (20%)
- Secrete very different hormones

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Adrenal Cortex: Outer Layer

- Three layers -
 - 1. Zona Glomerulosa Mineralcorticoids *Aldosterone blood pressure and electrolyte balance 24-hr urine test measure aldosterone
 - 2. Zona Fasciculata *Cortisol, *cortisone saliva and urine measure Immune system, metabolism (including sugars)
 - 3. Zona Reticularis –sex steroids: Androgens, Pregnenolone, Progesterone, DHEA all of these work to keep estrogen SAFE!
 - 4. Adrenal health is very important for all sex steroid hormone health
 - * made only in the adrenals

Medulla (inner part of adrenal glands)

Catecholamines (driven by sympathetic, fight or flight nervous system – rapid response for stress)

- 1. Adrenaline
- 2. Noradrenaline —(tyrosine helps thyroid but too much reduces noradrenaline production)

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Prioritized by Nature

- Next to the hippocampus, heart and parietal cells, the adrenal glands have one of the largest blood supplies in the body.
- As there are cortisol receptors on every cell in the body (along with its best friend, thyroid and vitamin A receptors)



Dr. John Lee – Australian Surgeon – Hashimoto's thyroidectomy specialist until...



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Cortisol helps thyroid deliver its complex signal Can't have a healthy thyroid without healthy adrenal glands.



Adrenal Diseases

- Cushing's Syndrome glucocorticoid excess
- Addison's disease glucocorticoid and mineralcorticoid insufficiency (aldosterone not tested by 24-hr cortisol saliva tests but by 24-hr urine as best way to test)
- But there is a world of possible dysfunction between the two.

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No man's land

• Addison's \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow Cushing's

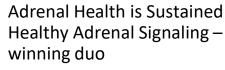
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Adrenal Dysregulation

(Often set into motion 1st 4 years of life with severe abuse)



PABA and BORON help Keep cortisol levels ZEN





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Symptoms of Adrenal Dysfunction

- Crashes of energy
 Wake up fatigued
 Chronic Recurrent Infections
 Orthostatic hypotension
- Decreased sexual interest
- Exhaustion after orgasming
- Exhaustion after exercise
- Orgasms have less power (seem not worth all that work)
- Muscular weakness
- Wake up exhausted
- Recurrent infections even at distance body tissues

Symptoms cont.

- Sex steroid issues ie estrogen alpha dominance in both men and women
- Thyroid malfunction and hard to get prescription right
- Increased PMS, Peri and Post menopausal symptoms
- Liver spots (chloasma)
- Increased allergies
- Edema (especially in ankles)
- May be an issues as sex steroid hormones are wanning. Remember hormones are a family.

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Symptoms Cont.

- Fatigue after exercise
- Procrastination especially more than historically
- Everything is taking more effort and not seeming worth it (aging issue as adrenals are aging)
- Poor stress tolerance
- Chemical sensitivities
- Need to lie down a lot
- Need to put feet up on something or feels almost painful
- IBS symptoms (constipation/diarrhea)
- Breathing oddities: hyperventilate frequent sighing, gasping, catch yourself holding your breath frequently
- Dyslexic energy, less in AM and more in PM

Symptoms Cont.

- Lack of concentration
- Mental fatigue, brain fog, memory issues, confusion
- Tendency to anxiety
- Emotionally labile, up and down
- Overreacts
- Sense of isolation, alienation withdrawal from community

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Symptoms cont.

- Communication skills are deteriorating
- Increase: risk taking, recreational drugs, alcohol, addictive behaviors
- History of Post Traumatic Stress Disorder Syndrome
- Abdominal fat can occur with excess or too little cortisol

Symptoms Cont.

