24-Hour Urine Comprehensive Hormone Profile Handbook

By

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Introduction to Hormone Panels for Bio-Identical HRT

By Ronald Steriti, ND, PhD

The bio-identical hormone replacement (BHRT) program advocated by Dr. Jonathan Wright, MD differs from conventional hormone replacement therapy (HRT) in several key areas.

Cutting-edge lab tests are used to measure hormone levels and assess the activity of key enzymes

BHRT uses hormones that are identical to that produced in the body (i.e. bio-identical)

Targeted nutritional and herbal therapies are used to support healthy hormone levels and modulate enzyme activity.

The Comprehensive PLUS Hormone Profile by Meridian Valley Laboratory measures over twenty hormone metabolites, including:

Adrenal Steroids: DHEA, Cortisone, Cortisol, Pregnenolone, Aldosterone, Etiocholanolone, Adrosterone, Creatinine, Pregnanetriol, Tetrahydrocortisone, Tetrahydrocortisol, Allo-Tetrahydrocortisol, Tetrahydrocorticosterone, Allo-Tetrahydrocorticosterone

Sex steroids: DHEA, Estrone, Estradiol, Estriol, Pregnenediol, Testosterone, Etiocholanolone, Androsterone, Creatinine, Pregnanetriol

2-Hydroxyestrogens, 16α-Hydroxyestrone, 2-Methoxyestrone, 2-Methoxyestradiol, 5α-Androstanediol, 5ß-Androstanediol, 11ß-Hydroxyandrosterone, 11ß-Hydroxyetiocholanolone

In addition, the following ratios are assessed:

2 / 16-alpha estrone

sodium / potassium

Androsterone / Etiocholanolone

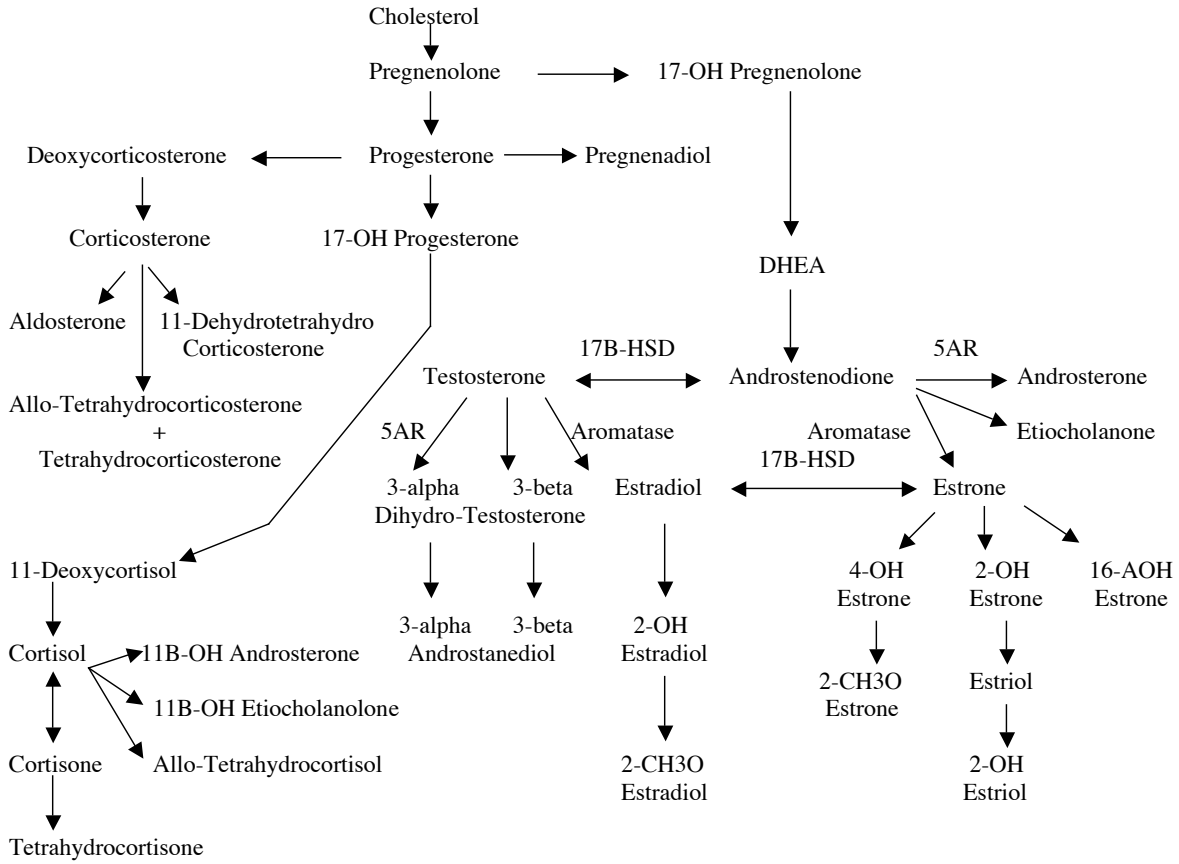
Allo-Tetrahydrocortisol / Tetrahydrocorticosterone

Cortisol / Cortisone

Tetrahydrocorticosterone + Allo-Tetrahydrocortisol / Tetrahydrocorticosterone

For those unfamiliar with modern steroid panels, this can be quite formidable.

Figure 1: Steroid Metabolism



Estrogens

By Wendy L. Ellis, ND and Ronald Steriti, ND, PhD

Estrogens are secreted by the ovarian follicles, corpus luteum, and the placenta during pregnancy. The adrenal glands and testes are also believed to secrete small quantities of estrogens.

In vivo and in vitro studies indicate that acetate, cholesterol, progesterone, and testosterone can all serve as precursors of estrogens.

Over 20 estrogens have been identified, although traditionally, only three have been clinically valuable. These three are estrone (E1), estradiol (E2), and estriol (E3). The most potent estrogen secreted by the ovary is estradiol.

It is important to note that estrogens are also produced by peripheral metabolism of androgens, especially the adrenal hormone, androstenedione. In healthy individuals, both male and female, approximately 1 to 7% (greater percentage if obese) of the secreted androstenedione is converted to estrone. Because this conversion occurs mostly in the adipose tissues, obese post-menopausal women may have elevated levels of estrone and other estrogens.

97% of circulating estrogens are bound to plasma proteins, essentially making them biologically inactive. We are testing only the biologically active ("free" and conjugated) hormones with the 24 hour urine analysis. Our ranges were calculated from female and male normals determined from various researchers, observation at Meridian Valley Lab in Renton, Washington, and other laboratories in the area. Clinical, in house, observations noted free and conjugated serum estrogen levels of 3-10% estrone, 3-10% estradiol, and 80-93% estriol. These values are used for interpretation of the hormone profiles.

Estrone (E1)

Estrone is the predominant estrogen in post-menopausal women and inter-converts with estradiol. This conversion is dependant on the bidirectional activity of 17-beta-hydroxysteroid dehydrogenase, which also converts testosterone to androstenedione (an intermediate of androsterone, etiocholanolone, and estrone). Boys with a deficiency of this enzyme fail to form testosterone, androstenediol, and estradiol in a normal manner. At puberty, the plasma concentrations of testosterone and DHT will be low, and plasma androstenedione and estrone will be elevated.

Clinical observation

When E1 is high in comparison to E2 or E3, consider switching the hormone dose (biest vs. triest), or consider using an iodine/iodide blend to encourage the conversion of estrone to estriol. The biochemical action of this is unknown, it is a clinical observation noted in women who are using iodine to treat fibrocystic breasts. Iodine and iodide may interfere with thyroid function,

therefore, monitoring thyroid funtion before and during treatment is recommended.

- Recommended dose of Lugol's iodine - 12.5mg bid.

Estradiol (E2)

Estradiol is the predominant active estrogen in premenopausal women. 97% of serum estrogen, which is bound, is estradiol.

Estriol (E3)

Estriol is less potent than E2. It is produced in large quantities by the placenta during pregnancy, and in substantial quantities by regularly cycling, healthy, premenopausal women. E3 has been shown to have antiproliferative and immunomodulatory activity.

A study of 26 non-pregnant, premenopausal women showed the fractionated serum estrogen concentration of estriol in every case was at least three times as great as the concentration of estradiol and estrone combined. This value suggests significant biological activity for this "weaker" hormone. (Wright, Schliesman et al. 1999)

Causes of Estrogen Imbalance in Women

Increased levels of Estrogens

hormone replacement therapy

“herbal” menopause preparations may contain estrogens

Normal pregnancy

DHEA, Testosterone or Pregnenalone supplementation

Estrogen hyperexcretion

Ovarian or adrenocortical tumors

Adrenocortical hyperplasia

Metabolic or hepatic disorder

Infertility treatment

Decreased levels of Estrogen

Menopause / perimenopause

Primary ovarian insufficiency (Stein-Leventhal syndrome)

Secondary ovarian insufficiency (pituitary or adrenal hypofunction)

Ovarian agenesis

High dose cortisol / prednisone

Anorexia nervosa

Metabolic disturbances

Causes of Increased Levels of Estrogens in Men:

- Testosterone, DHEA or pregnenalone supplementation
- Excessive aromatase activity (may be seen with obesity)
- Testicular, adrenal, or hepatic tumors
- Hepatic cirrhosis

- Adult onset adrenal hyperplasia, Adrenal neoplasm
- Consider insulin resistance, as this is sometimes associated with overly active aromatization (testosterone -> E2) in men

Estrogen Supplementation

Dose: 1.25 -2.5mg/ 0.1ml daily

Formulation: Biest (E2 and E3) or Triest (E1,E2,E3)

Route of Administration: Transmucosal to the vaginal labia.

Comments: 2-4 wks adjust based upon sx and hormone profile results

It is preferred to maintain levels in mid-range of the given laboratory reference ranges.

Symptoms of Too High Dosing

- Headache
- Breast tenderness
- Breakthrough Bleeding

Symptoms of Too Low Dosing

- Hot flashes
- Night sweats
- Breakthrough bleeding

If it is necessary to increase estrogen dosing, increasing the dose of progesterone is also recommended in order to avoid endometrial hyperplasia.

Depression

Estrogen replacement therapy may be beneficial for depression.

