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Saliva Hormones Interpretive Guide

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Disclaimer and Regulatory Statement

This Saliva Hormones Interpretive Guide is intended to be used in tandem with Vibrant Wellness's Salivary Hormone Test and this guide is provided to users pursuant to the Terms of Use Agreement (the "Terms") on its website www.vibrant-wellness.com. The content within this interpretive guide is not intended to be a stand-alone medical reference guide, nor is it intended to be a substitute for medical advice from a healthcare provider. The general wellness test and interpretive guide intended use relates to sustaining or offering general improvement to functions associated with a general state of health while making reference to diseases or conditions. The content in this guide is not meant to diagnose, treat, or cure any disease or condition.

The clients who receive Vibrant Wellness Salivary Hormone test results are advised to consult their physician and/or health care provider team for diagnosis and further follow up care, including but not limited to additional testing, prescription medication, and any treatment interventions including diet, exercise, or lifestyle management.

The Vibrant Wellness platform provides tools to track and analyze general wellness profiles and encourage a general state of health and well-being.

Vibrant testing does not demonstrate absolute positive and negative predictive values for any disease state or condition. Its clinical utility has not been fully established. Vibrant validates the accuracy and precision of the testing but not of its clinical or diagnostic value. So, these tests are for wellness and informational purpose only.

Vibrant is actively doing clinical research on these samples, de-identified from patients under an IRB and will make research publications towards the same as and when the clinical utility is well established. These tests have been laboratory developed and their performance characteristics determined by Vibrant America LLC, a CLIA-certified laboratory performing the test CLIA#:05D2078809. The test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). Although FDA does not currently clear or approve laboratory-developed tests in the U.S., certification of the laboratory is required under CLIA to ensure the quality and validity of the tests.

Advantages of Salivary Testing of Steroid Hormones

Saliva, as a diagnostic biofluid, has been labelled the 'mirror of the body' as it can reflect the health and disease processes within.¹ In the endocrine work up specifically, saliva offers several distinct advantages over serum and other testing methodologies.

The primary benefit of salivary testing is that steroid hormones collected from saliva are unconjugated and/or bioavailable rather than the total, or protein bound, hormones measured in serum.^{2,3} Due to this unique feature, salivary hormone testing has been well established to confer reliability and accuracy in many clinical scenarios.^{1,3,4} These include adrenal glucocorticoid measurements and diagnosis of Cushing's disease and adrenal insufficiency⁵ and more direct assessment of target tissue hormone levels.⁶ Salivary testing also assesses baseline hormone levels of menstruating females (i.e., luteal phase testing).

Regarding use of transdermal creams, such as progesterone, it has been shown that serum and whole blood levels consistently underestimate tissue levels of hormones following transdermal progesterone use.⁷ Due to the sensitivity of saliva in reflecting transdermal progesterone levels, and likelihood of underestimation of these values in serum, salivary progesterone testing is currently one of the more reliable testing methods available to prevent overdoses of progesterone from topical creams and gels.^{7,8}

In addition to these clinical advantages, collection of salivary hormones conveys more convenience than serum testing. Patients collect samples themselves, in their home. There is no incidence of "needle stick" injuries to medical personnel with salivary collection. There is no increased glucocorticoid release from the stress of venipuncture for the patient. Lastly, because of this ease of collection, salivary samples are convenient to collect throughout several points throughout the day and several points in a menstrual cycle, if desired.

SALIVARY TESTING STRENGTHS

Convenient & painless collection	Can be used to measure baseline levels of sex hormones	Can be used to measure bioavailable hormone	Can be used to measure cortisol & HPA axis dysregulation	Can be used to monitor various methods of HRT
✓	✓	✓	✓	✓

Advantages of Salivary Testing of Steroid Hormones

Saliva originates from pairs of the major salivary glands, the parotid, submandibular, and sublingual glands. Saliva also includes fluid from numerous small buccal glands which line the mouth.⁹

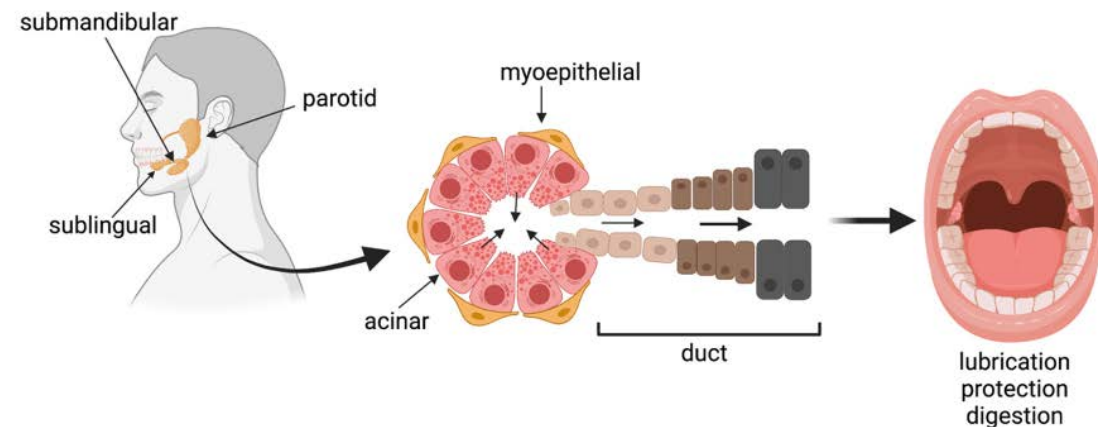


Figure 1. Piraino LR, Benoit DSW, DeLouise LA. Salivary Gland Tissue Engineering Approaches: State of the Art and Future Directions. Cells. 2021; 10(7):1723. <https://doi.org/10.3390/cells10071723> Open Access. CC by 4.0.

The salivary glands are lined with secretory units called acini, made up of acinar cells. (See Fig. 1) The acinar cells are surrounded by contractile cells, called myoepithelial cells. The myoepithelial cells contract the cell to produce the flow of secretions. Once the secretions are pulsed, salivary ducts which are connected to the acinar cells then collect the saliva and distribute it into the oral cavity.¹⁰

Hormones can enter saliva by a variety of mechanisms. For steroids such as cortisol and testosterone, which are neutrally charged, hormones enter the gland from rapid diffusion from the capillaries through the acinar cells of the glands.⁴ For positively charged steroids, like DHEAS, the mode of hormone entry is by diffusion between the tight junctions of the acinar cells. Steroids can also enter saliva from blood or plasma via oral abrasions or directly from oral intake.⁴

While small, lipophilic steroid hormones enter the salivary gland by passive diffusion, the gland membrane acts as a barrier to conjugated or tightly bound hormones. This results in free, unbound hormone in the saliva.⁶

What are Biologically Available Hormones and Why Should We Test Them?

Serum testing typically measures the carrier or protein-bound version of hormone that is travelling through the blood. Conversely, saliva measures biologically available hormone.

While free and albumin-bound hormone can enter tissues, only unbound hormone can exert actions on target cells. It is the combination of free hormones as well as loosely bound hormones (which can rapidly become unbound or free in tissue capillaries) that are collectively termed "bioavailable hormones"²

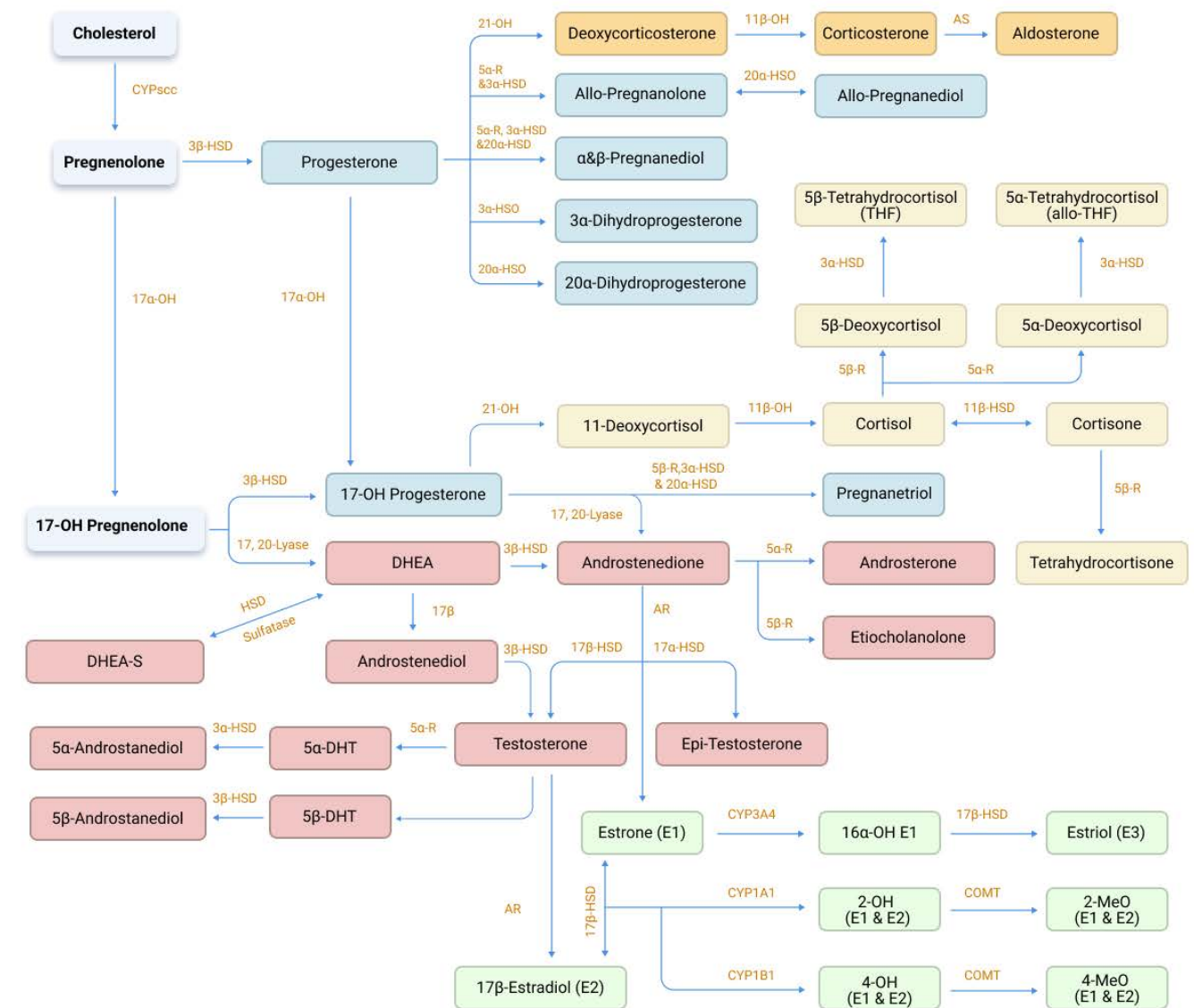
As changing physiological conditions affect levels of binding proteins, measurement of bioavailable hormones is thought to reflect hormone activity more accurately in many clinical situations.