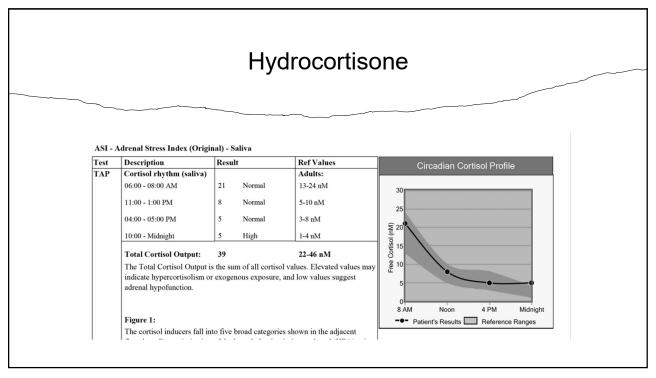
- Exercise Less
- Lay down more
- · Crave putting feet up
- Intolerance to carbs
- Cravings (sugar, salt, high fat and fried foods, and stimulants)
- Use caffeine, nicotine, sugar, carbs to keep going

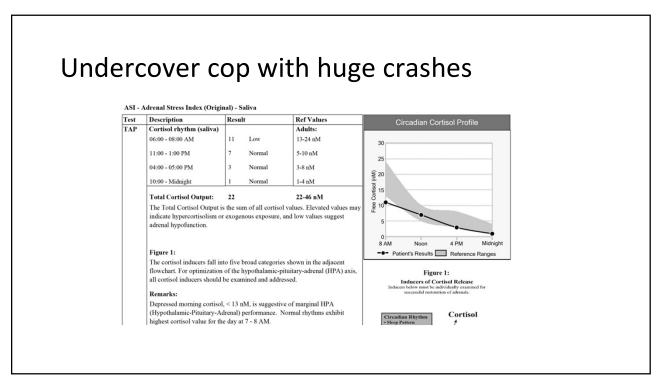
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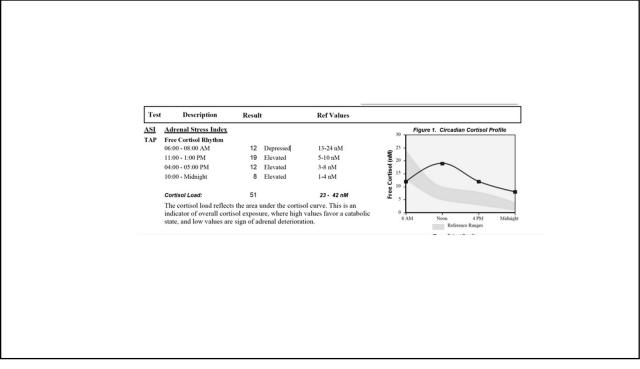
Low Morning Cortisol

- Immune dysregulation --- 8 AM to 10 AM cortisol sets the "immune capacity for the day"
- Extreme fatigue
- Non-restorative sleep
- · Increased incidence of autoimmune diseases
- Linked to health of SIgA
- Obesity
- Its putative role in the regulation of physiological function across the day (e.g., the immune system) and its sensitivity to psychosocial variables make it a prime
 candidate as an intermediary linking mind and health
- Severe highs or lows of cortisol lower SIgA.
- Low AM cortisol and/or flat line linked to chronic fatigue
- Cytozyme-AD loading 3 twice a day for 3 days and then two twice a day
- Hydrocortisone
- <u>Stress.</u> 2004 Mar;7(1):29-37. The awakening cortisol response: methodological issues and significance.
- Int J Psychophysiol, 1998 Dec;31(1):69-76. The relationship between salivary secretory immunoglobulin A and cortisol: neuroendocrine response to awakening and the diurnal cycle.
- <u>Psychoneuroendocrinology</u>, 2014 Apr;42:199-206. doi: 10.1016/j.psyneuen.2014.01.017. Epub 2014 Jan 30. The role of hypocortisolism in chronic fatigue syndrome.



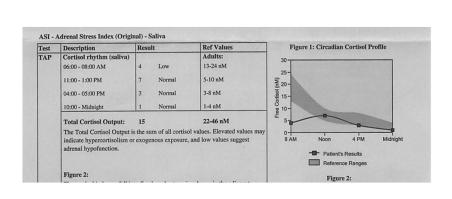


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Adrenal Hyperexcreter

- · ADHS
- · Adaptogenic herbs that lower elevated cortisol
- · Or raise insufficiencies



AM Cortisol

- · Sets immune system for the day
- Sets the anti-inflammatory balance of cytokines
- Sets the energy
- If below 12 may need hydrocortisone + Cytozyme AD
- If there is a huge slope from morning to early afternoon = but issues
- May need a way to tamp down excessive nightimare cortisol: herbs, progesterone, oxytocin and if nothing else gabapentin.