Estrogen augmentation of antidepressant medication has been an effective treatment in a subgroup of women experiencing affective symptoms during perimenopause. It has been suggested that estrogen facilitates serotonergic transmission in brain regions involved in mood disorders. In women with perimenopausal depression, physiologic brain changes in the right frontal region during estrogen augmentation were associated with remission of depression. (Morgan, Cook et al. 2007)

Although depression is not a uniform accompaniment of the menopausal transition, in some

women age-related changes in ovarian estrogen production may alter central nervous system function and predispose them to develop depression. (Schmidt 2005)

Many women stopped hormone therapy and reported onset of depression within 3 weeks of hormone discontinuation after than before publication of the Women's Health Initiative. Depression in most women responded to reinstitution of estrogen or initiation or increase in antidepressant dose. Discontinuation of hormone therapy appears to be associated with the rapid recurrence of depression in some women with a history of depression. (Stewart, Rolfe et al. 2004)

Memory Loss

Estradiol can improve motor skills by potentiating cerebellar plasticity and synapse formation. (Andreescu, Milojkovic et al. 2007)

Estrogen can improve spatial memory consolidation in aged females and that this effect can be attenuated by progesterone. (Harburger, Bennett et al. 2007)

The Women's Health Initiative Memory Study (WHIMS) found that among postmenopausal women aged 65 years or older, estrogen plus progestin did not improve cognitive function when compared with placebo. While most women receiving estrogen plus progestin did not experience clinically relevant adverse effects on cognition compared with placebo, a small increased risk of clinically meaningful cognitive decline occurred in the estrogen plus progestin group. (Rapp, Espeland et al. 2003)

Estrogen may have positive effects on oral reading and verbal memory in midlife, postmenopausal women. A study found that daily treatment with conjugated equine estrogens (Premarin, 1.25 mg; Wyeth-Ayerst Labs, Philadelphia, PA, USA) showed better oral reading and verbal memory performance than the placebo group. (Shaywitz, Naftolin et al. 2003)

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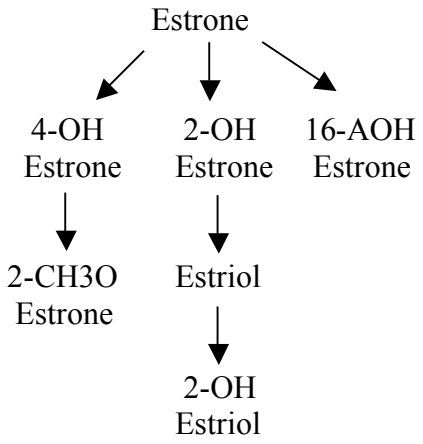
Estriol

By Ronald Steriti, ND, PhD

Estriol (E3) is a metabolite of estrone (E1). Estriol is considered a weak estrogen (when compared to estrone or estradiol). Triple estrogen contains 80% estriol, 10% estrone, and 10% estradiol. (Head 1998)



One milligram (mg) intravaginal estriol resulted in serum levels equivalent to 10 mg of the orally administered hormone. Vaginal application circumvents the first pass through the liver, where a large portion of estriol is immediately conjugated, an action believed to contribute to the short duration of action of the orally-administered hormone.

Estriol appears to have both estrogenically antagonistic and agonistic effects. When given alone, it generally exerts an estrogenic effect, the strength of which depends on the dosage. When given in conjunction with estradiol, it appears to exert antagonistic effects.

Estriol may be effective for several conditions, including:

> Menopause-related urinary incontinence, urgency, and persistent urinary tract infections (UTIs). (Dessole, Rubattu et al. 2004)
>
> Maintaining skin elasticity
>
> Immune modulation in multiple sclerosis (Soldan, Alvarez Retuerto et al. 2003) (Sicotte, Liva et al. 2002)

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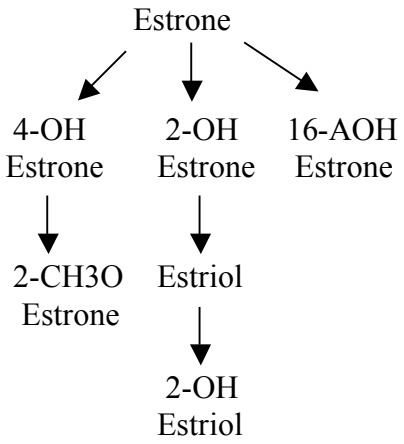
2-hydroxyestrone / 16-hydroxyestrone Ratio

By Wendy L. Ellis, ND and Ronald Steriti, ND, PhD

2-hydroxyestrone and 16-hydroxyestrone are Phase I metabolites of Estrone (E1). Their ratio is of clinical significance in pre and peri-menopausal women. In post-menopausal women it does not have the same clinical significance. It is, however, hypothesized that the 2/16 ratio is important in menopausal women who are on hormone replacement therapy (HRT).



Breast Cancer

In one study, significantly lower values of the 2/16 ratio and higher levels of 16-alpha-hydroxyestrone were observed in tumor tissues, reinforcing the hypothesis that an imbalance of 2- and 16-alpha-hydroxylation may be implicated in breast cancer development. Additionally, 16-alpha-hydroxyestrone levels are observed in larger amounts in carcinogenic breast tumors, however, when the tumors have higher amounts it correlates to a prolonged survival of breast cancer patients. (Castagnetta, Granata et al. 2002)

Another study's analysis of 16-alpha-hydroxyestrone in pre and post-menopausal women indicates that it is a strong risk factor for breast cancer. (Kabat, Chang et al. 1997) (Kabat, O'Leary et al. 2006)

The risk of breast cancer, in particular the estrogen receptor-positive type, was enhanced among postmenopausal women using estradiol-based HRT and among those who had a high 2-OHE concentration. (Wellejus, Olsen et al. 2005)

A common CYP1B1 polymorphism is associated with an increased 2/16 urinary estrone ratio.

(Paracchini, Pedotti et al. 2005)

Rheumatoid Arthritis And Systemic Lupus Erythematosus

Patients with rheumatoid arthritis and systemic lupus erythematosus have increased renal excretion of mitogenic estrogens in relation to endogenous antiestrogens. In patients with RA and SLE, the magnitude of conversion to the mitogenic 16-alpha-hydroxyestrone is greatly upregulated, which likely contributes to maintenance of the proliferative state in these diseases. (Weidler, Harle et al. 2004)

Bone Mineral Density

Increased hydroxylation to relatively non-estrogenic metabolites 2-hydroxyestrone (2OHE1) and 2-methoxyestrone (2MeOE1) was associated with low bone mineral density (BMD), while increased hydroxylation to the potent 16-alpha-hydroxyestrone and weakly estrogenic estriol was associated with higher BMD. (Armamento-Villareal, Napoli et al. 2004)

Thyroid disorders

Increased 16alpha-hydroxyestrone activity compared to 2-hydroxyestrone activity appears to be associated with proliferative thyroid disease.

A case-control study of 49 subjects with proliferative thyroid disorders found that fifty-one percent (25 of 49) of the cases had a low 2/16 ratio compared to 31% (15 of 49) in the control group while 20% (10 of 49) of the control group had a high 2/16 ratio as compared to 8% (4 of 49) in the case group (P value < 0.05). (Chan, Sepkovic et al. 2006)

Improving the 2/16 ratio

Diindolylmethane

Dietary indoles, present in brassica plants such as cabbage, broccoli, and brussel sprouts, have been shown to provide potential protection against hormone-dependent cancers. 3,3'-Diindolylmethane (DIM) is under study as one of the main protective indole metabolites. DIM-treated subjects, relative to placebo, showed a significant increase in levels of 2-OHE1, DIM, and cortisol, and a non-significant increase of 47% in the 2 /16 ratio from 1.46 to 2.14. The conclusion in this pilot study was that DIM increased the 2-hydroxylation of estrogen urinary metabolites. (Dalessandri, Firestone et al. 2004)

In another study, the percentage change in 2/16 urinary ratio, to a more favorable ratio, after indole treatment, was found to be significant. (Paracchini, Pedotti et al. 2005)

Indole-3-carbinol

One study found the ratio of urinary estrogens, 2OHE1/E3, was significantly increased in

obese women following indole-3-carbinol (400 mg for two months), reflecting induction of 2-hydroxylation in these women. (Michnovicz 1998)

Flaxseed

Flaxseed is a rich source of dietary lignans. Forty-three postmenopausal women consumed 7.5 g/day of ground flaxseed for 6 wk, followed by 15 g/day for an additional 6 wk. The mean urinary level of 16alpha -hydroxyestrone (16alpha -OHE1) was higher at the end of 12 wk compared to baseline (change of 1.32 ug/day, P = 0.02). There was no significant change in 2-OHE1 excretion. Mean urinary excretion of 2-methoxyestradiol was also lower at 12 wk than at baseline (P = 0.03). (Sturgeon, Volpe et al. 2010)

Sesame

Sesamin, a sesame lignan, was recently reported to be converted by intestinal microflora to enterolactone, a compound with estrogenic activity and also an enterometabolite of flaxseed lignans, which are known to be phytoestrogens. Whether sesame can be a source of phytoestrogens is unknown.

Twenty-six healthy subjects attended, and 24 completed, this randomized, placebo-controlled, crossover study. Half of them consumed 50 g sesame seed powder daily for 5 wk, followed by a 3-wk washout period, then a 5-wk 50-g rice powder placebo period. The other half received the 2 supplements in reverse order. Serum sex hormone-binding globulin and urinary 2-hydroxyestrone (n = 8) increased significantly by 15 and 72%, respectively, after sesame treatment. (Wu, Kang et al. 2006)

Prozac

A preliminary study of the effect of fluoxetine treatment on the 2:16-alpha-hydroxyestrone ratio in young women. In three of the four women who were nonsmokers, the 2OHE1:16OHE1 ratio was significantly higher after 5 weeks of fluoxetine therapy. (This is not an endorsement for prozac, purely informational) (Thompson, Kirshner et al. 2003)

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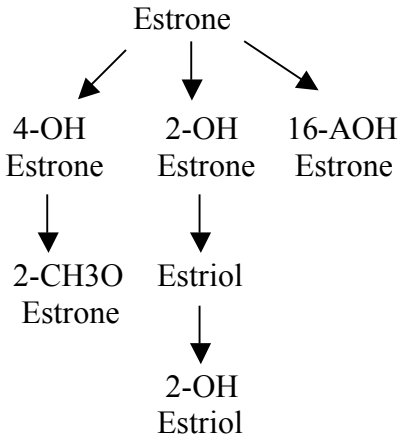
2-Methoxyestrone

By Ronald Steriti, ND, PhD

2-Methoxyestrone is a Phase II metabolite of estrone generated in the liver by UDP glucuonyltransferase via glucuronidation.



2-Methoxyestradiol (2-ME), a naturally occurring metabolite of 17beta-estradiol, is highly cytotoxic to a wide range of tumor cells but is harmless to most normal cells. However, 2-ME reduced osteoclast number by more than 95% and induced apoptosis in three cultured osteoclast model systems. (Maran, Gorny et al. 2006)

Recent studies indicate that women with predominant estrogen metabolism through the 2-hydroxyl (inactive) pathway have lower bone mineral density (BMD) compared with those with predominant 16-alpha-hydroxylation (active). (Napoli, Donepudi et al. 2005)

Sulfamoylation of 2-methoxyestrone (2-MeOE1) was shown previously to enhance its potency as an anti-proliferative agent against breast cancer cells. (Newman, Leese et al. 2004)

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2-methoxyEstradiol

By Ronald Steriti, ND, PhD

2-methoxy-estradiol is a metabolite of estrogen that has shown potent anti-proliferative and anti-angiogenic activity for various cancer cells, including:

Breast, (Fukui and Zhu 2009) (James, Murry et al. 2007) (Newman, Ireson et al. 2006) (Liu and Zhu 2004) (Raobaikady, Purohit et al. 2003)

Ovarian, (Day, Newman et al. 2003)

Prostate, (Van Veldhuizen, Ray et al. 2008) (Sweeney, Liu et al. 2005) (Sato, Fukuhara et al. 2005)

Adrenal (Montoya, Brown et al. 2008)

Thyroid (Roswall, Bu et al. 2006) (Wang, Myc et al. 2000)

Multiple myeloma (Rajkumar, Richardson et al. 2007)

2-methoxyestradiol may also be effective against inflammatory diseases such as rheumatoid arthritis. (Plum, Park et al. 2009) (Issekutz and Sapru 2008)

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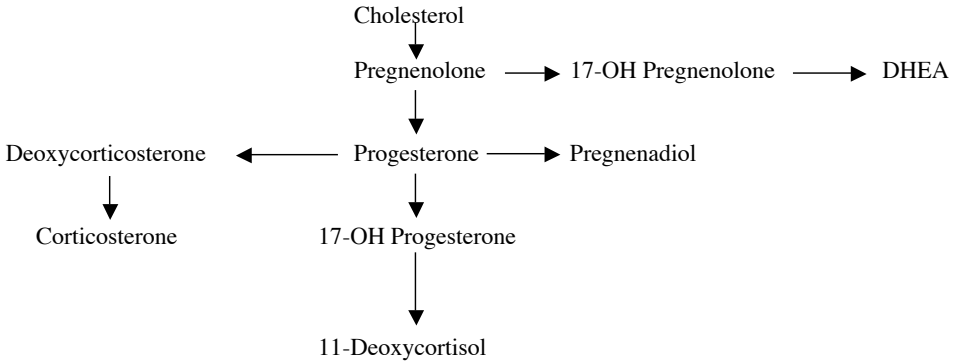
Progesterone

By Wendy L. Ellis, ND and Ronald Steriti, ND, PhD

Ovulating women naturally secrete progesterone from the ovary during the second two weeks of the menstrual cycle. Menopausal females secrete progesterone in smaller doses than ovulating women. It is a common misconception that progesterone should not be supplemented in females who have undergone a hysterectomy because progesterone receptors are found throughout the body. The bone, CNS, white blood cells, lungs, uterus, breast and colon all have progesterone receptors.