Lab Methodology for Salivary Hormone Testing at Vibrant America

Vibrant America utilizes liquid chromatography-tandem mass spectrometry (LC-MS/MS) exclusively for salivary hormone testing. This has the advantage of high specificity compared to immunoassays. LC-MS/MS also allows simultaneous measurements of multiple analytes and has a low limit of quantification which means precision and accuracy despite low levels of hormone in the sample.⁵

Hormone Cascade

The Steroid Hormone Cascade

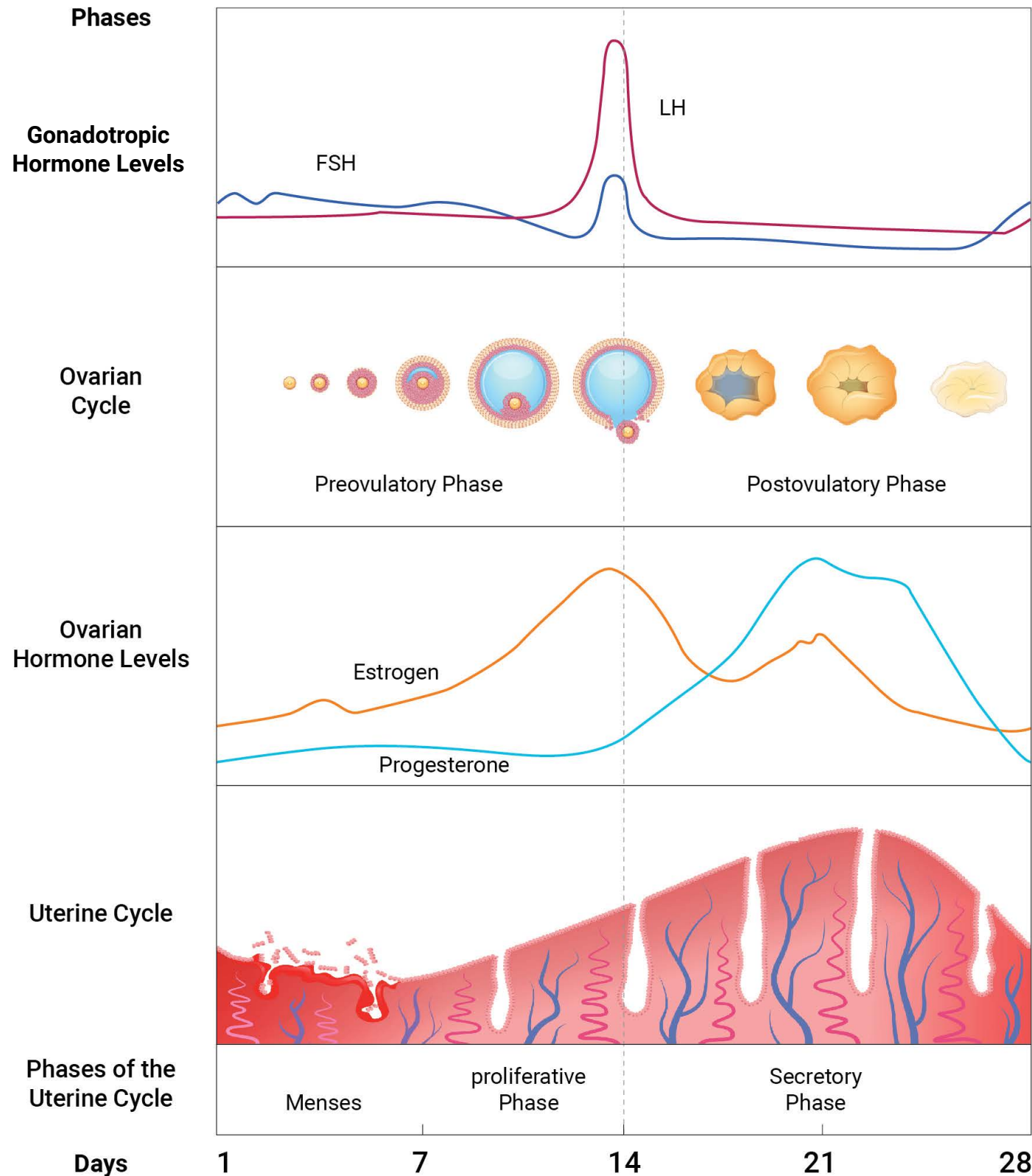


- Androgens
- Estrogens
- Glucocorticoids
- Mineralocorticoids
- Progestogens

Enzyme Abbreviations

5α-R	5α-Reductase	11β-HSD	11β-Hydroxysteroid dehydrogenase
5β-R	5β-Reductase	17α-HSD	17α-Hydroxysteroid dehydrogenase
11β-OH	11β-Hydroxylase	17β-HSD	17β-Hydroxysteroid dehydrogenase
17α-OH	17α-Hydroxylase	20α-HSD	20α-Hydroxysteroid dehydrogenase
17,20-Lyase	Same enzyme as 17α-OH	AR	Aromatase
21-OH	21-Hydroxylase	AS	Aldosterone Synthase
3α-HSD	3α-Hydroxysteroid dehydrogenase	CYP	Cytochrome p450 (sc, 1A1, 1B1 & 3A4)
3β-HSD	3β-Hydroxysteroid dehydrogenase	COMT	Catechol-O-Methyl-Transferase

The Menstrual Cycle



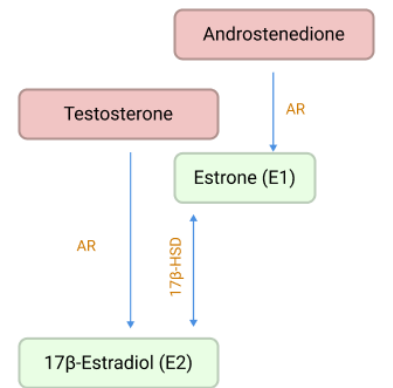
What is Estradiol (E2)?

The major estrogens produced are estradiol (17β-estradiol, E2), estrone (E1), and estriol (E3). Estradiol, commonly known as E2 or 17β-Estradiol, is the predominant and most biologically active estrogen in circulation in males and females.^{11,12} Estradiol plays a key role in the development of the female reproductive system and has non-reproductive roles in cognition and neuroprotection, lipid and glucose homeostasis, adipose distribution, cardiovascular health, pancreatic cell function, bone maintenance and wound healing.¹³

How is Estradiol (E2) Made?

E2 originates from cholesterol, which is converted through a cascade of progesterone and androgen intermediates, finally resulting in estradiol through aromatization from testosterone.¹⁴ In pre-menopausal women this occurs primarily in the ovary. In postmenopausal women, estradiol is sourced directly from the peripheral tissues, predominantly from estrone, sourced from adrenal precursors, and converted to estradiol via 17β-HSD.^{12,13} In postmenopausal women, the estradiol acts locally in a paracrine or endocrine manner and circulating estradiol spills over from these local areas.¹⁵

In males, E2 is predominantly produced by the testes.¹³ Males and postmenopausal women have significantly lower levels of estradiol than premenopausal women.