Cortisol - Fat

- Saliva was collected in a single morning from 478 residents in Eastern Highlands Province and Madang Province.
- After adjusting for age, region, and occupation, the morning salivary cortisol concentration was significantly negatively correlated with body mass index among men and women and waist circumference
- Men with total or abdominal excessive body fat displayed lower cortisol compared to men without such risk.
- Papua New Guinean adults with increased accumulation of body fat showed reduced cortisol concentration in morning saliva.

Am J Hum Biol. 2016 Jul;28(4):587-90. doi: 10.1002/ajhb.22823. Epub 2016 Jan 22.

Reduced morning cortisol concentration in saliva was associated with obesity: Evidence from community-dwelling adults in papua new guinea.

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Cytozyme

- Cytozyme AD loading first few days 3 twice a day with or without food
- · Then reduce to two twice a day
- Healing of the adrenals takes time up to 1.5 years depending on history of trauma etc.

Hydrocortisone – Safe Uses by Jeffries

- 2.5 to 15 mg in AM
- Again before lunch
- Later in afternoon controversial but Jeffries would give small amounts throughout the day
- There is a possible link of eye diseases, especially pressure issues with optic nerve, as related to adrenal insufficiency, cortisol, especially during the evening time.
- But some patients will not be able to sleep.

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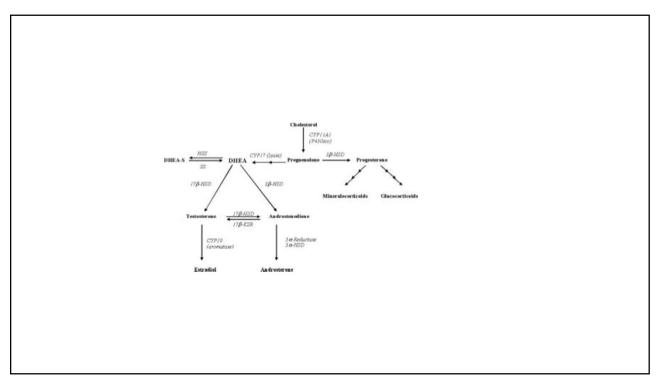
Adrenarche

- Adrenarche means "the awakening of the adrenal gland." 6-9 years of age. If any illness arises then, consider adrenal issues.
- The androgenic signs of adrenarche include adult-type body odor, greasy hair, acne and/or comedones, and axillary and/or pubic hair.
- In boys and girls in adrenarche, the adrenal androgen levels begin to rise,¹⁵ while the gonadal axis continues to be quiescent.
- Such early hormonal increases in the adrenal axis are generally not accompanied by any external physical changes.
- Ask about trauma in first 4 years of life which tamps down the brain/hormone cross talk.
- The adrenal gland is responsible for making hormones including androgens sex hormones that cause changes such as the development of pubic hair, oily skin, oily hair, and body odor.

DHEA

- Signals ER beta so is breast protective
- $\bullet \quad \text{Dehydroepiandrosterone has been thought to have physiological functions other than as an androgen precursor.} \\$
- PPAR alpha energy homostasis
- Pregnane receptor helps make bile acids and detoxify toxins
- ER beta controlled growth
- Gut wall adhesive proteins
- Anti-anxiety and collaborative oxytocin signals esp. in the brain.
- The previous studies performed have demonstrated a number of biological effects in rodents, such as amelioration of disease in diabetic, chemical carcinogenesis, and obesity models.
- To date, activation of DHEA binding to peroxisome proliferators activated receptor alpha, pregnane X receptor, and estrogen
 receptor beta by DHEA and its metabolites has been demonstrated.
- The biological actions of dehydroepiandrosterone involves multiple receptors. Drug Metab Rev. 2006;38(1-2):89-116. doi: 10.1080/03602530600569877. PMID: 16684650; PMCID: PMC2423429.