Pregnanediol is the major progesterone metabolite, and is present in appreciable quantities in the urine. Progesterone is not excreted in urine in detectable quantities. Thus, values of progesterone are very well "tracked" by pregnanediol values, and this value is an adequate reflection of free progesterone.



Progesterone Supplementation

Female

25-100mg qd, cream; Translabial or vaginal (preferred applications)

25-100mg qd hs; Days 11-25 of cycle; troche, pill, spray (oral)

Male

50-100mg qd; Troche, pill or spray (Oral, sublingual)

100mg/g; 1-4 gm qd; cream; Transdermal *

* Transdermal may be beneficial for milder forms of hard or enlarged prostate

Progesterone does not have the same tendency to metabolize to other hormones if taken orally. However, a vaginal application is recommended when possible to mimic nature as closely as possible. Oral progesterone is used more frequently when insomnia is of concern, as larger doses of oral progesterone at night contribute to better sleep patterns.

With estrogen doses of 1.25mg, 25mg of progesterone should be adequate. 50mg may be required in some cases. If breakthrough bleeding occurs, then decrease estrogen. If symptoms recur, maintain original estrogen dose and increase progesterone.

Causes of Progesterone Imbalance in Women

Increased Levels

- Progesterone supplementation
- Pregnancy
- Diffuse thecal luteinization
- Luteinized granulosa
- Theca-cell tumors

- Metastatic ovarian cancer
- High dose pregnenalone supplementation

Decreased Levels

- Peri-menopause / menopause
- amenorrhea
- anovulation

Causes of Increased Progesterone in Males

- High dose pregnenalone supplementation
- Testicular cancer

Testosterone

By Wendy L. Ellis, ND and Ronald Steriti, ND, PhD

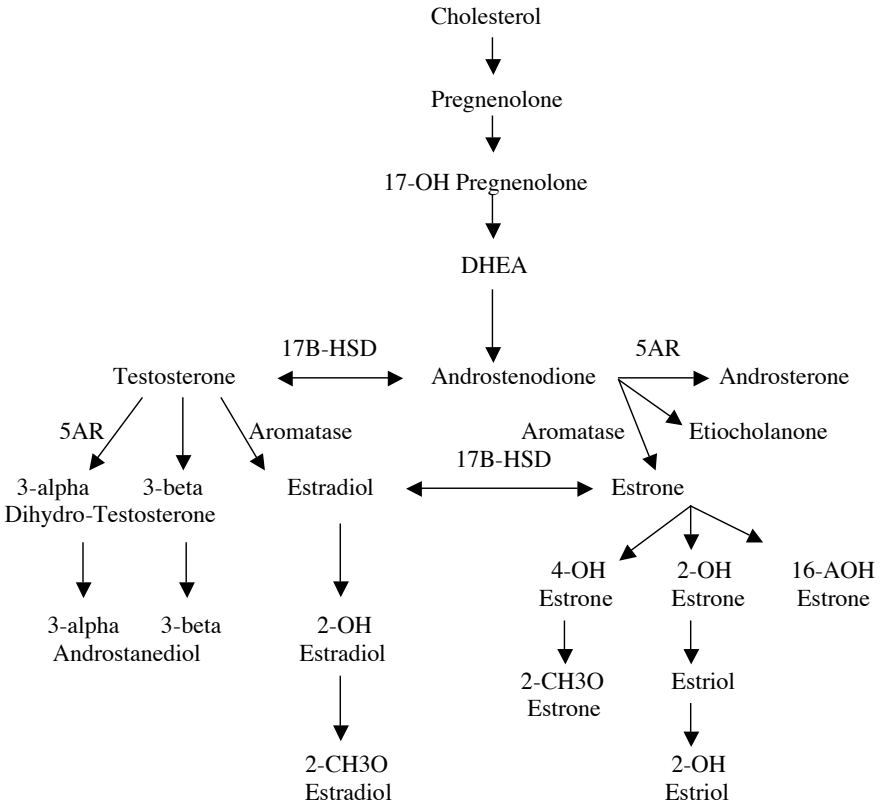
Testosterone is the major androgen in the body. It is converted to dihydrotestosterone by 5-alpha-reductase, and to estradiol by aromatase. Overall estrogen levels and individual estrogen levels (such as E2) should be monitored with use of testosterone to ensure aromatization to estrogen is not occurring. Oral and troche forms of testosterone have been clinically observed to convert to E2 compared to transmucosal.

Testosterone Metabolites

5-alpha-DHT is an active metabolite of testosterone dependant upon the 5-alpha-reductase enzyme.

5-beta-DHT is an active metabolite of testosterone dependant upon the 5-beta-reductase enzyme.

5-alpha-androstanediol and 5-beta-androstanediol are the direct metabolites of 5-alpha and 5-beta-DHT, respectively. These metabolites are dependant upon the 3-alpha-hydroxysteroid dehydrogenase enzyme.



Testosterone Supplementation

Females: 1 – 5 mg qd; cream; Transmucosal

Males: 25-50 mg qd; cream; Transmucosal (scrotum or rectal)

In men, always monitor PSA and % Free PSA when supplementing testosterone within 6 weeks of treatment initiation.

Causes of Testosterone Imbalance in Women

Increased Levels

- Testosterone, pregnenalone, DHEA supplementation
- Polycystic ovaries

- Insulin Resistance
- Congenital adrenal hyperplasia
- Adult onset adrenal hyperplasia
- Ovarian neoplasm

Decreased Levels

- Declines with age.

Causes of Testosterone Imbalance in Men

Increased Levels

- testosterone, pregnenalone, DHEA supplementation
- XYY syndrome
- Aromatase inhibitors - Aromasin (Exemestane) Arimidex (Anastrozole) ,Femera (Letrozole).

Decreased Levels

- declines at variable range with age
- excessive aromatase activity (testosterone -> estradiol) *
- hypogonadism
- Klinefelter syndrome
- marijuana use

Depression

Studies suggest that testosterone (TT) replacement may have an antidepressant effect in depressed patients. Seven studies (N=364) were identified that included a placebo-control group in a double-blind design. Meta-analysis of the data from these seven studies showed a significant positive effect of TT therapy on Hamilton Rating Scale for Depression response in depressed

patients when compared with placebo (z=4.04, P<0.0001). Subgroup analysis also showed a significant response in the subpopulations with hypogonadism (z=3.84, P=0.0001) and HIV/AIDS (z=3.33, P=0.0009) as well as in patients treated with TT gel (z=2.32, P=0.02). (Zarrouf, Artz et al. 2009) (Orengo, Fullerton et al. 2004) (Carnahan and Perry 2004)

Memory Loss

Testosterone improves spatial and verbal memory in healthy older men may help decrease the memory problem of old age. (Lim, Flicker et al. 2003) (Cherrier, Asthana et al. 2001)

Testosterone supplementation may benefit selective cognitive functions in men with Alzheimer disease and mild cognitive impairment. (Cherrier, Matsumoto et al. 2005)

Sex steroid loss and replacement have effects on specific cognitive processes in older men. Furthermore, estrogen has the potential to reverse the neurotoxic effects on memory performance caused by androgen deprivation. (Beer, Bland et al. 2006)

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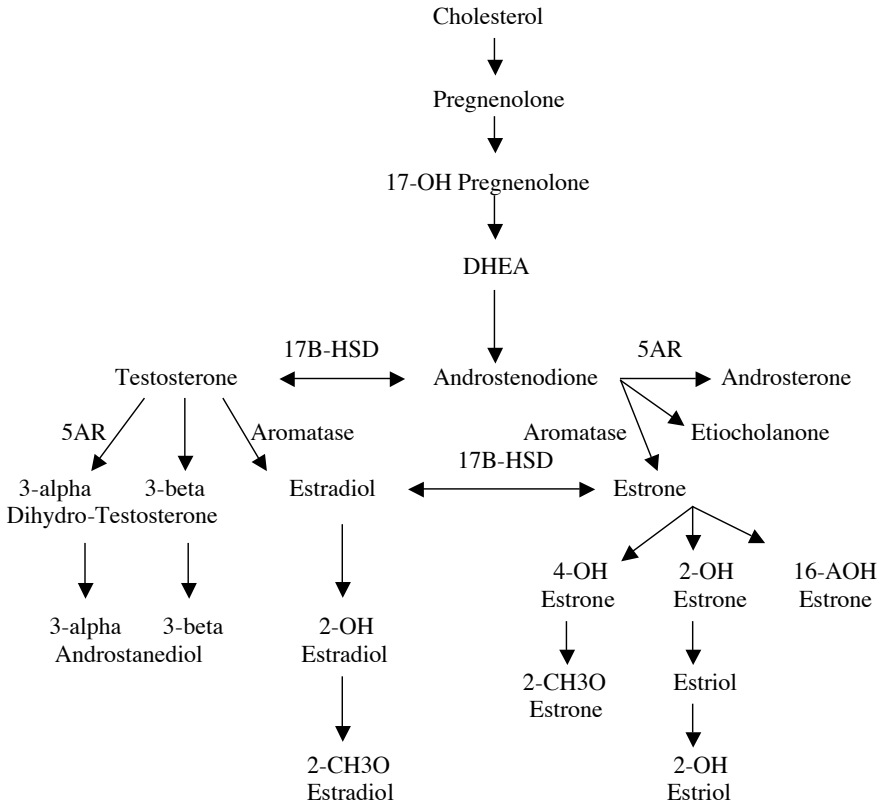
DHEA

By Wendy L. Ellis, ND and Ronald Steriti, ND, PhD

Dehydroepiandrosterone (DHEA) is an androgen precursor and excitability neurosteroid. Levels peak around 25-30 years of age and decline thereafter. Levels are decreased in adrenal insufficiency and unipolar depression, and increase in adrenal hyperplasia. (2001) (Arlt 2004)

DHEA is metabolized down many different pathways. It is converted to the intermediate metabolite androstenedione, which may become testosterone, estrone, androsterone, or etiocholanolone. For a male patient with BPH or prostate concerns, DHEA should be closely monitored to evaluate the possibility of aromatization to estrogens or metabolism to testosterone, and thus, DHT. Chrysin or "Myo-mins" are aromatase inhibitors that may be used if aromatization to estrogens is occurring. Saw palmetto is a 5-alpha-reductase inhibitor that may be used to inhibit conversion of testosterone to DHT and androstenedione to androsterone.



DHEA Supplementation

Females: 25-50 mg qd; Troche (sublingual) or Cream (Transmucosal)

Males: 10-15 mg qd; Troche (sublingual) or Cream (Transmucosal)

The high end of dosing is considered in adrenal dysfunction.