Causes of High Estradiol (E2)

High estradiol can be the results of excess aromatase activity, environmental exposures to xenoestrogens, chronic liver disease, hyperthyroidism, dysregulated gut microbiome, or ectopic production of estradiol from cancerous tissues.^{13,16,17,18} Inflammation can also contribute to excess estrogen, as acidic diet and other inflammatory triggers cause lowered pH, which activates aromatase enzyme.¹⁴ Other causes of increased aromatase activity include factors such as age, obesity, insulin, gonadotropins, and alcohol.¹⁹

Conditions associated with High Estradiol (E2)^{13,14}

- PCOS
- Uterine Cancer
- Gastric Cancer
- Multiple Sclerosis
- Obesity
- Endometriosis
- Prostate Cancer
- Thyroid Cancer/goiter
- Schizophrenia
- Gynecomastia
- Breast Cancer
- Pituitary Cancer
- SLE
- Oligospermia
- Male hypogonadism
- Breast Cysts
- Gallbladder Dz
- Fibroids
- Ovarian Cancer

Symptoms of High Estradiol (E2)^{14,20,21,22}

- Heavy menstruation
- Nervousness/irritability
- Mood swings
- Headaches
- Weight gain
- Sleep disturbances
- Fibrocystic breasts
- Bloating
- Worsened PMS
- Fatigue
- In males, excess estrogen is linked to depression
- infertility, and enlarged breasts

Causes of Low Estradiol (E2)

Most commonly, menopause, ovariectomy, and aging result in low estradiol. However, there can be many other causes. Compounds which cause aromatase inhibition or increased prolactin (luteotropic hormone or luteotropin) will reduce aromatase activity resulting in lower estrogen.

Drugs which increase prolactin include the following: antidepressants, antipsychotics, anticonvulsants, opiates, estrogens, anti-androgens, anti-hypertensive drugs, and H2-receptor antagonists.

Drugs or toxicants which increase aromatase inhibition include the following: aromatase inhibitors (anastrozole, exemestane, herbicides (glyphosates, Roundup etc.) agricultural antifungals, immunosuppressive drugs (glucocorticosteroids, methotrexate), antimalarials and cigarette smoke.¹⁴

Anti-mullerian hormone and smoking are also miscellaneous factors that reduce aromatase activity. *Please note that Vibrant America Clinical Lab does not measure anti-mullerian hormone at this time.*

Lastly, hypogonadism and genetic disorders such as 17 α -hydroxylase/17,20-lyase deficiency or estrogen resistance syndrome can result in low estradiol levels.¹³

Conditions Associated with or Worsened by Low Estradiol (E2)^{14,23}

- Alzheimer's disease
- Osteoarthritis
- Diabetes Mellitus
- Osteoporosis
- Parkinson's Disease
- Eclampsia
- Colorectal Cancer

Low Estrogen Symptoms^{12-14, 21,22,24}

- Hot flashes
- Night sweats
- Urinary infections
- Urinary incontinence
- Irregular bleeding
- Low libido
- Painful intercourse
- Osteoporosis
- Episodes of rapid heartbeat
- Depression
- Emotional instability
- Deficits in multi-tasking, short term memory and executive function

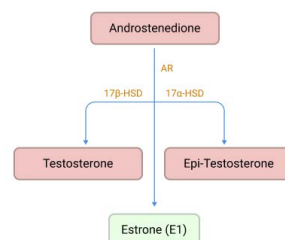
Estrone (E1)

What is Estrone (E1)?

Estrone (E1) is a weaker estrogen than estradiol (E2); by some estimates it has less than 10% the strength of estradiol.²⁵ While levels of E1 do not differ significantly in pre- vs. post-menopausal women,¹⁵ E1 is the predominant estrogen in post-menopausal women²⁶ by a factor of 100-fold compared to E2.²⁵ In post-menopausal women, E1 concentrations have been positively correlated with bone mineral density and breast cancer risk, and inversely correlated with colon cancer risk.¹⁵ Serum estrone levels are an important indicator of serum estradiol levels in post-menopausal women.¹⁵

How is Estrone (E1) Made?

Like all estrogens, estrone originates from cholesterol and subsequent progesterone and androgen intermediates. Specifically, estrone (E1) is derived from the conversion of androstenedione by an aromatase enzyme, 17- β HSD, found in peripheral and adipose tissues. Estrone is converted to small amounts of estradiol in peripheral tissues.



Causes of High Estrone (E1)

High levels of estrone are commonly found in women who use hormone replacement therapy (HRT), even if the estrogen is estradiol rather than estrone, as they can interconvert.²⁷ Of note is that advanced age and obesity will further elevate estrone values in users of HRT.²⁸ Liver disease,²⁹ hyperthyroidism,³⁰ and hormonally producing tumors of ovary, adrenal gland, etc also can raise estrone.^{31,32}

Conditions associated with High Estrone (E1)

Refer to section on elevated estradiol for a full list of estrogen associated conditions.

Causes of Low Estrone (E1)

Estrone levels appear to be similar in pre and postmenopausal women,¹⁵ however there is wide variation in hormone levels in the normal range. Factors such as DHEA and testosterone levels, SHBG levels, genetic predisposition, adiposity, and aromatase activity affect estrone levels.¹⁵ Low estrone levels, below reference ranges, primarily result from decreased aromatase activity. Refer to the Low Estradiol section of this guide for a comprehensive list of medications that can decrease aromatase activity.

Conditions Associated with Low Estrone (E1)

Refer to section on low estradiol for a full list of low estrogen associated conditions.

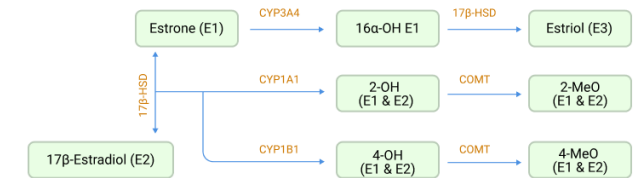
Estriol (E3)

What is Estriol (E3)?

Estriol (E3) is the weakest of the three estrogens: it dissociates rapidly from estrogen receptors.³³ Estriol is the predominant estrogen of pregnancy where it regulates uterine/placental blood flow and placental vascularization. Lab testing for E3 has been most used as a maternal screening for fetal anomalies.³³ E3, as a hormone, is used off-label for menopausal symptoms such as hot flashes, vaginal atrophy, and bone density. It has also been studied for use of immunomodulation and neuroprotection in multiple sclerosis and protection from atherosclerosis.³⁴

How is Estriol (E3) Made?

All estrogens originate from cholesterol and androgen intermediates, notably aromatization from testosterone and androstenedione. E2 is reversibly oxidized to estrone and most estriol is formed from estrone via CYP3A4 metabolism and 17-Beta HSD, as seen to the right.³⁴ Both E2 and E1 can be irreversibly converted to estriol in the liver.



Causes of High Estriol (E3)

Elevated estriol is most common in pregnancy or use of bioidentical hormone replacement prescriptions.³⁵

Conditions that create elevated estradiol may also increase estriol, refer to Estradiol section for further reference.

Causes of Low Estriol (E3)

Most of the data on low estriol results from studies involving maternal fetal screening results. Low estriol during pregnancy is a marker of fetal compromise and can indicate genetic disorders, fetal growth restriction, placental sulfatase deficiency.³⁶ It can also be associated with congenital adrenal hyperplasia, aromatase deficiency, fetal adrenal insufficiency and/or fetal loss.³⁷

Low estradiol conditions may contribute to a low estriol status in non-pregnant women, for further reference refer to section on Low Estradiol.

Ratio of E3/E1+E2

What is the Ratio of E3/E1-E2?

The ratio of estriol (E3) to the sum of estrone (E1) + estradiol (E2) is known as the EQ or estrogen quotient. This equation was popularized by Henry Lemon, MD, a breast cancer researcher. The estrogen quotient quantifies the concept that a higher ratio of estriol relative to the two stronger estrogens has value for both prevention and outcomes in breast cancer. From his research with 24-hour urine samples in female participants, he suggested that a ratio value of E3/E1+E2 of 1 or 1.5 is more optimal.³⁸

Vibrant America's salivary hormone test reference range for the ratio of E3/E1+E2 is based on average values found in samples from healthy women of varying ages. The high and low results from these reference ranges on the salivary hormone test are not based on Dr. Lemon's findings in urinary estrogens. Thus, the ratio of E3/E1+E2 is provided for comparative use of estrogens only. Clinical application of the results should be based on the provider's discretion.

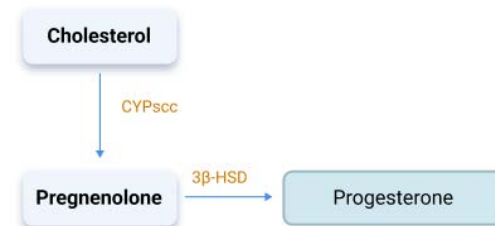
Progesterone

What is Progesterone?

Some researchers have postulated³⁹ that "Life is not possible without progesterone" due to its critical role across multiple systems. In a menstruating woman, after monthly ovulation the corpus luteum in the ovary produces progesterone, which halts endometrial growth and induces secretory changes in the uterine lining to promote successful implantation. Withdrawal of progesterone is associated with the onset of menses.⁴⁰ Progesterone also has vital roles on breast development and during pregnancy and lactation. In men, progesterone influences spermiogenesis and testosterone biosynthesis in the Leydig cells.⁴¹ In men and women progesterone plays a vital role as a precursor to critical steroid hormones such as aldosterone, cortisol, testosterone, and estradiol. It also has important roles in the cardiovascular, renal, and musculoskeletal systems.⁴² Further, progesterone is a neuroprotectant and neuromodulator and aids with sleep. Lastly, progesterone plays a role in immune support and cancer protection against endometrial, colorectal cancers and potentially others.³⁹

How is Progesterone Formed?