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Dehydroepiandrosterone: A Nutraceutical with Interesting Biological Function

- Because the decline in production DHEA in the human adrenal gland is associated with some of the pathophysiological effects of aging, many people supplement their own "declining" DHEA levels with exogenous DHEA and even refer to DHEA as the "fountain of youth hormone."
- Although appropriate physiological doses are not well-defined and differ in men and women, many clinical studies have been conducted using 50 mg/day for women and 100 mg/day for men.
- The biological actions of dehydroepiandrosterone involves multiple receptors. Drug Metab Rev. 2006;38(1-2):89-116. doi: 10.1080/03602530600569877. PMID: 16684650; PMCID: PMC2423429.

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DHEA

- Currently, DHEA is available over-the-counter as a dietary supplement and is therefore not regulated by the Food and Drug Administration; however, this has not always been the case.
- DHEA was once marketed for weight loss, and in 1985 the FDA banned over-the-counter sales of DHEA.
- DHEA is still outlawed by the International Olympic Committee and the National Collegiate Athletic Association, but since the passage of the Dietary Supplement Health and Education Act of 1994, DHEA has again been widely available in health food stores in the US (and elsewhere) where it is marketed as a dietary supplement.

Dosages

- Women start at 5 mg and up to 10-15
- Males start at 10 mg and up to 25 mg
- Ideal in blood is close to 100 μg/dL
- If elevated rule out cancer or benign growth in adrenal gland

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Largest concentration in blood second only to cholesterol so must be important

- Although DHEA is a primary sterol produced in these biosynthetic pathways, DHEA is largely found in circulation in its sulfated form, DHEA 3β-sulfate (DHEA-S), which can be inter-converted with DHEA by DHEA sulfotransferases and hydroxysteroid sulfatases
- In its sulfated form, DHEA is the most abundant circulating sterol in humans, followed by ADIONE.
- During fetal development, plasma DHEA-S levels are around 100–200 $\mu g/dL$ (3–7 $\mu M), but fall rapidly after birth and remain low until adrenarche.$
- Blood DHEA levels then rise and peak at around 300 µg/dL (10 µM) during the third decade of postnatal life, followed by an age-dependent decline. Additionally, there are clear gender differences in circulating levels of DHEA-S, with higher levels found in men than women.

DHEA/Cholesterol

- As DHEA lowers
- Cholesterol levels rise
- Check DHEA in elevated lipid patients or TG over 150
- The decline in circulating levels of DHEA and its sulfate derivative appear to be inversely correlated to the rise in cholesterol and the pathophysiological effects of aging (<u>Barret-Connor et al., 1999</u>). This has recently been supported by the <u>Baltimore Longitudinal Studies</u> in men that showed a positive correlation between decreased morbidity in life and levels of DHEA-S
- Endogenous levels of dehydroepiandrosterone sulfate, but not other sex hormones, are associated with depressed mood in older women: the Rancho Bernardo study. *J. Am. Geriatr. Soc.* 1999;47:685–691.

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DHEA Paradox

- · IF lowers DHEA in women
- · Thought caloric restriction is linked to longevity

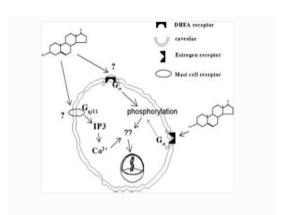
DHEA

- · Helps activate membrane receptors
- Which all the sex steroids have, and also include: parathyroid hormone, epinephrine, and insulin.
- Had a renal patient with high PTH and gave boron and DHEA and came down to normal.
- So consider DHEA levels when see elevated PTH, low epi and abnormal insulin.
- The biological actions of dehydroepiandrosterone involves multiple receptors. Drug Metab Rev. 2006;38(1-2):89-116. doi: 10.1080/03602530600569877. PMID: 16684650; PMCID: PMC2423429.

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DHEA

· DHEA helps stabilize mast cells



Cancer?