Causes of DHEA Imbalance In Women

Increased DHEA in Women

- DHEA supplementation
- Tribulus or Rhodiola supplementation
- Congenital adrenal hyperplasia
- Adult onset adrenal hyperplasia
- Adrenal neoplasm
- High dose pregnenolone supplementation

Decreased DHEA in Women

- Declines with age (> 35 y.o.)
- Prednisone ingestion
- Adrenal insufficiency

Causes of DHEA Imbalance in Men

Increased DHEA in Men

- DHEA or pregnenoalone supplementation
- Tribulus or Rhodiola supplementation
- Congenital adrenal hyperplasia
- Adult onset adrenal hyperplasia
- Adrenal neoplasm

Decreased DHEA in Men

- Declines with age (> 35 y.o.)
- Prednisione ingestion
- Adrenal insufficiency

Depression

Dehydroepiandrosterone (DHEA) and its sulfate, DHEA-S, are plentiful adrenal steroid hormones that decrease with aging and may have significant neuropsychiatric effects. (Wolkowitz, Reus et al. 1997)

Hypercortisolaemia has been well described in depression and may be a factor associated with treatment resistance. The role of the more abundant adrenal steroid dehydroepiandrosterone (DHEA) has been recently investigated, with some evidence that it may have an antiglucocorticoid effect. This study measured cortisol, DHEA and their ratio in treatment resistant depression (TRD) and healthy controls and also related these measures to treatment outcome. In addition to cortisol, the cortisol/DHEA ratio is raised in TRD; thus, there is no evidence that DHEA levels could negate the increased glucocorticoid activity in TRD. Patients with a more abnormal cortisol/DHEA ratio, possibly indicating greater biological dysfunction, responded preferentially to inpatient therapy, though the raised cortisol/DHEA ratio persisted after response. The cortisol/DHEA ratio is stable throughout the day and may be a more practical biological marker of TRD. (Markopoulou, Papadopoulos et al. 2009)

Androsterone and Etiocholanolone

Androsterone and etiocholanolone are terminal androgen metabolites, useful in monitoring DHEA supplementation. 5-alpha-reductase and 3-alpha-HSD are the enzymes involved in metabolism to androsterone. 5-beta-reductase and 3-alpha-HSD are the enzymes involved in metabolism to etiocholanolone.

** When looking at the metabolites, look for patterns in the enzymatic pathways. For example, if the patient is taking a 5-alpha-reductase inhibitor, all of its metabolites will be decreased, and the reaction will be shunted down another metabolic pathway.*

Causes of Androsterone and Etiocholanolone Imbalance in Men and Women

Increased Levels

- DHEA, pregnenalone supplementation
- Androgen producing gonadal tumors
- Congenital adrenal hyperplasia
- Adult onset adrenal hyperplasia
- Serious illness/ shock - burns, etc.

Decreased Levels

- Declines as DHEA declines
- adrenal insufficiency
- anorexia nervosa
- panhypopituitarism

Occasionally you will note adrosterone increased and etiocholanolone decreased. In this circumstance, it is important to look at the enzymes driving the metabolic pathways, and determine the cause for the imbalance.

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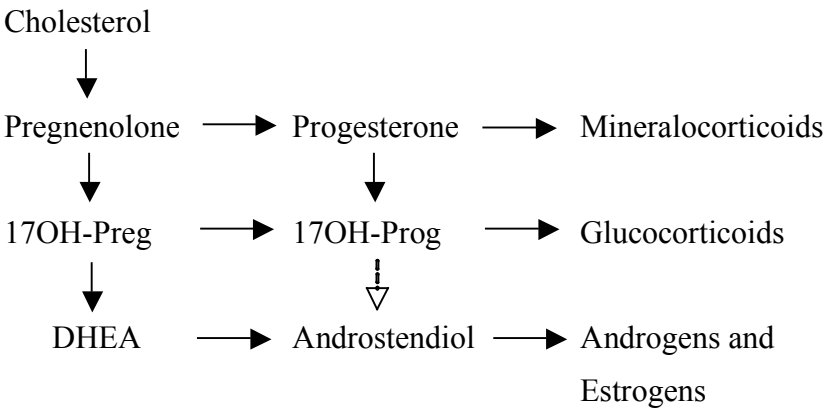
Pregnenolone

By Ronald Steriti, ND, PhD

Pregnenolone is a steroid hormone involved in the steroidogenesis of progesterone, mineralocorticoids, glucocorticoids, androgens, and estrogens.



Pregnenolone and its sulfate, like dehydroepiandrosterone (DHEA) and its sulfate and progesterone, belong to the group of neurosteroids that are found in high concentrations in certain areas in the brain, and are synthesized there. Neurosteroids affect synaptic functioning, are neuroprotective, and enhance myelinization. (Wojtal, Trojnar et al. 2006)

Pregnenolone is being studied for potential therapeutic use in:

Spinal cord injury (Guth, Zhang et al. 1994)

Alzheimer's disease (Akan, Kizildag et al. 2009) (Kato-Negishi and Kawahara 2008)

Pregnenolone and its sulfate ester are under investigation for their potential to improve cognitive and memory functioning. (Vallee, Mayo et al. 2001)

Pregnenolone sulfate was shown to activate the Transient Receptor Potential M3 ion channel in hepatocytes and pancreatic islets causing calcium entry and subsequent insulin release. (Wagner, Loch et al. 2008)

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5-Alpha Reductase

By Wendy L. Ellis, ND and Ronald Steriti, ND, PhD

5-alpha-reductase is the enzyme that converts:

Testosterone into 3-alpha-dihydro-testosterone

Androstenodione into andosterone

Cortisol into allo-tetrahydro-cortisol

Two ratios are commonly used to assess 5-alpha-reductase activity:

Andosterone : Etiocholanone

Allo-tetrahydro-cortisol : tetrahydro-cortisol

Elevated 5-alpha-reductase activity is associated with polycystic ovary syndrome and hirsutism in women; benign prostatic hypertrophy and premature baldness in men; and obesity and insulin resistance in both genders. Low 5-alpha-reductase activity may result in reduced conversion of testosterone to DHT and under-virilization in men. (Vassiliadi, Barber et al. 2009)

Obesity and insulin resistance are related with elevated 5-alpha-reductase activity. (Tomlinson, Finney et al. 2008)

Natural Therapies

5-alpha reductase inhibitors include:

Gamma-linolenic and eicosapentaenoic acids (GLA and EPA) (Pham and Ziboh 2002)

Vitamin D3 (Lou, Murtola et al. 2005)

Zinc. (Om and Chung 1996) (Stamatiadis, Bulteau-Portois et al. 1988)

Serenoa repens (Saw palmetto) (Abe, Ito et al. 2009) (Habib, Ross et al. 2005) (Raynaud, Cousse et al. 2002) (Bayne, Donnelly et al. 1999)

Zinc deficiency reduces circulating luteinizing hormone and testosterone concentrations, alters hepatic steroid metabolism, and modifies sex steroid hormone receptor levels, thereby contributing to the pathogenesis of male reproductive dysfunction. (Om and Chung 1996)

Lauric acid, oleic acid, myristic acid, and linoleic acid, major constituents of Saw palmetto extract, exerted binding activities of alpha(1)-adrenergic, muscarinic and 1,4-DHP receptors and inhibited 5alpha-reductase activity. (Abe, Ito et al. 2009)

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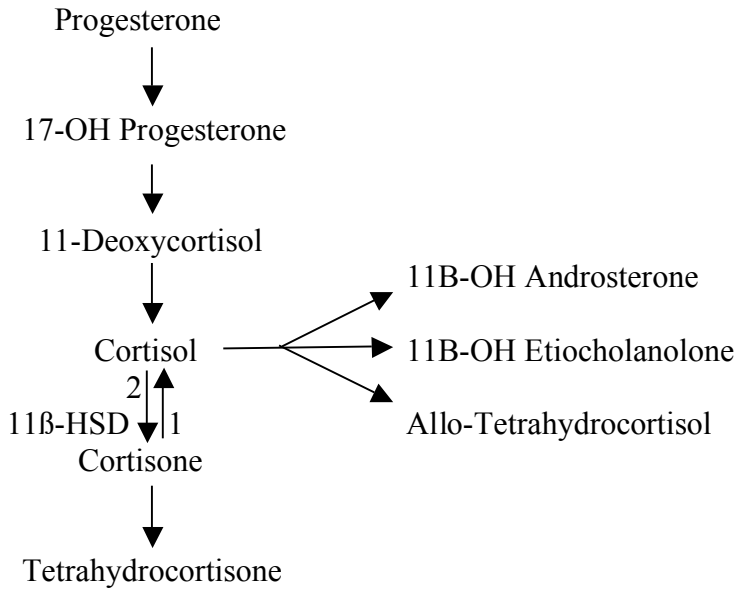
11-Beta-Hydroxysteroid Dehydrogenase

By Wendy L. Ellis, ND and Ronald Steriti, ND, PhD

The intracellular enzyme 11-beta-hydroxysteroid dehydrogenase (11ß-HSD) catalyzes the inter-conversion between biologically active cortisol and inactive cortisone. There are two distinct isozymes: 11-beta-HSD type I and II.



Causes of Increased 11-beta-hydroxysteroid dehydrogenase Activity:

- Obesity
- Insulin resistance

Causes of Decreased 11-beta-hydroxysteroid dehydrogenase Activity:

- Apparent mineralocorticoid excess symptoms
- Licorice (glycyrrhetinic acid) supplementation

- Carbenoxolone ingestion
- Dithiocarbamates inhibit type II 11 beta dehydrogenase, but not type I

11-Beta-HSD Type I

Type I acts mainly as a reductase producing active cortisol from cortisone in cells. It amplifies the effect of glucocorticoids, whereby free cortisol is generated from the relative excess of circulating free cortisone. This enzyme also plays an important role in the xenobiotic carbonyl compound detoxification processes. 11-beta-HSD type I is expressed in a wide array of tissues, with highest levels in the liver and adipose.

11-Beta-HSD Type II

11-beta-HSD type 2 functions as a dehydrogenase inactivating cortisol into cortisone. It irreversibly catalyzes the dehydrogenation of active 11-beta-hydroxycorticoids before they occupy mineralocorticoid receptors (MR) and thus, allows for aldosterone selectivity for inherently nonselective MR. 11-beta-HSD type 2 is expressed in a wide array of tissues. Highest levels are found in mineralocorticoid target cells such as the renal and outer medullary collecting ducts

Disease Associations

Cushing's Syndrome

Both animal and human studies have demonstrated that alterations in 11-betaHSD type I activity in liver and adipose tissues are associated with metabolic syndrome, possibly reflecting a tissue-specific (omental) Cushing's syndrome. (Anagnostis, Athyros et al. 2009) (Schnackenberg 2008)

Obesity

Increased adipocyte 11-beta-HSD type I is a common mechanism for visceral obesity. (Wiegand, Richardt et al. 2007)

One study found that alterations in 11HSD1 and hepatic 5alpha-reductase activity are associated with generalized, rather than central, obesity in humans. Indices of obesity (body mass index, whole-body percentage fat, waist/hip ratio) were associated with higher urinary excretion of 5alpha- and 5beta-reduced cortisol metabolites (for percentage fat, $P < 0.05$ and $P < 0.01$, respectively) and increased adipose 11HSD1 activity ($P < 0.05$). (Westerbacka, Yki-Jarvinen et al. 2003)

Diabetes

Pharmacological inhibition of 11-beta-HSD type I activity provides an interesting mechanism for the possible development of therapeutic agents to treat type-2 diabetes mellitus. (Hughes, Webster et al. 2008)

Hypertension

Mice deficient in 11HSD type 2 have hypertension and impaired endothelial nitric oxide activity. 11HSD2 may influence vascular function by directly by limiting glucocorticoid-mediated inhibition of endothelium-derived nitric oxide. (Christy, Hadoke et al. 2003) (Yang and Zhang 2004)

A recent study found that a mere three-fold increase in the concentration of the natural glucocorticoid cortisol (from 30 to 100 nmol/L) significantly decreased the expression level of eNOS in human endothelial cells. (Liu, Mladinov et al. 2009)