Progesterone can be formed from tissues in ovaries and placenta, testes, adrenal gland, and brain. Mechanistically, free cholesterol converts to pregnenolone via CYP450scc enzyme activity and then converts to progesterone via 3-β-HSD (hydroxysteroid dehydrogenase) activity.⁴² Progesterone produced from the gonads travels through the blood and exerts hormonal effects, while progesterone of adrenal origin is converted into glucocorticoids and androgens.⁴²



Causes of High Progesterone

Progesterone is commonly elevated beyond luteal phase values in pregnancy and with exogenous progesterone supplementation or exposure. Other situations whereby progesterone can be increased are ovarian cysts, ovarian tumors and testicular tumors which increase progesterone secretion. Also, adrenal hyperplasia from congenital or oncologic origin can increase progesterone through overproduction of progesterone precursors. Stress and caffeine have also been linked to slightly elevated levels.^{43,44}

Conditions of High Progesterone

It is unclear if endogenously produced progesterone elevations result in any specific medical condition, aside from elevated progesterone symptoms, listed below.

Synthetic progestins have been positively associated with breast cancer risk.^{45,46} Observational studies suggest, in menopausal women, estrogen and (bioidentical) progesterone use may be associated with lower breast cancer risk compared to estrogen and synthetic progestin combinations.⁴⁷ One recent study, in postmenopausal women not on hormone replacement, suggests that endogenously elevated progesterone is associated with elevated breast cancer risk in menopausal women, however this predominates in women with moderate to high estradiol levels. In this study, women with low estradiol levels and elevated progesterone had a reduced breast cancer risk.⁴⁸ More studies in all aspects of bioidentical progesterone and breast cancer risk would help clarify ongoing questions.

Symptoms Associated with High Progesterone⁴⁹

- Drowsiness
- Headache
- Acne
- Dizziness
- Weight gain
- Water retention/bloating

Causes of Low Progesterone

In a non-pregnant woman, low progesterone can be caused by irregular or anovulatory cycles (including during breastfeeding), PCOS, aging and menopause, thyroid disorders, obesity, over exercise, hyperprolactinemia, anorexia, long term use of NSAIDs,⁵⁰ oral contraceptives,⁵¹ and endometriosis. Environmental toxicants such as phthalates, pesticides, herbicides, etc., show pre-clinical evidence of reduced steroidogenesis, including progesterone.⁵²

Low progesterone in pregnancy can be caused by ectopic pregnancy or complications or failure with the fetus or placenta. Later in pregnancy, low progesterone can be caused by toxemia or pre-eclampsia of pregnancy.

In men, while sudden dramatic reductions in progesterone are uncommon, waning progesterone can occur as a sequelae of reduced androgens that occur gradually over time after the 4th decade in men.⁵³

Conditions Associated or Worsened by Low Progesterone⁵⁴

- Amenorrhea
- Endometrial hyperplasia
- Abnormal uterine bleeding
- Luteal deficiency
- Decreased ovarian function
- Anovulatory menstrual cycles
- Ectopic pregnancy
- Turner's syndrome
- Hypogonadism
- PCOS
- Eclampsia
- Miscarriage
- Menopause and aging

Symptoms Associated with Low Progesterone⁵⁵

- Headaches
- PMS Symptoms
- Mood swings
- Bloating
- Insomnia
- Infertility
- Breast tenderness
- Anxiety/depression
- Dysmenorrhea
- Irregular menstrual cycles

The Progesterone to Estradiol Ratio – PG/E2 Ratio

What is the Progesterone to Estradiol Ratio – PG/E2 Ratio?

The Pg/E2 ratio is commonly used empirically as a marker of "Estrogen Dominance," developed, and popularized by the late John Lee, MD.⁵⁶ Conventionally, the Pg/E2 ratio is also used in IVF research for pregnancy rates and has been studied for assorted characteristics of menstrual cycles and fibrocystic breast disease.⁵⁷⁻⁵⁹

↑ Elevated Pg/E2 Ratio Causes

An elevated Pg/E2 ratio can be caused by exogenous progesterone use (most common), increased endogenous progesterone production (i.e., common in pregnancy), and/or decreased estradiol production. Empirically this is termed "Progesterone Dominance."

↑ Conditions Associated with Increased PG/E2 ratio

Clinically, progesterone dominance can be associated with symptoms of increased progesterone (refer to progesterone section) as well as increased symptoms of estrogen deficiency due to hormone receptor down-regulation.

Progesterone is hyperthermic, thus, an increase in the Pg/E2 ratio across the menstrual cycle is associated with increased average body temperature.⁵⁷

In IVF treatments, increased Pg/E2 ratio during the follicular phase is associated with decreased pregnancy as compared to later luteal rise in Pg/E2.⁵⁸

↓ Decreased Pg/E2 Ratio Causes

A decreased Pg/E2 ratio infers low progesterone relative to estradiol concentrations. A low ratio can be caused by natural perimenopausal reductions in progesterone which precede reductions in estradiol. It can also occur later in menopause and andropause with natural aging and reduced progesterone levels.

A decreased Pg/E2 ratio can additionally reflect sub-optimal clearance of estradiol and/or estradiol metabolites related to metabolic health conditions, impaired detoxification pathways and/or environmental xenoestrogen exposure.

↓ Conditions Associated with Decreased Pg/E2 Ratio

A decreased Pg/E2 ratio is empirically known as "Estrogen Dominance" as coined by John Lee, MD.⁵⁶ Clinically this produces estrogen excess symptoms and progesterone deficiency symptoms. Refer to respective progesterone and estradiol sections for a thorough listing of these symptoms.

There is some research to suggest decreased Pg/E2 ratio is associated with fibrocystic breast disease and luteal mastodynia.⁵⁹

In IVF treatments, a significantly decreased Pg/E2 ratio during the late follicular phase is associated with decreased pregnancy rates.⁶⁰

Lifestyle Considerations for Estrogen and Progesterone Hormone Imbalances

ESTROGEN DOMINANCE/PROGESTERONE DEFICIENCY

Treatment objectives: Consider which of the following single or combination of therapeutic approaches is the best fit for the patient with estrogen dominance and/or progesterone deficiency

- Reduce circulating estradiol, estrone and xenoestrogens
- Target microbiome support for enhanced estrogen clearance
- Decrease aromatization from androgens to estrogens, especially with excess adiposity
- Increase progesterone and Pg/E2 ratio when indicated

HOLISTIC TREATMENT CONSIDERATIONS FOR ESTROGEN DOMINANCE/PROGESTERONE DEFICIENCY

Lifestyle Considerations	Reduction of Estrogens and Xenoestrogens	Support Microbiome for Estrogen Clearance	Decrease Aromatase Activity	Increase Progesterone and Pg/E2 Ratio
Specific Supplements	<p>DIM up to 300mg per day⁶¹</p> <p>Sulforaphane*⁶²</p> <p>Vitamin D Repletion in deficient women (to blood levels above 32ng/mL) ↑SHBG and ↓bioavailable E2 and testosterone⁶³</p>	<p>Lactobacillus spp^{64*}</p> <p>Calcium D - glucarate 1500mg or higher/day*</p>	<p>Numerous flavonoids show preclinical evidence of decreased aromatase activity*: Resveratrol⁶⁵</p> <p>Grape Seed extract⁶⁶</p> <p>Citrus Peels/citrus flavonoids⁶⁷</p> <p>Apigenin⁶⁵</p> <p>Chrysin^{68,69}</p>	<p>Vitex agnus castus 40mg per day⁷⁰</p> <p>Vitamin C 750mg/day⁷¹</p> <p>B6 pyridoxine 200mg per day⁷²</p> <p>White peony root—daily tea or 3-5 g of root/day⁷³</p> <p>Evening Primrose Oil^{74*}</p>
Additional Pathways to consider for support:	<p>Phase II Liver Support</p> <p>Methylation Support</p> <p>COMT Support (if genetic variants are present)</p>			
Diet	<p>Brassica family vegetables – 1.5 servings/day⁶³</p> <p>Wheat sprout juice -100ml/day⁷⁵</p> <p>Broccoli sprouts^{62*}</p>	<p>Fiber from fruit/veggies - 30 g/day⁷⁶</p> <p>Flaxseed meal – 10 -30 g/day^{77,78}, positive benefits with 50mg lignans per day⁷⁷</p> <p>Kefir^{64*}</p>	<p>White button mushrooms^{66*}</p> <p>Foods with apigenin and/or resveratrol: grapes, berries, celery, parsley, onions, oranges, chamomile, thyme, basil, oregano, red wine⁷⁹</p> <p>Kale, collards⁶⁶</p>	<p>Increase foods high in zinc, B6, Vitamin C, Magnesium^{71,72}</p>

Exercise/ Sauna	Dry Sauna- 15 minutes 3x per week* Exercise – 100-300minutes/week treadmill/aerobic reduces estrogen⁸⁰	Moderate exercise benefits microbiome diversity⁸¹	150 minutes moderate activity per week if weight loss is needed	
Misc. Lifestyle Factors	Reduce or avoid exogenous OCP, HRT Avoid endocrine disruptors such as phthalates, BPA, growth hormones in meat, pesticides ⁸²		Weight loss if obesity or PCOS is present ⁸³ Lifestyle support to reduce inflammation secondary to obesity ⁸⁴	Consider Progesterone replacement therapy with oral micronized, transdermal, or compounded prescription. **

* Dosage information for this indication is not well established, refer to empiric guidelines of safe and effective use

** Assess risk/benefit analysis for the specific individual prior to giving hormone replacement therapy

Further testing for further treatment avenues for consideration for estrogen dominance:

1. **Nutripro or Methylation panel** by Vibrant Wellness testing for genetic snp's which may lead to estrogen metabolism issues (MTHFR, COMT)
2. **Gut Zoomer** testing for microbiome and beta glucuronidase influences
3. **Urinary Hormones** testing for estrogen and progesterone metabolites
4. **Environmental Toxins** Test- for plasticizers and other environmental toxicant burden
5. **Cardiometabolic** Testing with Vibrant America Cardiac Health and Diabetes Panel.
6. **Neural Zoomer Plus or Neurotransmitter** testing – progesterone is a neuroprotectant and neuromodulator, progesterone deficiency may affect these pathways

ESTROGEN (E2) DEFICIENCY SYMPTOMS

Treatment Objectives- Consider which of the following single or combination of therapeutic approaches is the best fit for the patient with estrogen deficiency symptoms.