- Ongoing research has shown now that pharmacological levels of DHEA and most of its metabolites lead to activation *in vivo* of a number of nuclear (PPARα, PXR, ERB) and membrane-associated receptors.
- In pharmacologic dosages in animals it is pro-carcinogenic.
- So this has been the big debate with DHEA supplement in cancer patients.
- The biological actions of dehydroepiandrosterone involves multiple receptors. Drug Metab Rev. 2006;38(1-2):89-116. doi: 10.1080/03602530600569877. PMID: 16684650; PMCID: PMC2423429.

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6 months oral DHEA to early (50-55) and later menopause (55+)

- Levels of DHEA, DHEAS, androstenedione, testosterone and dihydrotestosterone increased progressively from the first month
 of treatment.
- Levels of estradiol and estrone significantly increased after the first/second month of treatment.
- Levels of SHBG significantly decreased from the second month of treatment only in overweight late postmenopausal women, while the other groups showed constant levels.
- Progesterone levels remained constant in all groups, while 17-OH progesterone levels showed a slight but significant increase in all groups.
- Allopregnanolone and plasma beta-endorphin levels increased progressively and significantly in the four groups, reaching
 values three times higher than baseline.
- Levels of cortisol and gonadotropins progressively decreased in all groups.
- Lowers cortisol increases progesterone.
- The endometrial thickness did not show significant modifications in any of the groups of postmenopausal women during the 6 months of treatment.
- Treatment with DHEA was associated with a progressive improvement of the Kupperman score in all groups, with major positive effects on the vasomotor spasms and other symptoms.
- Six-month oral dehydroepiandrosterone supplementation in early and late postmenopause. Gynecol Endocrinol. 2000 Oct;14(5):342-63. doi: 10.3109/09513590009167703. PMID: 11109974.

Menopause

- Evidence Acquisition A review of the literature from 1985 to 2021 on the potential benefits and risks of androgen prohormones in women.
- Enderose Synthesis Studies have examined the potential benefit of DHEA therapy for anti-aging, sexual dysfunction, infertility, metabolic bone health, cognition, and wellbeing in hormone-deficient states such as primary adrenal insufficiency, hypopituitarism, and anorexia as well as administration to normal women across the lifespan.
- Conclusions Data support small benefits in quality of life and mood but not for anxiety or sexual function in women with primary or secondary adrenal insufficiency or anorexia. No consistent beneficial effects of DHEA administration have been observed for menopausal symptoms, sexual function, cognition, or overall wellbeing in normal women. Local administration of DHEA shows benefit in vulvovaginal atrophy. Use of DHEA to improve induction of ovulation response in women with diminished ovarian reserve is not recommended. Risks of high physiologic or pharmacologic use of DHEA include androgenic and estrogenic side effects which are of concern for long-term administration.
- Should Dehydroepiandrosterone Be Administered to Women? J Clin Endocrinol Metab. 2022 May 17;107(6):1679-1685. doi: 10.1210/clinem/dgac130. PMID: 35254428; PMCID: PMC9113789.

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Peri menopause

- Progesterone 40 mg/ mid month and 20 mg other days except menstruation
- The more bleeding and clots and anxiety = the more PR
- DHEA 10 mg
- Receptor Detox
- Hormone Balance and Protect
- If any breast issues then add additional iodine

Case Report

- A 49-year-old woman with Addison's disease who is on low dose estrogen with cyclic progesterone therapy for menopausal symptoms returns for follow-up.
- She is on a stable glucocorticoid replacement strategy of hydrocortisone 10 mg in the morning and 5 mg in the early afternoon and fludrocortisone 0.05 mg each morning.
- She has read on the internet that additional therapy with DHEA may help her overall quality of life and libido.
- She asks whether she should add this therapy to her regimen and at what dose.