Atherosclerosis

Selective inhibitors of 11beta-hydroxysteroid dehydrogenase type 1 have been shown recently to ameliorate cardiovascular risk factors and inhibit the development of atherosclerosis. (Hadoke, Iqbal et al. 2009)

There is also promising studies that indicate inhibition ameliorates metabolic syndrome and prevents progression of atherosclerosis in mice. (Hermanowski-Vosatka, Balkovec et al. 2005) (Lloyd, Helmering et al. 2009)

Metabolic Syndrome

Inhibition of 11ß-HSD is currently being explored to control metabolic syndrome. (Morton and Seckl 2008; Morton 2009)

One study found 11beta-HSD1 expression in lean women was found to be significantly lower than in lean males. The up-regulation associated with obesity may be relatively more devastating in women than in men, and may help explain the higher relative risk of cardiovascular disease in women suffering from the metabolic syndrome. (Paulsen, Pedersen et al. 2007)

Inflammation

Glucocorticoids have an anti-inflammatory effect. In general, 11ß-HSD1 expression is increased and 11ß-HSD2 decreased by pro-inflammatory stimuli or during inflammation. (Chapman and Seckl 2008) (Chapman, Coutinho et al. 2009)

Colon Cancer

A recent study showed that inhibition of 11beta-hydroxysteroid dehydrogenase type II selectively

blocks the tumor COX-2 pathway and suppresses colon carcinogenesis in mice and humans. (Zhang, Xu et al. 2009)

Osteoporosis

Urinary measures of 11beta-HSD1 activity predict the response of bone formation markers to glucocorticoids, and this appears to reflect increased generation of active glucocorticoids within osteoblasts. (Cooper, Blumsohn et al. 2003) (Cooper 2008)

Glaucoma

One study found that inhibition of 11beta-hydroxysteroid dehydrogenase type 1 lowers intraocular pressure in patients with ocular hypertension. (Rauz, Cheung et al. 2003)

One study found that primary open-angle glaucoma exhibit increased peripheral vascular sensitivity to glucocorticoids. Patients with primary open-angle glaucoma exhibited a greater cutaneous vasoconstrictor response to glucocorticoids than patients with ocular hypertension and normal subjects (20.7 +/- 3.1 vs. 8.5 +/- 4.4 and 8.6 +/- 4.5 arbitrary units, respectively; $P < 0.05$ in each case). (Stokes, Walker et al. 2003)

Polycystic Ovary Syndrome

One study found that lean polycystic ovary syndrome had (among other endocrine/ hormonal abnormalities) reduced 11beta-HSD1 activities when compared with lean controls. (Tsilchorozidou, Honour et al. 2003)

An earlier study found no relationship. (Chin, Shackleton et al. 2000)

Therapies

Diet

Preliminary research shows that diets high in fat or simple carbohydrates affect 11beta-HSD in ways that promote obesity. (London and Castonguay 2009)

Sucrose and Fructose

One study showed that that sucrose can promote increased 11beta-HSD-1 and hexose-6-phosphate dehydrogenase message in mesenteric fat while concomitantly decreasing 11beta-HSD-1 message and increasing exose-6-phosphate dehydrogenase message in liver. (London, Lala et al. 2007)

Fructose-6-phosphate increased the activity of 11beta-HSD1 reductase (McCormick, Wang et al. 2008)

NADPH

Reduced NADPH is a co-factor for 11beta-HSD-1. (Agarwal 2003)

11beta-HSD1 acts predominantly as an oxoreductase using NADP(H) as a cofactor to generate cortisol, whereas 11beta-HSD2 acts exclusively as an NAD-dependent dehydrogenase, inactivating cortisol to cortisone. (Walker and Stewart 2003)

DHEA

One study showed that DHEA induces a shift from 11beta-HSD1 to 11beta-HSD2 expression, increasing conversion from active to inactive glucocorticoids. (Balazs, Schweizer et al. 2008)

Licorice

18beta-glycyrrhetinic acid (GA), a metabolite of the natural product glycyrrhizin, is not selective and inhibits both 11beta-HSD1 and 11beta-HSD2. 18alpha-GA selectively inhibits 11beta-HSD1 but not 11beta-HSD2. This is in contrast to 18beta-GA, which preferentially inhibits 11beta-HSD2. (Classen-Houben, Schuster et al. 2009)

Inhibition of 11 beta-dehydrogenase after licorice ingestion results in cortisol acting as a potent mineralocorticoid. (Stewart, Wallace et al. 1990)

A study published in *Lancet* showed that in seven normal subjects given licorice, sodium retention is associated with a significant change in cortisol metabolism indicating inhibition of 11-beta-hydroxysteroid dehydrogenase. (Stewart, Wallace et al. 1987)

Glycyrrhizic acid (glycyrrhetinic acid glucuronide), when given orally to rats, partially inhibited renal 11 beta-dehydrogenase. (Monder, Stewart et al. 1989)

A recent article warns that licorice is contraindicated in patients with a 11ß-HSD type 2 mutation. (Harahap, Sasaki et al. 2009)

Vitamin D3

One study found that cortisol production was dose dependently augmented (2- to 6-fold, $p < 0.001$) by 1,25-dihydroxyvitamin D3 (0.1 to 10 nM). 1,25-Dihydroxyvitamin D3 dose dependently increased 11beta-HSD 1 expression up to 2-fold ($p < 0.01$). (Morris and Zemel 2005)

Vitamin A

One study showed that retinoic acid (vitamin A) stimulates the expression of 11beta-hydroxysteroid dehydrogenase type 2. (Tremblay, Hardy et al. 1999) (Aubry and Odermatt 2009)

Glutathione

One study found that oxidized glutathione (GSSG) attenuated 11beta-HSD1 reductase activity by 40% while reduced glutathione (GSH) activated the reductase in liver. Fat microsomes were unaffected because they lack glutathione reductase. (McCormick, Wang et al. 2008)

Cadmium and Lead

Cadmium, a common environmental pollutant and a major constituent of tobacco smoke, has been identified as a new class of endocrine disruptors with a wide range of detrimental effects on mammalian reproduction. During human pregnancy, maternal cadmium exposure, via the environment and/or cigarette smoking, leads to fetal growth restriction (FGR). One study showed that cadmium reduces human placental 11 beta-HSD2 expression and activity by suppressing HSD11B2 gene transcription. (Yang, Julan et al. 2006)

17-beta-Hydroxysteroid dehydrogenase was reduced to 33%, 38%, and 24% on treatment of lead, cadmium, and co-exposure (Pb + Cd)(Pandya, Pillai et al. 2009)

Male adult Wistar rats treated with cadmium (2.5 mg/kg body wt, five times a week for 4 weeks) showed decreased body weight, paired testicular weight, relative testicular weight, serum testosterone, luteinizing hormone, follicle-stimulating hormone, and testicular total antioxidant capacity (TAC) and protein levels. Testicular steroidogenic enzymes, such as 3beta-hydroxysteroid dehydrogenase (3beta-HSD) and 17beta-hydroxysteroid dehydrogenase (17beta-HSD), and marker enzymes, such as sorbitol dehydrogenase (SDH), lactate dehydrogenase (LDH), acid phosphatase (ACP), alkaline phosphatase (ALP), and glucose-6-phosphate dehydrogenase (G6PD), showed a significant decrease in activities whereas that of gamma-glutamyl transferase was significantly increased after cadmium exposure. The results have revealed that concurrent treatment with diallyl sulfide (DAS), a sulfur-containing volatile compound present in garlic, or zinc restored key steroidogenic enzymes, SDH, LDH, and G6PD and increased testicular weight significantly. DAS restored the TAC level and increased testosterone level and relative testicular weight significantly. Zinc restored testicular protein level and body weight. (Sadik 2008)

Estradiol

One article proposed that inhibition of 11ß-HSD type 1 by estradiol is an explanation for the detrimental effects of postmenopausal hormone replacement therapy. (Cohen 2005)

A recent article showed that 17Beta-estradiol inhibits 11beta-hydroxysteroid dehydrogenase type 1 activity in rodent adipocytes. The authors propose that this provides a novel insight into the anti-obesity mechanism of estrogen. (Tagawa, Yuda et al. 2009)

Growth Hormone and Insulin-like Growth Factor

One study found that growth hormone (GH) and/or insulin-like growth factor (IGF) inhibits 11ß-HSD type 1. Thus, GH deficiency effectively increases cortisol production in key target tissues

including liver and adipose tissue, promoting insulin resistance and visceral adiposity. (Stewart, Toogood et al. 2001) (Agha and Monson 2007)

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17-Beta-Hydroxysteroid Dehydrogenase

By Ronald Steriti, ND, PhD

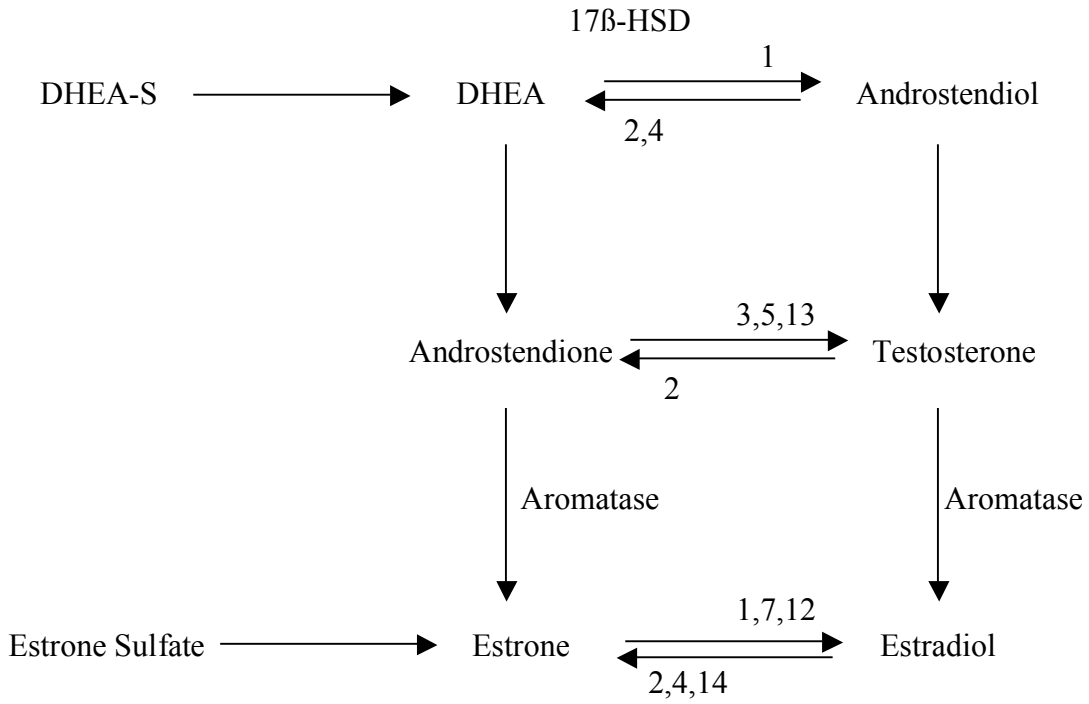
17-beta-hydroxysteroid dehydrogenase (17ß-HSD) converts

- Estrone into Estradiol
- Testosterone to androstenedione

Androstenedione is an intermediate of androsterone, etiocholanolone, and estrone.

Boys with a deficiency of 17ß-HSD fail to form testosterone, androstenediol, and estradiol in a normal manner. At puberty, the plasma concentrations of testosterone and DHT will be low, and plasma androstenedione and estrone will be elevated.

Figure 1: 17ß-HSD Metabolism



Types

There are 14 types of 17ß-HSD enzymes.