- Modulate and reduce vasomotor symptoms, insomnia, mood disturbances
- Enhance quality of life during natural transitions in aging
- Prevent sequelae of severe estrogen deficiency conditions i.e., cognitive, bone and cardiometabolic

HOLISTIC TREATMENT CONSIDERATIONS FOR ESTROGEN (E2) DEFICIENCY

Lifestyle Considerations	Vasomotor symptom/mood support
Supplements *	<p>Black Cohosh for mood and hot flashes 40-127mg/day⁸⁵</p> <p>Soy Isoflavones for vasomotor symptoms, bone loss, hypertension – trial doses ranged from 40-120mg isoflavones per day ⁸⁶ Use organic, non-GMO isoflavones</p> <p>Maca 3.0 g/d for libido, depression in menopausal women; improvement in testosterone, but not estradiol, in women⁸⁷</p> <p>Kudzu (Pueraria spp.)- may aid vasomotor symptoms, bone loss, vaginal symptoms – 20 mg to 2.5g/day in most human clinical studies for menopausal symptoms. Topical doses 0.5–1.0 g/day in gel^{88,89,90}</p> <p>Red Clover for hot flashes ≥ 80mg/d⁹¹</p> <p>Red Ginseng 0.9-3mg/day for fatigue, memory, hot flashes⁹²</p> <p>Ashwagandha 300mg 2x/day for vasomotor symptoms, increased estradiol in perimenopausal women in one study⁹³</p> <p>Vitamin E 800 IU/day for hot flashes⁹⁴</p> <p>Fenugreek seed 600mg/day de-husked seed extract for vasomotor symptoms⁹⁵</p>
Diet	<p>Mediterranean diet to reduce menopausal symptoms⁹⁶& cardiometabolic issues⁹⁷</p> <p>Diet with increased fruit/veg, fiber & less sugar and fat improves vasomotor symptoms⁹⁶</p> <p>High fiber and soy isoflavones decrease vasomotor symptoms⁹⁶</p>
Exercise/Sauna	<p>150 minutes moderate aerobic + strength training ⁹⁸ - support for bone health, general estrogen deficiency symptoms</p> <p>Yoga – variable practices aid vasomotor and psychological health⁹⁹</p>
Stress Management	<p>Cognitive Behavioral Therapy for vasomotor symptoms, insomnia¹⁰⁰</p> <p>Hypnosis for reduction in hot flash severity¹⁰¹</p> <p>Aromatherapy/massage¹⁰¹</p> <p>Mindfulness Meditation for distress from vasomotor symptoms¹⁰²</p> <p>Acupuncture for hot flashes¹⁰³</p>
Miscellaneous Support	<p>Nutrient and Bone Support via diet, supplements and exercise as indicated for osteoporosis prevention</p> <p>Cardiometabolic support via diet, exercise and supplements as indicated</p> <p>ERT or HRT - consider for severe symptoms or prevention of severe estrogen deficiency sequelae **</p>

* Use of some supplements could result in specific hormone increases with use. Always research a specific product prior to use with patients, especially those at higher risk for hormone related cancer.

** Fully research the individual patient's risk/benefit analysis regarding hormone related cancer and other side effects or ERT or HRT prior to recommending.

Further testing considerations for estrogen deficiency

- **Cardiovascular Health** and CardiaX tests from Vibrant America
- **DEXA** testing for osteoporosis
- **APOE** testing for Alzheimer's Disease
- **Colorectal cancer screening**

LIFESTYLE CONSIDERATIONS FOR LOW ESTRIOLOL RATIO - E3/E2+E1

Treatment objectives for estriol ratio lower than 1.0:

- Modify excess E2 and E2 through lifestyle interventions as suggested in estrogen dominance section
- Assess and correct for any pre-existing iodine deficiency

Integrative medicine physicians have used iodine therapy empirically to balance effects of a low E3/E2+E1 ratio and potentially reduce risk of breast disease. This has been based on combining ideas from clinical studies regarding estriol risk and fibrocystic breast disease and breast cancer,^{38,104} as well as pre-clinical evidence that iodine/iodide can modulate estrogen metabolic pathways to favor inactivation of E2.¹⁰⁵⁻¹⁰⁸ Further clinical trials needed.

Iodine interventions, beyond diet suggestions for deficiency, require physician oversight including measures such as initial thyroid and iodine testing, ongoing monitoring, and careful consideration of dose, form, and length of iodine usage. Iodine excess may precipitate hyperthyroidism, hypothyroidism, goiter, and/or thyroid autoimmunity.¹⁰⁹

LIFESTYLE CONSIDERATIONS FOR LOW PROGESTERONE/ESTRADIOL RATIO

Refer to table for Holistic Treatment Considerations for Estrogen Dominance/Progesterone Deficiency.

Testosterone

What is Testosterone?

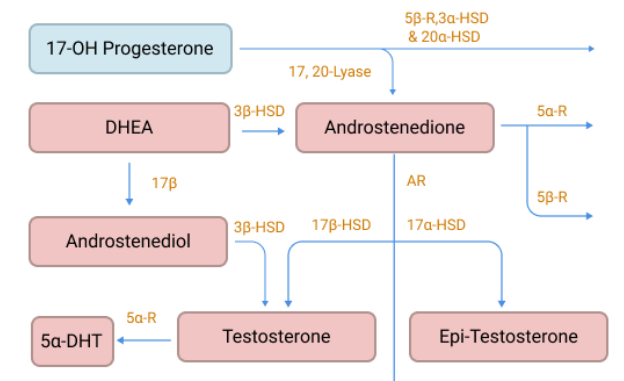
Testosterone is the predominant androgen produced in males and females. In both males and females, testosterone supports reproductive function and libido, maintains muscle mass and bone structure, supports cardiac health and promotes optimal brain function.¹¹⁰ In males, at puberty, testosterone promotes the development of the male sexual organs and secondary sex characteristics such as deep voice, body hair and libido. It also contributes to the anabolic status of tissues such as red blood cells, muscle mass, linear growth and bone density.¹¹¹

In females, testosterone is produced by ovarian production as well as adrenal secretion. Ovarian production of testosterone increases during the follicular phase of the menstrual cycle and reaches the highest levels at ovulation and the luteal phase. In advancing age, ovarian production of testosterone decreases gradually throughout age, rather than suddenly in a menopausal transition.¹¹² Nonetheless, by menopause total testosterone levels in women aged 65-74 years is approximately one-third that observed in women who are aged 20 years.¹¹⁰

The benefit of salivary testosterone testing is that it is consistent with serum free testosterone rather than total testosterone levels. Levels of serum total testosterone are often influenced by sex hormone binding globulin levels which are affected by numerous conditions such as obesity and metabolic syndrome, thyroid disorders, steroid use, PCOS, pregnancy, etc.¹¹³

How is Testosterone made ?

Testosterone is produced primarily by the gonads, i.e., testes and ovaries, in men and women. Secondly it is produced by the adrenal glands, as well as in peripheral tissues from metabolites originating in gonads and adrenal glands. The main precursor is DHEA, which is converted to androstenedione or androstenediol by the enzyme 3 β -HSD2, and then to testosterone via 17 β -HSD or 3 β -HSD2 respectively.



Causes of High Testosterone

Endogenously high testosterone in males is uncommon, however can be a result of precocious puberty, adrenal hyperplasia or tumor, testicular tumor, and CNS lesion. Commonly it can also reflect exogenous supplementation whether from prescriptions or adulterated over the counter "libido boosting" or "male enhancing" supplements.

In females, high testosterone can be a result of idiopathic hirsutism, polycystic ovary syndrome, abnormal menstrual cycles, congenital adrenal hyperplasia, ovarian tumors and intersex physical characteristics.

It can also be higher in smokers, those exposed to pollutants (polychlorobiphenyls, hexachlorobenzene), and with eating disorders. It can also be high with use of the following drugs: anticonvulsants, atrial natriuretic hormone, barbiturates, cimetidine, clomiphene, estrogens, gonadotropin (males), kaliuretic hormone, oral contraceptives, and vessel dilator hormone.¹¹⁴

Conditions Associated with High Testosterone¹¹⁵

- Androgenetic alopecia (males)
- Infertility
- Breast Cancer (inconclusive studies with exogenous testosterone use)
- Polycythemia/erythrocytosis (with exogenous testosterone use)
- Obstructive sleep apnea with polycythemia (with exogenous testosterone use)
- Prostate enlargement/prostate carcinoma (exogenous testosterone use, conflicting studies)
- Hepatotoxicity (with methyl testosterone use)
- Hypertension and cardiovascular events (inconclusive studies with exogenous testosterone use)
- PCOS (female)
- Virilization in pre-pubertal males and females

Symptoms of High Testosterone

In adult women, increased adrenal androgen production causes hirsutism, acne, male-pattern baldness, menstrual irregularities, oligomenorrhea or amenorrhea, infertility. In more extreme clinical situations, frank virilization can occur at varying ages, which involves a more severe hirsutism along with broad range of signs suggestive of androgen excess such as ambiguous external genitalia, deepening of the voice as well as the above symptoms.