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Anorexia Nervosa

- There are profound effects of DHEA on the endocrine system in women with anorexia.
- Investigators examined the effects of DHEA 50 mg daily for potential beneficial effects in premenopausal women with anorexia on wellbeing and bone density.
- In 30 women randomized to DHEA 50 mg daily compared with standard hormonal therapy with an oral contraceptive for a year, they noted that patients receiving DHEA exhibited improvement on 3 validated psychological instruments (Eating Attitudes Test, Anorexia Nervosa Subtest, and Spielberger Anxiety Inventory).
- $\bullet \qquad {\tt DHEA}\ administration\ also\ improved\ bone\ turnover\ markers.$
- In another small study, DHEA resulted in resumption of menses in 50% of women via a hypothesized increase in estradiol levels. These data again support that DHEA action is via conversion to androgens and estrogens in different target tissues.

Sexual Dysfunction

- In a systematic review and meta-analysis of 23 trials in 1188 postmenopausal women, DHEA therapy was not associated with an improvement in libido or other sexual function outcomes when compared with placebo.
- The Endocrine Society guidelines and recent international guidelines agree on the lack of data supporting the use of DHEA for sexual dysfunction.

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Fernand Labrie MD PhD

- Conclusions: By a local action in the vagina, DHEA applied daily at doses at which serum steroids remain well within normal postmenopausal values exerts relatively potent beneficial effects on all four aspects of sexual dysfunction.
- Such data indicate that combined androgenic/estrogenic stimulation in the three layers of the vagina exerts important beneficial effects on sexual function in women without systemic action on the brain and other extravaginal
- tissues.

Labrie Intracrinology

- Dehydroepiandrosterone (DHEA) is not a hormone but it is a very important prohormone secreted in large amounts by the adrenals in humans and other primates, but not in lower species. It is secreted in larger quantities than cortisol and is present in the blood at concentrations only second to cholesterol.
- This new field of endocrinology has been called intracrinology
- In women, after menopause, all estrogens and almost all androgens are made locally in peripheral tissues
 from DHEA which indirectly exerts effects, among others, on bone formation, adiposity, muscle, insulin
 and glucose metabolism, skin, libido and well-being. In men, where the secretion of androgens by the
 testicles continues for life, the contribution of DHEA to androgens has been best evaluated in the prostate
 where about 50% of androgens are made locally from DHEA.
- Is dehydroepiandrosterone a hormone? J Endocrinol. 2005 Nov;187(2):169-96. doi: 10.1677/joe.1.06264. PMID: 16293766.

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Is vulvovaginal atrophy due to a lack of both estrogens and androgens

- DHEA exerts both estrogenic and androgenic activity in the three layers
 of the vagina, the stimulatory effect on nerve density being 100%
 androgenic. Taking vaginal weight as a global parameter, the stimulatory
 effect of DHEA in the rat vagina is about equally estrogenic and
 androgenic, thus illustrating the importance of androgens in vaginal
 morphology and function, and the likely importance of androgens in
 vulvovaginal atrophy of menopause.
- DHEA plus oxytocin increase density of nerves and vaginal vault non tumorgenic cells lines.
- Is vulvovaginal atrophy due to a lack of both estrogens and androgens?
 Menopause. 2017 Apr;24(4):452-461. doi:
 10.1097/GME.0000000000000768. PMID: 27875388.



DHEA

- · Peaks at 25 years of age
- Declines progressively By 70 years old about 20% of level at 25 years of age
- · Keeps estrogen "breast friendly" versus not
- This decline overlaps with increasing in manifestations of aging
- Most "reactive" hormone next to progesterone
- Can de-sensitize or also take 7-keto form

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Many Applications Clinically

- No recognized DHEA deficiency but linked to accelerated aging and increasing cholesterol levels.
- Most of DHEA is made in adrenal glands in women and if have adrenal insufficiency than DHEA levels can be very low
- Not so with males as testis produce high levels of DHEA
- Protects estrogens from acting pro-carcinogenic (work of Labrie France) as it signals ER beta
- Large dosages shown to reduce autoimmunity especially when given with PABA (Hormone Balance & Protect)

Cytozyme-AD

Glandular loading 3 BID
Then 2 BID
Give along with PABA Daily Hormone Balance
for better sustained results!