17HSD1 catalyzes the reduction of estrone to estradiol with NADP(H) as a cofactor and is mostly expressed in breast tumor tissue. (Miettinen, Mustonen et al. 1996)

17HSD2 catalyzes the oxidation of estradiol to estrone with NAD(H) as a cofactor and is expressed in normal epithelium of the breast but is frequently lost in malignant cells.

High expression of 17HSD1 and amplification of HSD17B1, the gene coding for 17HSD1, as well as low expression of 17HSD2 have been associated with decreased survival in estrogen receptor (ER)-positive breast cancer. (Jansson, Delander et al. 2009)

High expression of 17ß-HSD types 1, 2 and 4 is seen to correlate with bad prognosis in breast, colon and prostate tumors, respectively. (Meier, Moller et al. 2009)

One study found pronounced increases in 17HSD10 levels to 179% in multiple sclerosis and to 573% in Alzheimer disease when compared to the age-matched controls. (Kristofikova, Bockova et al. 2009)

Cinnamic acids

A recent study showed that flavonoids, their biosynthetic precursors (cinnamic acids and coumaric acid), and their derivatives inhibited 17ß-HSD type 1. (Brozic, Kocbek et al. 2009)

Phytoestrogens

Among naturally present substances, phytoestrogens are the most potent inhibitors of 17ß-HSDs. (Meier, Moller et al. 2009) (Morrissey and Watson 2003) (Adlercreutz 2002) (Deluca, Krazeisen et al. 2005)

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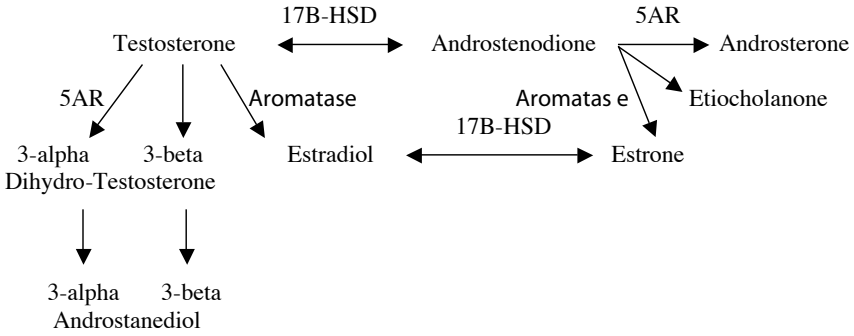
Aromatase

By Wendy L. Ellis, ND and Ronald Steriti, ND, PhD

Aromatase converts testosterone into estradiol and androstenadione into estrone.



In men, increased aromatase activity results in reduced testosterone and increased estradiol concentrations, ultimately resulting in a decrease in muscle mass and an increase in total fat mass. Increased fat mass contributes to oxidative stress, inflammation, and increased aromatase activity. (Cohen 2001) (Cohen and Holbrook 2004)

Decreased aromatase activity has been found in obesity, and metabolic syndrome. Estrogen deficiency has been implicated, and many now believe that androgen levels must be balanced in both men and women. (Jones, McInnes et al. 2007)

Although serum testosterone levels decrease acutely in critically ill patients, estrogen levels rise. One study that found the primary cause of increased estrogen levels in acute illness is increased aromatase P450 gene expression, resulting in enhanced aromatization of androgens to estrogens. (Spratt, Morton et al. 2006)

Kidney stones increase after menopause, suggesting a role for estrogen deficiency. A recent research study in mice found that aromatase deficiency causes altered expression of molecules critical for calcium reabsorption in the kidneys of female mice, and proposed that estrogen deficiency caused by aromatase inactivation is sufficient for renal calcium loss. (Oz, Hajibeigi et al. 2007)

One study showed that patients with SLE had decreased androgen and increased estrogen levels. Aromatase activity in SLE patients had significant direct correlation with estrogen levels. Among SLE patients the aromatase activity varied inversely with disease activity. (Folomeev, Dougados et al. 1992)

Hyper-Aromatization

Hyper-aromatization is a term used to describe excessive aromatase activity, which results in conversion of testosterone into estrogen. Although possible in both sexes, hyper-aromatization is particularly difficult for men and often accompanies low testosterone and obesity related to metabolic syndrome X and insulin resistance. (Yazici and Sayin 2008)

Strong formulas are often necessary to reverse hyper-aromatization. These include Myomin or Chrysin.

> Myomin is a combination of Smilax glabra Roxb., Curcuma zedoria, Cyperus rotundus and Aralia Dasyphylla Mig. (Chi 2008)
>
> Chrysin is a naturally occurring flavone chemically extracted from the blue passion flower (Passiflora caerulea). (Brown, Vukovich et al. 2001) (Brown, Vukovich et al. 2001) (Monteiro, Azevedo et al. 2006) (Balunas, Su et al. 2008)

Lignans

Lignans are precursors of enterolacton, which inhibits aromatase and reduces the ratio of 16-OH over 2-OH oestrogen metabolites. The resulting reduction in estrogen load may favorably influence Sertoli cell function. (Comhaire and Mahmoud 2003)

Clomiphene citrate

Infertility is a common complication of PCOS. Studies have reported PCOS as the major cause of infertility in up to 20% of couples.

Currently, clomiphene citrate is considered first-line therapy for ovulation induction for women with PCOS and infertility. It has variable efficacy (20–25% of women are clomiphene citrate resistant), discrepancies between ovulation and conception rates, and a long half-life (~5 days), which may result in negative endometrium and cervical mucus effects. (Eckmann and Kockler 2009)

Common adverse drug reactions associated with the use of clomifene (≥1% of patients) include: hot flashes, abdominal discomfort, visual blurring (dose-dependent), and/or reversible ovarian enlargement and cyst formation. Infrequent adverse effects (0.1–1% of patients) include: abnormal uterine bleeding, nausea, and/or vomiting. Rare adverse effects (<0.1% of patients) include: reversible alopecia and/or ovarian hyperstimulation syndrome.

Clomiphene can lead to multiple ovulation, hence increasing the chance of twins (3-5% of births instead of the normal ~1%). In comparison to treatment with purified FSH, the rate of ovarian hyperstimulation syndrome is low. There may be an increased risk of ovarian cancer and weight gain.

Aromatase-Inhibitor Induced Side Effects

Aromatase inhibitors lead to profound estrogen suppression and may be expected to increase the risk of Carpal Tunnel Syndrome in postmenopausal women receiving adjuvant therapy for early breast cancer. (Sestak, Sapunar et al. 2009) (Nishihori, Choi et al. 2008)

Natural Aromatase Inhibitors

The natural product extracts that were most active in the microsomal aromatase inhibition assay reported as PCA included five red wine varieties (*Vitis* L. sp.) from various wineries, with the most active being Cabernet Sauvignon from Tanglewood (France). (Balunas, Su et al. 2008)

Alcohol

Alcohol consumption increases in estrogen levels. One study proposed that increased aromatization may be a mechanism for feminization of some male alcoholics, as well as for the reported increases in plasma estrogen levels in postmenopausal women subjected to moderate alcohol consumption. (Purohit 2000)

Vitamin D and DHEA

One article proposed that vitamin D and DHEA might be beneficial for aromatase metabolism by contributing to the local production of estrogens. (Yanase, Suzuki et al. 2003)

Turnera diffusa

One study showed the extract of Turnera diffusa (Damiana) and two isolated compounds pinocembrin and acacetin could significantly suppress aromatase activity. They also showed that apigenin 7-glucoside, Z-echinacin and pinocembrin showed estrogenic activity. (Zhao, Dasmahapatra et al. 2008)

Genestein

One study found the phytoestrogen genestein induced aromatase activity in hepatic cells. (Ye, Chan et al. 2009)

Another study found that genestein stimulates growth of estrogen-dependent human tumor cells (MCF-7) in a preclinical mouse model for postmenopausal breast cancer. The authors recommend caution with consumption of dietary genestein by postmenopausal women with estrogen-dependent breast cancer taking letrozole (an aromatase inhibitor) treatment.(Ju, Doerge et al. 2008)

An earlier study found that the degree of soy flour processing affects the estrogenicity of products containing a constant amount of genistein. Collectively, these findings suggest that for postmenopausal women with estrogen-dependent breast cancer, the consumption of foods containing soy flour is more advisable than consuming isoflavones in more purified forms.

(Allred, Allred et al. 2004)

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Sex Hormone Binding Globulin

By Wendy L. Ellis, ND and Ronald Steriti, ND, PhD

Sex hormone-binding globulin (SHBG) is a glycoprotein possessing high affinity binding for 17 beta-hydroxysteriod hormones such as testosterone and estradiol. Other steroid hormones such as progesterone, cortisol, and other corticosteroids are bound by transcortin. (Selby 1990) (Pugeat, Crave et al. 1996)

Increased SHBG

Sex hormone binding globulin (SHBG) is increased with: hyperthyroidism, pregnancy, and when using antiepileptic drugs.

> Oral birth control use (past or present) is associated with increased SHBG. (Warnock, Clayton et al. 2006) (Panzer, Wise et al. 2006)
>
> One study found that in both men and women higher levels of SHBG were associated with an increased risk for Alzheimer's disease and overall dementia. (Muller, Schupf et al. 2008)

Decreased SHBG

SHBG level is decreased by high levels of insulin and insulin-like growth factor 1 (IGF-1). High androgen levels decrease SHBG, while high estrogen and thyroxine levels increase it.

It is decreased in: hypothyroidism, and androgen excess.

> In both men and women, plasma levels of sex hormone-binding globulin are strong correlates of obesity and risk factors for cardiovascular disease, and more importantly, the relationships between low SHBG and altered plasma lipid levels appear to be independent from the concomitant increased levels of visceral adipose tissue. (Tchernof and Despres 2000)
>
> Low circulating levels of sex hormone-binding globulin are a strong predictor of the risk of type 2 diabetes in women and men. (Ding, Song et al. 2009)
>
> SHBG levels may be useful as a biomarker for metabolic syndrome risk in adolescents as well as adults. (Oya, Schoppen et al. 2009)
>
> Sex hormone-binding globulin levels predict insulin sensitivity, disposition index, and cardiovascular risk during puberty. (Sorensen, Aksglaede et al. 2009)
>
> Low sex hormone-binding globulin is associated with low high-density lipoprotein cholesterol and metabolic syndrome in women with polycystic ovary syndrome (PCOS).

(Chen, Yang et al. 2006)

> Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. (Haffner, Shaten et al. 1996)

If a patient has adequate serum estrogen levels, yet still has clinical symptoms of estrogen deficiency, check the levels of sex hormone binding globulin. When SHBG is high women are more apt to have clinical symptoms because bound hormones are not "biologically" active. SHBG has the highest affinity for DHT (the direct metabolite of testosterone), and the lowest affinity for estradiol. (Tietz, pg 1603). Be sure to assess thyroid supplementation status, as this may increase the SHBG.

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Cortisone and Cortisol

By Wendy L. Ellis, ND and Ronald Steriti, ND, PhD

Cortisone is an inactive metabolite of cortisol. It is interconverted to cortisol by 11-beta-hydroxysteroid dehydrogenase and is therefore considered cortisol "storage."

Cortisol is a major glucocorticoid that also has some mineralcorticoid activity. It is considered the body's key stress hormone. 24 hour urinary free cortisol excretion rate in normal subjects ranges between 20 and 80 ug/d. (Tietz Clinical Textbook of Chemistry, pg 1543).

Conversion of 17-OH Progesterone to 11-deoxycortisol is performed by the 21-hydroxylase enzyme. 11-deoxycortisol is then metabolized to cortisol. A deficiency in this enzyme is the most common form of congenital adrenal hyperplasia. An elevation in 17-alpha-hydroxyprogesterone is characteristic of this defect. Elevations in progesterone, 17-alpha-hydroxypregnenolone, pregnenolone, the adrenal hormones DHEA and DHEA-S, and plasma androstenedione and testosterone will also be noted when 21-hydroxylase is deficient. Women often present with hirsuitism. (Tietz Clinical Textbook of Chemistry, pg 1553).