In males, symptoms of acne, hirsutism, oligospermia, hypo-fertility, and elevated anxiety and aggression can be caused from excess endogenous androgen production.¹¹

Causes of Low Testosterone

There can be many common causes of low testosterone such as: Increased body mass, heavy alcohol use, hypopituitarism, hyperprolactinemia, hypothyroidism, and late-onset hypogonadism (andropause).¹¹⁷ In women, oophorectomy and menopause are also common contributing causes.¹¹⁴

Other causes can be the following: cirrhosis, COPD (moderate to severe), Klinefelter syndrome, Down syndrome, obstructive sleep apnea, end-stage renal disease, adrenal insufficiency, epilepsy, trauma to gonads or head, hemochromatosis, human immunodeficiency virus, and male hypogonadism.

Drugs which contribute to low testosterone include anabolic steroids, cyproterone, dexamethasone, diethylstilbestrol, digitalis, digoxin (males), estrogen therapy (increases SHBG), ethyl alcohol, glucose, glucosteroids, gonadotropin-releasing hormone analogs, finasteride, halothane, ketoconazole, metoprolol, metyrapone, opioids, phenothiazines, spironolactone, and tetracycline.¹¹⁴

Conditions Associated with Low Testosterone¹¹⁸

- Diabetes Mellitus Type 2 (Total but not free testosterone)
- Frailty, Sarcopenia
- All-cause mortality, cardiovascular mortality
- Alzheimer's Disease (Free but not total testosterone)
- Adiposity
- Anemia
- Dysthymia
- Osteoporosis and Fractures
- Androgenetic alopecia
- Gynecomastia (males)
- Infertility
- Erectile dysfunction

Symptoms Associated with Low Testosterone¹¹⁷

Symptoms of androgen deficiency are numerous and include the following:

- Low libido
- Reduced bone strength
- Poor concentration
- Depression
- Breast discomfort in males
- Fatigue
- Decreased motivation
- Loss of muscle mass
- Memory issues
- Disturbance of normal sleep pattern
- Reduced physical performance ability
- Delayed development of secondary sex characteristics in prepubertal males
- Decreased body hair
- Weight gain

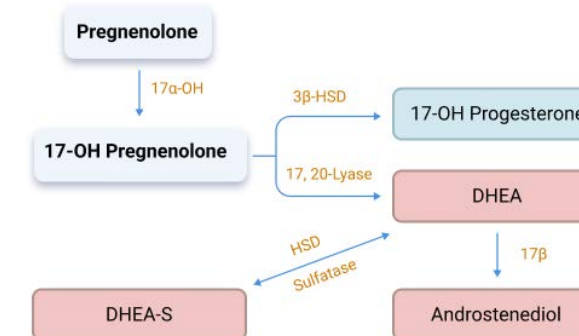
DHEA-S

What is DHEA-S?

DHEA-S is quantitatively the most abundant circulating steroid hormone produced by the adrenal glands. DHEA-S is the sulphated, most abundant, version of DHEA; compared to DHEA it has a longer half-life, does not have diurnal variation, and provides a stable circulating pool from which to measure adrenal androgen activity. By itself, DHEA and DHEA-S are just slightly androgenic but serve as a precursor to androgens and estrogen in the periphery.¹¹⁹ DHEA-S is known to be active as a neurosteroid and a buffer from the effects of oxidation and glucocorticoids.^{120,121} Typically, females are referred for DHEA-S testing for virilization and/or PCOS evaluation. Males are referred for DHEA-S testing for congenital adrenal hyperplasia, primary or secondary adrenal insufficiency, adrenal tumors hypertension and alopecia.

How is DHEA-S Made?

DHEA-S, like all steroid hormones, begins with the conversion of cholesterol into pregnenolone by the mitochondrial enzyme p450_{scc}. Pregnenolone is then converted into 17-OH pregnenolone by a 17 α -hydroxylase reaction. The 17,20-lyase reaction follows which converts 17-OH pregnenolone to DHEA. The sulfation of DHEA into DHEA-S is catalyzed by the enzyme hydroxysteroid sulfotransferase (HST, SULT2A1), commonly known as DHEA sulfotransferase. DHEA-S can also be converted back into DHEA by steroid sulfatase (STS).¹²¹



Causes of High DHEA-S

DHEAS can be mildly elevated for idiopathic reasons; other considerations include exogenous supplementation, androgen secreting adrenal tumor, elevated cortisol, PCOS, steroid sulfatase (STS) deficiency, precocious puberty, and congenital adrenal hyperplasia.^{122,123}

Symptoms of High DHEA-S

In males, often there are not noticeable symptoms of elevated DHEA. Men can, however, experience symptoms of estrogen excess through peripheral conversion of androgens to estrogen. Women experience androgenic symptoms from elevated DHEA.

Causes of Low DHEA-S

Biological aging in males and females produces lower DHEA-S levels. Also, chronic stress, chronic inflammation,¹²⁴ primary and secondary adrenal insufficiency, and hypothyroidism can result in lower DHEA-S levels. Low levels in amniotic fluid indicate anencephaly in the fetus. Drugs include carbamazepine, dexamethasone, opioids, phenytoin.¹²²

Conditions Associated with Low DHEA-S:

There are numerous conditions in which there are associated low DHEA-S values as seen below.^{120,121}

- SLE
- Progressive systemic sclerosis
- Inflammatory Bowel Disease
- Rheumatoid arthritis
- Inflammatory Bowel Disease
- Increased coronary heart disease
- Increased All-Cause Mortality
- Septic Shock
- Depression/Anxiety
- Bipolar Disorder
- Alzheimer's Disease
- Sarcopenia
- Androgen Deficiency symptoms

Lifestyle Treatment Considerations for Androgens

ANDROGEN EXCESS

Treatment Objectives: Consider which of the following single or combination of therapeutic approaches is the best fit for the patient with symptoms related to androgen excess.

- Reduce circulating free androgens
- Increase insulin sensitivity
- Increase sex hormone binding globulin (SHBG) to decrease circulating free androgens
- Weight loss if obesity is present

HOLISTIC TREATMENT CONSIDERATIONS FOR ANDROGEN EXCESS

Lifestyle Considerations	Reduce free androgens in women/improve insulin sensitivity	Interventions that may increase SHBG (Sex Hormone Binding Globulin)
Supplements	<p>NAC in PCOS patients 600mg/3x per day¹²⁵</p> <p>Vitamin D – 4000iu/day¹²⁶ Additionally, repletion in deficient women (to blood levels above 32ng/mL) ↑SHBG and ↓bioavailable E2 and testosterone⁶³</p> <p>Myo-inositol 4g/day or D-chiro inositol 1g/day^{127,128}</p> <p>Soy isoflavones 50g/day¹²⁹</p> <p>Berberine – 400mg/TID – improves insulin sensitivity¹³⁰</p> <p>Chromium* – Improve insulin resistance, may lower DHEA levels in adipose tissue in PCOS patients¹³¹</p> <p>Zinc, Magnesium and Selenium to counter deficiencies in diet¹³²</p>	<p>DIM 300mg/day¹³³</p> <p>Refer to Insulin Modulating interventions - increased insulin decreases SHBG¹³⁴</p>
Diet	<p>DASH Diet -reduce insulin resistance promotes weight loss in PCOS¹³⁵</p> <p>Mediterranean Diet – reduces insulin¹³⁵</p> <p>Calorie Restriction Diets -reduce insulin resistance promotes weight loss in PCOS¹³⁵</p> <p>Low Glycemic/Ketogenic diet¹³²</p> <p>Almonds 46 g/d¹³⁶</p> <p>Walnuts 36 g/d¹³⁶</p> <p>Prebiotics/ Probiotics* -Increased microbiome diversity¹³⁷</p> <p>Soy isoflavones in diet – 50g/d¹²⁹</p> <p>Spearmint tea¹³²</p>	<p>Coffee, Tea and other caffeine containing beverages *¹³⁹</p> <p>Walnuts 36g/day¹³⁶</p> <p>Soy milk 30g/day¹⁴⁰</p> <p>Olive Oil*¹⁴¹</p> <p>High Fiber diet, vegetarian diet¹⁴¹</p> <p>Insulin Modulating interventions as increased insulin decreases SHBG¹³⁴</p>

	<p>Green tea¹³²</p> <p>Licorice tea¹³²</p> <p>Flax seed meal 30g/day¹³⁸</p>	
Exercise/ Sauna	<p>Vigorous aerobic exercise – minimum of 120 minutes per week alone or with resistance training – reduce insulin resistance in PCOS, aid body composition¹³²</p>	<p>Moderate intensity exercise 225 min/week¹⁴²</p>
Misc Factors	<p>Optimizing sleep aids with regulation of dysglycemia¹³²</p>	<p>Drugs that increase SHBG include Tamoxifen and other selective estrogen-receptor modulators (SERM's), oral estrogen, metformin, and anti-seizure medications</p>

* Dosage information is variable or not well established for this specific benefit; refer to empiric or published standards of safe use

Additional treatment options:

- If hirsutism is present consider including use of 5-alpha-reductase enzyme blocking herbal supplements such as: Serenoa repens, Camellia sinensis, Rosmarinus officinalis, Glycyrrhiza glabra, etc.¹³²
- Pharmacologic therapy such as spironolactone, or spironolactone in combination with licorice¹³²

Further testing considerations for androgen excess:

- **Fasting Glucose, Insulin, HgbA1c**
- **Thyroid Panel**
- **IGF-1**
- **Prolactin**
- **Liver function tests**
- **SHBG**
- **Urine Hormones Test** from Vibrant America for testosterone and estrogen metabolites
- **Environmental Toxins Test** from Vibrant America to assess xenoestrogen compounds

TESTOSTERONE/ANDROGEN DEFICIENCY

Treatment Objectives: Consider which of the following single or combination of therapeutic approaches is the best fit for the patient symptoms of testosterone/androgen deficiency.