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DHEA

- Double-blind studies show that DHEA replacement in adrenal insufficiency or aging:
- Increase overall well-being
- Decrease anxiety, depression
- Improve energy
- Improve sexuality
- Improves insulin resistance especially in women with adrenal dysregulation

Dosages

- Women: 5-15 mg/dayMen: 10-20 mg/day
- Reverse many issues of aging: poor appetite, poor muscle mass, weakness
- Rapid bone density improvement
- Higher than physiologic dosages clinically appear to help autoimmune diseases by clinical observation of Lamson and Gaby

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Blood Testing

- DHEA biologically active form
- DHEAS 1000 times higher in blood
- Not exactly sure if blood levels represent tissue levels Labrie
- Father of Intracrinology

DHEA - cancer

- No clear evidence that it increases risk in humans but in animals that do not have much it does increase carcinogenesis.
- In postmenopausal women, doses 300-500 mg/day topically for one year did not cause endometrial proliferation
- Does not promote prostate cancer
- One case study of a man with prostate cancer was taking 200-700 mg/d and worsened

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DHEA + Prednisone

- Lowers when patients are on oral glucocorticoids (prednisone) as they suppress adrenal glands
- This may be why bone loss occurs on prednisone as DHEA protects bone
- So, it may be good to give along with prednisone prophylactically but no clear evidence

DHEA + Thyroid

 About 10% of patients taking thyroid replacement get hyperthyroid on DHEA so may need to reduce dose and certainly need to track thyroid

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BHRT and DHEA

- In a double-blind study giving postmenopausal women **oral 2 mg of estradiol** for 12 weeks causes a 23% reduction in DHEAS.
- Suggests that BHRT increases the need for DHEA.
- Since DHEA goes to either E or T, it may reduce need for dosage of BHRT.

DHEA & Progesterone

- DHEA does not convert to P, but it has been linked to increasing P levels.
- · Norm Shealy MD PhD
- Appears to make GH more available and if on it may reduce the dosage needed.
- Long-term low-dose DHEA orals supplementation in early and late postmenopause. Ferti & Steril. 2003:80:1495-1501

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Over-the-Counter

- A 1998 study found that 7 of 16 DHEA products sold in health food stores contained 90 to 110% of amount of DHEA stated on the label.
- One product had none.
- One product had 150% more.
- Another study found higher levels than what was on the label.
- Quality control of DHEA supplement products. JAMA 1998.280:1565

Adverse Effects

- Acne dermatitis
- Greasy oily skin
- Alopecia
- Breast tenderness
- Vertigo
- Increase odor of sweat in larger doses in some
- Occasionally, hirsutism (excessive body hair)

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Adjunctive Care for Lupus

- Numerous studies demonstrate a reduction in Systemic Lupus Erythematosus activity
- Even more so if on glucocorticoids but also if not
- At 100-200 mg but some show marked improvement up to 600 mg/day, especially reducing fatigue and improving emotional wellbeing

DOSING

- While daily intravaginal administration of 0.50% (6.5 mg) dehydroepiandrosterone (DHEA, prasterone) for 12 weeks has shown
 clinically and statistically significant effects on moderate to severe (MS) dyspareunia as the most bothersome symptom (MBS), the
 present study analyzes the effect of a reduced dosing regimen on MBS vaginal dryness.
- Prasterone (Dhea) Insert
- Daily intravaginal 0.50% prasterone for 2 weeks followed by twice weekly for 10 weeks versus placebo.
- Maximal beneficial changes in vaginal parabasal and superficial cells and pH were observed at 2 weeks as observed for intravaginal 10 μg estradiol (E2).
- No significant adverse event was observed. Vaginal discharge related to the melting of Witepsol was reported in 1.8% of subjects.
- The present data show that daily dosing with 0.50% DHEA for 2 weeks followed by twice-weekly dosing is a suboptimal treatment
 of the symptoms/signs of vulvovaginal atrophy resulting from a substantial loss of the efficacy achieved at daily dosing.

Climacteric. 2015;18(4):590-607. doi: 10.3109/13697137.2014.992012. Epub 2015 Mar 3.

Decreased efficacy of twice-weekly intravaginal dehydroepiandrosterone on vulvovaginal atrophy.

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DHEA 5 to 25 mg or more for autoimmune diseases