Causes of Cortisol and Cortisone Imbalance in Men and Women

Increased Levels

- Cushing's syndrome / disease
- Ectopic ACTH production
- unipolar depression
- sleep deprivation
- generalized anxiety order
- post traumatic stress disorder
- panic disorder, early stage
- exogenous cortisol
- licorice root supplementation
- Intensive physical exercise
- Acute ingestion of alcohol (cortisol only)

Decreased Levels

- Adrenal insufficiency - follow up with ACTH stimulation test or multi-point serum or saliva cortisol.
- Chronic fatigue syndrome
- fibromyalgia,
- rheumatoid arthritis

*With urinary analysis, hypo-adrenal patients seem to show up with low terminal cortisiol metabolites, and then if untreated, cortisol and cortisone also become suboptimal. Terminal metabolites are a measure of daily cortisol production, including what is metabolized. The sum of tetrahydrocortisol, allo-tetrahydrocortisol, and tetrahydrocortisone equals about 1/2 of the total daily production of cortisol. If they add up to 5000 micrograms (5 mg), then the body is making about 10 mg/day. The urinary cortisol values reflect the amount of circulating cortisol.

Apparent Mineralocorticoid Excess (AME)

AME is a result of the impairment of 11-beta-hydroxysteroid dehydrogenase enzyme activity. This enzyme inactivates cortisol in the kidney by converting it to cortisone. As a result, cortisol accumulates in the kidney, and cortisone concentrations decrease. Cortisol may reach as much as ten times the concentration of cortisone in the urine. The excess cortisol binds to mineralocorticoid receptors in the distal tubule, which is normally the site of aldosterone binding.

The 11-beta-hydroxysteroid dehydrogenase enzyme has bidirectional activity depending on the tissue. 11beta-HSD isoform type 2 uni-directionally inactivates cortisol, while type 1 isoform acts bi-directionally. This enzyme has a reductase activity in the liver, and a dehydrogenase activity in the kidney, which is why there are two isoenzymes for this enzyme.

Clinical symptoms of AME include hypertension, low plasma rennin-aldosterone levels, hypokalemia, normal plasma cortisol levels, and low plasma aldosterone levels.

Treatment may involve using a high-potency glucocorticoid to suppress endogenous production of cortisol. This may also bind to the mineralocorticoid receptor. Concentrations given are less than that of endogenous cortisol. Spironolactone may also be used, however, the anti-androgenic and progestational side effects limit long term use.

Tetrahydrocortisone, Tetrahydrocortisol and Allo-Tetrahydrocortisol

Tetrahydrocortisone, Tetrahydrocortisol and Allo-Tetrahydrocortisol are terminal cortisol metabolites that reflect approximately 50% of daily cortisone synthesis. These will often reflect a chronic adrenal picture if levels are out of normal limits. The sum of these values should fall between 5000-7000 ug/24hr for normal daily output of cortisol. 5-alpha-reductase is the enzyme which converts cortisol to allo-tetrahydrocortisol.

Tetrahydrocorticosterone and Allo-tetrahydrocorticosterone

These are the terminal markers of corticosterone and sensitive markers of adrenal stress. “Acute” adrenal stress would produce elevated values. Adrenal fatigue would produce decreased values.

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Aldosterone

Aldosterone is a major mineralocorticoid in the body. Excretion varies inversely with salt intake or potassium supplementation.

Causes of Aldosterone Imbalance in Males and Females

Increased Aldosterone

- Low salt diet
- Primary aldosteronism with low renin hypertension (polyuria, hypokalemia)
- High dose pregnenoalone
- Spironolactone usage

Decreased Aldosterone

- High salt diet
- Adrenal insufficiency

Hypertension

Primary aldosteronism is recognized as the most frequent cause of secondary hypertension. Primary aldosteronism is prevalent in 17-22% of individuals with resistant hypertension, which is defined as hypertension that requires more than three drugs in full doses to adequately control pressure. (Pizzolo, Pavan et al. 2007) (Tomaschitz, Pilz et al. 2009)

Obesity and Metabolic Syndrome

Increased aldosterone has been associated with obesity and the metabolic syndrome. (Sowers, Whaley-Connell et al. 2009) (Krug and Ehrhart-Bornstein 2008)

HIV

One study found that aldosterone was higher in HIV-infected women with increased visceral adipose tissue. (Lo, Looby et al. 2009)

Hearing Loss

A recent study found that mineralocorticoids (aldosterone and fludrocortisone) were effective in reducing the inflammatory response, suggesting that their fluid transport function helped clear disease. Thus, steroid control of middle ear disease may be useful in alleviating symptoms faster and reducing the risk to the inner ear. (MacArthur, DeGagne et al. 2009) (MacArthur, Kempton et al. 2008)

Recent studies have found a correlation between serum aldosterone and age related hearing loss. Low serum aldosterone was noted in patients with presbycusis, thus suggesting aldosterone may have a protective effect on hearing in old age. (Tadros, Frisina et al. 2005)

Postmenopausal Syndrome

One study found that plasma renin activity and aldosterone levels were higher during the late luteal phase in women with premenstrual syndrome compared with controls. (Rosenfeld, Livne et al. 2008)

Polycystic Ovarian Syndrome

One study found that women with polycystic ovarian syndrome show an insulin resistance related increase in serum aldosterone levels. {Cascella, 2006 #22}

Licorice

Excessive consumption of licorice can cause pseudoaldosteronism characterized by hypokalemia, rhabdomyolysis, metabolic alkalosis with respiratory compensation, and increased urinary cortisol levels. (Kinoshita, Okabayashi et al. 2009) (Yasue, Itoh et al. 2007)

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Growth Hormone

By Ronald Steriti, ND, PhD

Growth hormone (GH) is a protein-based poly-peptide hormone that stimulates growth and cell reproduction and regeneration in humans and other animals. Somatotropin refers to the growth hormone produced natively and naturally in animals, whereas the term somatropin refers to growth hormone produced by recombinant DNA technology, and is abbreviated “rhGH” in humans.

HGH is synthesized and secreted from the anterior pituitary gland in a pulsatile manner throughout the day; surges of secretion occur at 3- to 5-hour intervals. The plasma concentration of GH during these peaks may range from 5 to even 45 ng/mL. The largest and most predictable of these GH peaks occurs about an hour after onset of sleep. Otherwise there is wide variation between days and individuals.

Increased GH

- Gigantism in children
- Acromegally in adults
- Drugs (oral contraceptives, estrogen, insulin, arginine, glucagon)

Decreased GH

- Dwarfism in children,
- Hypopituitarism,
- Obesity
- Drugs (steroids)

Growth hormone is used clinically to treat children’s growth disorders and adult growth hormone deficiency. Reported effects on GH deficient patients include decreased body fat, increased muscle mass, increased bone density, increased energy levels, improved skin tone and texture, increased sexual function and improved immune system function.

GH stimulates production of insulin-like growth factor 1 (IGF-1, formerly known as

somatomedin C), a hormone homologous to proinsulin

In addition to increasing height in children and adolescents, growth hormone has many other effects on the body:

- Increases calcium retention, and strengthens and increases the mineralization of bone
- Increases muscle mass through sarcomere hyperplasia
- Promotes lipolysis
- Increases protein synthesis
- Stimulates the growth of all internal organs excluding the brain
- Plays a role in fuel homeostasis
- Reduces liver uptake of glucose
- Promotes gluconeogenesis in the liver
- Contributes to the maintenance and function of pancreatic islets
- Stimulates the immune system

Melatonin

By Ronald Steriti, ND, PhD

Melatonin is produced by pinealocytes in the pineal gland and also by the retina, lens and GI tract. It is naturally synthesized from the amino acid tryptophan (via synthesis of serotonin) by the enzyme 5-hydroxyindole-O-methyltransferase.

Melatonin levels are high at night where it facilitates deep sleep. Production of melatonin by the pineal gland is inhibited by light and permitted by darkness.

Melatonin is a powerful antioxidant, however, once oxidized, cannot be reduced to its former state because it forms several stable end-products upon reacting with free radicals. Therefore, it has been referred to as a terminal (or suicidal) antioxidant.

Melatonin may be helpful in several situations:

Preventing ischemic damage (Lee, Kuan et al. 2007) (Dominguez-Rodriguez, Abreu-Gonzalez et al. 2007)

Alzheimer's disease (Olcese, Cao et al. 2009) (Mahlberg, Kunz et al. 2004)

ADHD and chronic sleep onset insomnia (Hoebert, van der Heijden et al. 2009) (Van der Heijden, Smits et al. 2007)

Migraines and Cluster Headaches (Gagnier 2001) (Dodick and Capobianco 2001)

Cancer (Mills, Wu et al. 2005)

Breast cancer prevention (Grant, Melan et al. 2009) (Schernhammer, Berrino et al. 2008)

As an adjunct in radiation treatment of cancer (Shirazi, Ghobadi et al. 2007)

Gallbladder stones (Koppisetti, Jenigiri et al. 2008)

Amyotrophic lateral sclerosis (Weishaupt, Bartels et al. 2006)

Breast Cancer Prevention

Recent studies have suggested that the pineal hormone melatonin may protect against breast. Melatonin works through receptors and distinct second messenger pathways to reduce cellular proliferation and to induce cellular differentiation. In addition, independently of receptors melatonin can modulate oestrogen-dependent pathways and reduce free-radical formation, thus preventing mutation and cellular toxicity. (Grant, Melan et al. 2009)

The Nurses' Health Study II cohort, we measured the concentration of the major melatonin metabolite, 6-sulphatoxymelatonin (aMT6s), in the first morning urine of 147 women with invasive breast cancer and 291 matched control subjects. In logistic regression models, the relative risk (reported as the odds ratio [OR]) of invasive breast cancer for women in the highest quartile of urinary aMT6s compared with those in the lowest was 0.59 (95% confidence interval [CI] = 0.36 to 0.97). These prospective data support the hypothesis that higher melatonin levels, as measured in first morning urine, are associated with a lower risk of breast cancer. (Schernhammer, Berrino et al. 2008)

Adverse Effects

One study reported that three mg of melatonin taken in the evening raised prolactin levels in six out of seven women. Melatonin also lowers FSH levels. It is believed that these hormonal changes could in some women impair fertility. (Terzolo, Revelli et al. 1993)

A more recent study of insomniacs, however, found that serum concentrations of prolactin, FSH, TSH, or estradiol did not exhibit changes after 6 months of melatonin administration, nor were any indications of hematologic or blood biochemistry alteration found. (Siegrist, Benedetti et al. 2001)

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Interpreting the Comprehensive Hormone Profile

This manual is intended for those who have attended the Bioidentical Hormone Society seminar on hormone replacement, and for those using the comprehensive hormone profile steroid tests provided by Meridian Valley Laboratory. Use this handbook to increase understanding and interpretation of the test components, and clinically apply the results.

Suggestions from our staff

Begin with a brief overview of the test values.

Look for patterns within the values (consistent highs or lows, etc.).

When you have assessed the highs and lows, out of range or perhaps high or low normal, draw associations between these values and endocrine abnormalites).

Look into enzyme activity.

For example - are all the low values associated with a 5-alpha-reductase enzyme? You can reference the "Metabolism or Selected Steroids" chart provided with the test results to determine enzyme activity.

Is the patient taking saw palmetto, thus driving the metabolism in a different direction?

The patient may be taking a other supplement or medication that interfere with the results.