- Reduce aromatase activity
- Support symptoms of low androgens
- Reduce obesity and insulin resistance to reduce aromatase production
- Reduce exposure to phthalates and heavy metals

HOLISTIC TREATMENT CONSIDERATIONS FOR TESTOSTERONE DEFICIENCY

Lifestyle Interventions	Symptomatic Support/Increase Testosterone	Decrease Aromatase Activity
Supplements	<p>Withania somnifera (Ashwagandha) studied to boost testosterone in men – i.e KSM-66 300mg/ BID or TID, Shoden brand 21mg withanolide glycoside/d or 5g root powder/day¹⁴³⁻¹⁴⁶</p> <p>Trigonella foenum-graceum (Fenugreek) 500-600mg/day seed extract boosts testosterone & libido in males¹⁴⁷</p> <p>Mucuna pruriens - 5g/day seed powder improves T in infertile men and boosts semen quality¹⁴⁸</p> <p>Eurycoma longifolia (Long jack) – 200-400mg/day increased libido, testosterone, ED in men, ¹⁴⁷ conflicting studies on efficacy</p> <p>Korean Red Ginseng 1500mg/BID – Improves serum testosterone in men with metabolic syndrome,¹⁴⁹ conflicting studies on efficacy¹⁴³</p> <p>DHEA >50g/day^{150**} may boost T levels, esp. in women</p> <p>Nigella Sativa – improves semen parameters in infertile men¹⁴⁷</p> <p>Tribulus terrestris – 750mg/day – improved sexual enhancement in women,¹⁴⁷ several studies show no increase in T in men,¹⁴³ may enhance libido</p> <p>Maca -1500mg root/BID – improvement in testosterone/libido/sexual function in women on SSRI,⁸⁷ several studies in men show no increase in T¹⁴³</p> <p>Saw palmetto - Increased T, with decreased DHT and Estrogen in men at 800mg - 2000mg/day ⁶⁶</p>	<p>Numerous flavonoids show preclinical evidence of decreased aromatase activity*:</p> <p>Resveratrol⁶⁵</p> <p>Grape Seed extract⁶⁶</p> <p>Citrus Peels/citrus flavonoids⁶⁷</p> <p>Apigenin⁶⁵</p> <p>Chrysin (Honey/propolis) ^{68,69}</p>
Diet	<p>Diets that aid weight loss - In obese men and/or men with metabolic syndrome – weight loss through a variety of diet and exercise or bariatric surgery programs consistently increase testosterone ¹⁵¹</p>	<p>White button mushrooms* ⁶⁶</p> <p>Foods with apigenin and/or resveratrol: grapes, berries, celery, parsley, onions, oranges, chamomile, thyme, basil, oregano, red wine ⁷⁹</p> <p>Kale, collards ⁶⁶</p>

Exercise/Sauna	Exercise programs that aid weight loss - In obese men and/or men with metabolic syndrome – multiple, varied diet/exercise programs that resulted in weight loss significantly improve testosterone levels. ¹⁵¹	150 minutes moderate activity per week ⁸³
Stress Management	Optimize sleep , sleep deprivation (<5hours/night) linked to decreased testosterone ¹⁵¹ High occupational stress is linked to lower testosterone levels. ¹⁵¹ Stress management interventions may be helpful.	
Miscellaneous Support	Aromatase inhibitors, SERM's and hCG have been shown to raise testosterone ¹⁵¹ Varicocele repair significantly improves testosterone levels ¹⁵² Testosterone replacement therapy (TRT) is an option for hypogonadal men. It has shown to improve sexual function, muscle strength, bone density, and mood and cognition ^{***}	Metformin may aid increases in T in men with metabolic syndrome ¹⁵³

* Dosage information for this indication is not well established, refer to empiric guidelines of safe and effective use.

** May increase estrogen and other hormone levels, use under physician supervision and hormonal lab monitoring.

*** Fully research the individual patient's risk/benefit analysis regarding hormone related cancer and other side effects of testosterone replacement therapy (TRT) prior to recommending. Side effects of TRT include erythrocytosis, male infertility, testicular atrophy, and gynecomastia.¹⁵² There are also concerns but inconclusive data regarding the role of exogenous testosterone with cardiovascular risks, prostate cancer risks and venous thromboembolism.¹⁵²

Further Support for Testosterone Deficiency includes:

- Avoidance of phthalates and heavy metals in foods and household products. These can reduce testosterone levels through various mechanisms. Further resources for avoidance and elimination of environmental toxicants can be found from the National Association of Environmental Medicine at <https://envmedicine.com>

Further testing considerations for testosterone deficiency:

- Serum LH and FSH to determine if hypogonadism is primary or secondary in males
- Semen analysis in men with infertility
- CBC to rule out anemia
- Environmental Toxins Test from Vibrant America for phthalates and heavy metals

Salivary Hormone Assessment, Monitoring, and Evaluation of Transgender Persons

Gender-affirming hormone therapy is a multidisciplinary treatment that may involve endocrinologists, primary care practitioners, and specialists. Clinicians should be knowledgeable about the diagnostic criteria for gender-affirming hormone therapy and should aim to maintain physiologic levels of gender-appropriate hormones and persistently monitor hormone levels and metabolic parameters for adverse effects, risks, and complications of treatment. A comprehensive resource to guide gender-affirming hormone therapy is the clinical practice guideline from the Endocrine Society entitled, Endocrine Treatment of Gender Dysphoric/Gender Incongruent Persons: An Endocrine Society Clinical Practice Guideline.¹⁵⁴

Adrenal Hormone Testing – A Window into HPA Axis Function

HYPOTHALAMIC PITUITARY AXIS INFOGRAPHIC

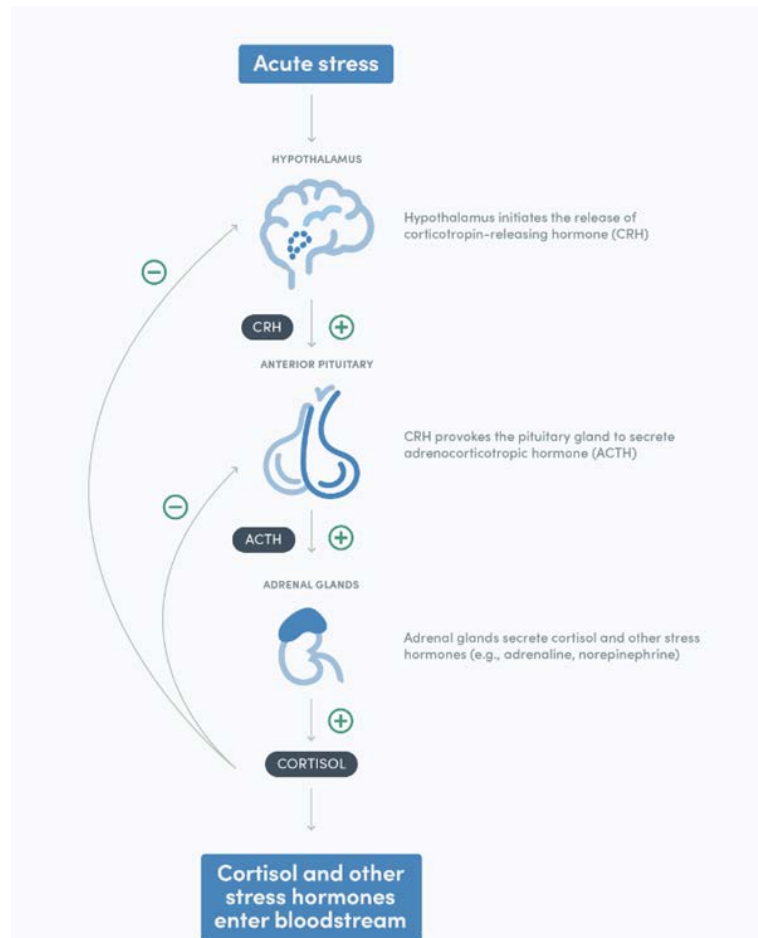


Figure 2. HPA Axis Infographic. Referenced from <https://fullscript.com/practice-resources?g=all>. Adapted and used with permission.