Certain pathologies may interfere with hormone metabolism (insulin resistance, hypothyroidism, etc.), and this may alter your results. For example, if a patient has PCOS, you may see a higher DHEA, pregnanetriol and testosterone levels, however, if the patient has adrenal hypofunction, this may show a low DHEA and pregnanetriol value.

PubMed www.pubmed.org is a useful tool to research health conditions associated with enzyme activity, new research articles arise daily on the subject matter.

The 24-hour urinary profile is a very valuable test that offers a great deal of useful information to the clinician. It provides the information needed to determine how patients metabolize their hormones (information you need to properly administer hormone replacement therapy). It also provides you with information on adrenal function, including metabolites and enzyme activity that help identify additional pathological considerations.

We want you to get the most out of our test. If you have further questions, please feel free to contact Meridian Valley Lab and speak with one of our physicians. We look forward to working with you.

Urinary Potassium

By Ronald Steriti,ND, PhD

The urine potassium test is usually recommended to detect or confirm the presence of conditions that affect body fluids (for example, dehydration, vomiting, diarrhea) or disorders of the kidneys or adrenal glands, which are the source of aldosterone. The hormone aldosterone regulates kidney removal of sodium and potassium. The following are the differential diagnosis for increased and decreased urinary potassium.

Increased Urinary Potassium

Primary renal diseases, diabetic and renal tubular disease, Albright-type renal disease, starvation (onset), primary and secondary aldosteronism, Cushing's disease, treatment with ACTH or hydrocortisone, Fanconi's syndrome, Bartter's syndrome, Drugs (acetozolamide and other diuretics, cortisone, sulfates, EDTA anticoagulant, penicillin, carbenicillin, thiazides, licorice, sulfates, insulin)

Decreased Urinary Potassium

Addison's disease, severe renal disease (pyelonephritis, glomerulonephritis), Drugs (amiloride, diazide, epinephrine, glucose, prolactin)

Potassium

Potassium (K) is a nutrient present in a wide array of foods, with the richest sources being leafy green vegetables, fruit from vines, and root vegetables, and a component of many foods and beverages that constitute a healthy eating pattern.

In human feeding studies, participants randomly assigned to the Dietary Approaches to Stop Hypertension (DASH) trial's combination diet had significantly higher urinary K excretion than those consuming a typical American diet. The beneficial effects of the dietary intervention on blood pressure, the outcome of interest, occurred without a change in dietary sodium (Na) or body weight. (Mente, Irvine et al. 2009)

Until recently, humans consumed a diet high in potassium. However, with the increasing consumption of processed food, which has potassium removed, combined with a reduction in the consumption of fruits and vegetables, there has been a large decrease in potassium intake which now, in most developed countries, averages around 70 mmol/day, i.e. only one third of our evolutionary intake. (He and MacGregor 2008)

Very powerful mechanisms for excreting potassium from the body and conserving salt within the

body were developed. However, with the advent of civilized societies, cooking and processing of food have greatly reduced the potassium content, and this in combination with a large increase in the consumption of processed foods and a reduction in the consumption of fruit and vegetables have led to a significant decrease in potassium intake and a large increase in salt intake. The average potassium intake, in most developed countries, is now around 70 mmol/day and salt intake is between 170 and 200 mmol/day. (Stamler 1997) These dietary changes have occurred over the past 5000 years (brief, by evolutionary standards); thus, there has been little time for the physiological systems to adapt.

High Blood Pressure and Cardiovascular Disease

A low potassium intake combined with a high salt intake causes a rise in blood pressure (He and MacGregor 1999) and increases the risk of cardiovascular disease. (Khaw and Barrett-Connor 1987)

A single 24-hour urine K measurement has been shown to be a significant predictor of coronary heart disease events and all-cause mortality. (Tunstall-Pedoe, Woodward et al. 1997)

Glucose Intolerance and Diabetes

Glucose intolerance often occurs in clinical conditions where there is severe hypokalaemia and a deficit in potassium balance such as primary or secondary aldosteronism or after prolonged treatment with diuretics. A recent analysis of 59 clinical trials of thiazide diuretics showed a strong relationship between hypokalaemia and glucose intolerance (Zillich, Garg et al. 2006). This study, as well as others, suggests that treatment of thiazide-induced hypokalaemia with potassium supplementation or potassium-sparing diuretics could lessen glucose intolerance and possibly prevent the development of diabetes. (He and MacGregor 2008)

Kidney Stones

By reducing urinary calcium excretion, a high potassium intake reduces the risk of kidney stone formation, as calcium is the main component of most urinary stones.

An increased potassium intake lowers urinary calcium excretion and plays an important role in the management of hypercalciuria and kidney stones. (He and MacGregor 2008)

A recent study found that supplementation with potassium citrate may decrease the risk of renal stone formation during and immediately after spaceflight. (Whitson, Pietrzyk et al. 2009)

Urinary alkalization with potassium citrate/bicarbonate is a highly effective treatment, resulting in dissolution of non-obstructing uric acid stones. (Trinchieri, Esposito et al. 2009)

Long-term potassium citrate significantly decreases the stone formation rate. (Robinson, Leitao et al. 2009)

A 4-year prospective study of 45,619 men aged 40–75 years showed that potassium intake was

inversely related to the risk of kidney stones. (Curhan, Willett et al. 1993)

Experimental studies in hypertensive rats have shown that a high potassium intake prevents the development of renal vascular, glomerular and tubular damage, independent of its effect on blood pressure. (Tobian, MacNeill et al. 1984)

Osteoporosis

Several population-based studies have shown beneficial effects of dietary potassium or fruit and vegetables on bone health. (Macdonald, New et al. 2005) (New, Bolton-Smith et al. 1997) (New, Robins et al. 2000) (Tucker, Hannan et al. 1999)

A low potassium intake combined with a high salt intake may cause bone demineralization. (New, Bolton-Smith et al. 1997)

An increase in dietary potassium intake reduces urinary calcium excretion and causes a positive calcium balance. (Lemann, Pleuss et al. 1993)

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Urinary Sulfites

By Ronald Steriti, ND, PhD

Sulfite sensitivity is caused by a relative deficiency of the enzyme sulfite oxidase. According to FDA estimates, only 1% of our population suffers from sulfite sensitivity and those suffering from true sulfur sensitivity is even less than this. (Vally, Misso et al. 2009)

Sulfite sensitivity is a condition characterized by asthma-like symptoms, including wheezing, chest tightness, coughing, extreme shortness of breath, and even loss of consciousness. Other symptoms include flushing, angioedema, itching, hives, contact dermatitis, swelling of eyes, hands and feet, nausea and diarrhea, and anaphylactic shock.

Many people, although not severely sulfite sensitive, will exhibit the "red-wine stuffy nose" after drinking just a single glass of red wine. Others get a characteristic alcohol flush on the face and neck when drinking red wine, beer, or hard liquor. (2006)

Molybdenum

Sulfite oxidase is an oxidoreductase class enzyme that catalyzes the reaction from sulfite to sulfate. This is a mitochondrial molybdohemoprotein meaning molybdenum is a necessary co-factor in the synthesis of this enzyme. Not enough molybdenum, not enough sulfite oxidase is produced possibly resulting in sulfite sensitivity. (2006)

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Thyroid Hormones

By Ronald Steriti, ND, PhD

Thyroid hormones include:

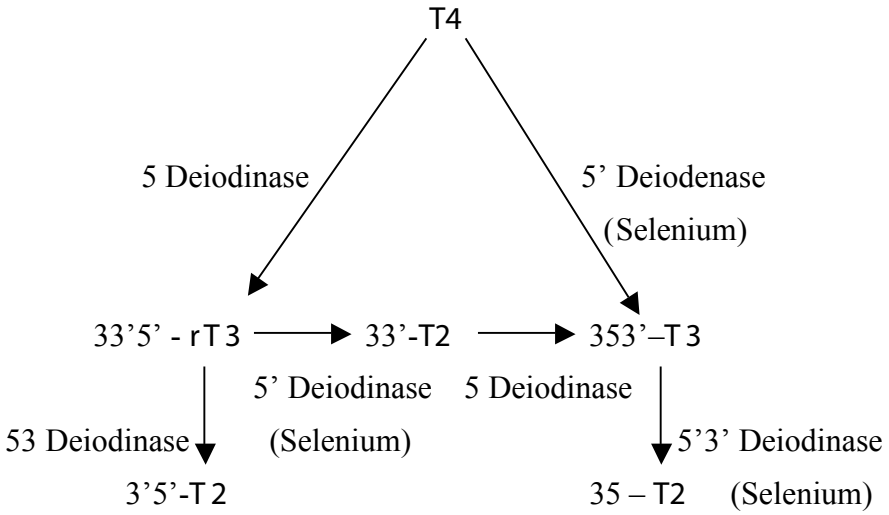
T4, Thyroxine, or 3,5,3',5'-tetraiodothyronine

T3, Triiodothyronine

rT3, reverse T3, 3,3',5'-triiodothyronine

The current diagnosis of hypothyroidism relies on blood tests of thyroid stimulating hormone (TSH) and T4. However, this single point in time test could miss patients with mild symptoms. The 24-hour urine FT3/FT4 test provides better indicators for diagnosis.

According to a clinical study conducted by Dr. Baisier et. al., urine free T3 corresponds best with symptoms of hypothyroidism. The authors conclude that "the 24 hour urine free T3 seems to be a reliable test, more accurate than the serum T4 and serum TSH test in the diagnosis of thyroid diseases and their follow up treatment. It correlates well with the clinical status of the patient and is not influenced by binding globulins."



Iodine and Tyrosine

Iodine and tyrosine are required to make T3 in thyroid gland.

Selenium

All three deiodinases that convert thyroxine (T4) into triiodothyronine (T3) contain selenocysteine. A low 24-hour urinary selenium level likely correlates with overall selenium deficiency and decreased tissue availability of T3 due to decreased conversion of T4 to T3. (Duntas 2006)

T3 (Triiodothyronine)

Guggul (Indian frankincense) increases production of T3. (Panda and Kar 1999)

One study found that T3 significantly inhibited proliferation on ER negative MDA-MB-231 breast cancer cells. (Cestari, Figueiredo et al. 2009)

Lithium

The common clinical side effects of the drug lithium are goitre in up to 40% and hypothyroidism in about 20%. (Lazarus 2009)

Passive smoking

A recent study showed that one hour of passive smoking at bar/restaurant levels is accompanied by significant increases in metabolism and thyroid hormone (T3 and free T4) levels. (Metsios, Flouris et al. 2007)

Lycopus

Lycopus europaeus (Gypsywort) may be helpful in in slight forms of hyperthyroidism. The urinary T4 excretion was significantly increased in Lycopus europaeus-treated patients ($p=0.032$). (Beer, Wiebelitz et al. 2008)

L-Carnitine

L-carnitine inhibits both triiodothyronine (T3) and thyroxine (T4) entry into the cell nuclei. One study showed that 2 and 4 grams per day of oral L-carnitine are capable of reversing hyperthyroid symptoms as well as preventing (or minimizing) the appearance of hyperthyroid symptoms. Since hyperthyroidism impoverishes the tissue deposits of carnitine, there is a rationale for using L-carnitine at least in certain clinical settings. (Benvenga, Amato et al. 2004)

2/16 Ratio

Increased 16alpha-hydroxyestrone activity compared to 2-hydroxyestrone activity appears to be associated with proliferative thyroid disease.

A case-control study of 49 subjects with proliferative thyroid disorders found that fifty-one percent (25 of 49) of the cases had a low 2/16 ratio compared to 31% (15 of 49) in the control

group while 20% (10 of 49) of the control group had a high 2/16 ratio as compared to 8% (4 of 49) in the case group (P value < 0.05). (Chan, Sepkovic et al. 2006)

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