SALIVARY TESTING AND HPA AXIS DYSREGULATION

Testing of salivary cortisone and cortisol can offer a window into HPA (Hypothalamic pituitary axis) function and dysregulation. A normal physiological response of the HPA axis to a stressful event is characterized by a quick increase in cortisol level, followed by a decrease once the stressor is gone.¹⁵⁵ This process is controlled by the self-regulatory system of the HPA axis. Disturbances in this regulation can be observed in one-time or the diurnal pattern of cortisol release and have been linked to the development of stress-related body and mental disorders. These disorders include conditions such as: Type 2 diabetes, Cushing's disease, hypertension, CFS, fibromyalgia, chronic pain, depression, PTSD, and schizophrenia, among others.

As discussed previously, the primary advantage of salivary, versus plasma, cortisol and cortisone measurement in the endocrine workup is that it measures bioavailable, unbound hormones. Regarding glucocorticoids, approximately 90 -95% of serum total cortisol is bound to proteins such as corticosteroid-binding globulin (CBG) and albumin.^{156,157} These proteins are affected by a wide variety of clinical conditions and medications, even common situations such as estrogen replacement therapy, which can increase CBG, and inflammatory states, which can decrease CBG. Thus, by measuring unbound hormones, the clinician obtains a more accurate picture of glucocorticoid activity in target tissues without fluctuations related to binding proteins.¹⁵⁶

FOR MONITORING HPA AXIS PERFORMANCE, TEST, DON'T GUESS!



Uncovering an HPA axis dysregulation component of a clinical condition provides a new, actionable clinical target for improving outcomes. Furthermore, in monitoring glucocorticoid values over time, changes in patterns can be associated with aspects of clinical care such as treatment responsiveness, probability of disease relapse and recovery rate.²¹⁴

RE-TEST, DON'T GUESS!

Glucocorticoids – Cortisol and Cortisone

Figure 3. Glucocorticoid Production.

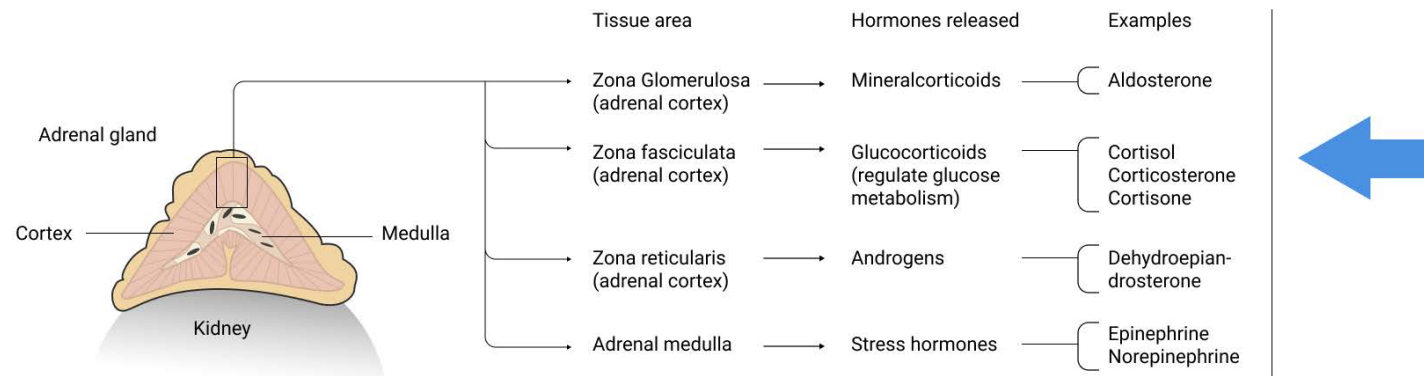


Illustration Source: Anatomy & Physiology, Connexions Web site. <http://cnx.org/content/col11496/1.6/>, Jun 19, 2013. OpenStax College, CC BY 3.0, via Wikimedia Commons. Adapted by Vibrant America.

Cortisol is widely known as “the stress hormone,” and nearly all tissues of the body have glucocorticoid receptors to respond to the actions of cortisol. Cortisol plays a significant role in maintaining glucose and protein homeostasis, mediation of the stress and immune response, and suppression of inflammation.¹⁵⁸

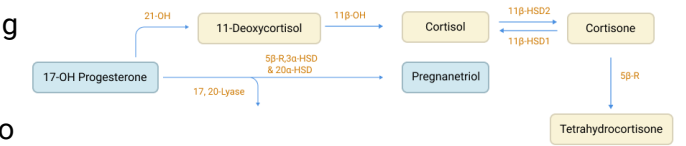
The hypothalamus-pituitary-adrenal axis (HPA axis) regulates production and secretion of cortisol. It does this through release of CRH, corticotropin releasing hormone, from the hypothalamus which signals ACTH, adrenocorticotropin hormone, release from the pituitary gland to the adrenal cortex, which then releases cortisol. After cortisol is released in response to these signals, cortisol sends a negative feedback loop to suppress further production of ACTH and CRF. (See Figure A on preceding page.)

The HPA axis function follows a diurnal pattern of release, therefore cortisol levels are highest in the morning after waking and lowest at night around bedtime.¹⁵⁸ Aside from diurnal secretion of hormones, and measured pulsatile releases of hormones, HPA axis function and release of cortisol are also triggered by stressors, both acute and chronic.

Cortisol and Cortisone

How is Cortisol Made?

Cortisol undergoes steroidogenesis similarly to other steroid hormones, originating from cholesterol and progressing to progesterone. From 17-OH progesterone, cortisol goes through two hydroxylation steps to arrive at 11-deoxycortisol which is then further hydroxylated by 11 β -hydroxylase to arrive at cortisol, as pictured to the right.



In the tissues, the glucocorticoids (cortisol, cortisone and corticosterone) are regulated by 11 β hydroxysteroid dehydrogenases, type 1 and type 2.

Local Tissue Regulation of Cortisol Cortisone

Initially cortisol is unidirectionally converted to cortisone, an inactive metabolite, by 11 β hydroxysteroid dehydrogenase type 2 (11 β -HSD2). 11 β -HSD2 is highly expressed in aldosterone-selective target tissues such as the distal nephron, colon, skin and the salivary glands in particular.¹⁵⁷ Due to this enzyme activity, concentration of cortisone in saliva is 2–6 times higher than that of cortisol.¹⁵⁹

The function of 11 β -HSD2 to convert cortisol to cortisone is critical in tissues to protect from overexposure to active cortisol and corticosterone.¹⁶⁰ Otherwise, these active hormones would occupy mineralocorticoid receptors and produce a cascade effect of mineralocorticoid excess symptoms such as sodium retention, hypertension, and hypokalemia.¹⁶¹

Local Tissue Regulation of Cortisone Cortisol

In contrast, in metabolically active tissues such as the liver (20-40% of daily production) adipose tissue, and skeletal muscle, 11 β -Hydroxysteroid dehydrogenase, type 1 (11 β -HSD1), reversibly catalyzes the 11 β -reduction of cortisone to cortisol, and regenerates cortisol within these tissues.^{161,162}



BENEFIT OF BOTH CORTISONE AND CORTISOL IN SALIVARY MEASUREMENTS

Salivary cortisol has been a mainstay of bioavailable glucocorticoid measurements for over 20 years. Salivary cortisone is a newer addition to salivary hormone testing due to advances in testing. Nonetheless, salivary cortisone, like salivary cortisol, has also been found to be strongly associated with serum cortisol levels.¹⁵⁵ In addition, salivary cortisone has been found to be a better marker of serum free cortisol than salivary cortisol in situations when serum cortisol levels are low, or during hydrocortisone therapy or excess.¹⁵⁹

“Salivary cortisone has been found to be a better marker of serum free cortisol than salivary cortisol in situations where serum cortisol levels are low, or during hydrocortisone therapy or excess”¹⁵⁶

CLINICAL TIP

How to Evaluate Diurnal Cortisol Values

Generally, environmental as well as biological stressors can influence cortisol output throughout the day. In addition to any underlying disease condition as noted in tables below, look for sporadic stressors such as **hunger or glycemic dysregulation, pain, caffeine, cigarette or drug intake, exercise, commuting, job stress, marital stress, depression, or even chronic loneliness** when evaluating out of range values.

Elevated Timed Cortisol Samples (AM, NOON, EVENING, NIGHT)

↑ **Pooled Cortisol** -Pooled cortisol reflects overall diurnal cortisol output, collected from all samples given. Thus, it can be a measure of general HPA axis functionality. Some evidence shows that elevations in pooled cortisol reflect chronic stress. ¹⁶⁹

↑ **AM Cortisol** – In addition to the above variables, elevated waking AM cortisol values can specifically reflect depression, early stages of burnout, pain, glycemic dysregulation or job-related stress.¹⁷⁰ Severe obstructive sleep apnea has been shown to produce irregular AM cortisol values in studies (both high and low).^{171,172}

↑ **Noon Cortisol** – As a solo elevation, this generally reflects sporadic or situational stress triggers as listed above. One recent study showed that elevations specifically of noon or night cortisol accurately predicted job stress and/or burnout better than frequently studied cortisol awakening response (CAR) values (not measured with this test) which show conflicting results regarding burnout.¹⁷³

↑ **Evening Cortisol** – In addition to the above variables, high evening cortisol can be related to glycemic dysregulation due to late-day, prior to dinner collection time. In the literature it has also been associated with autism spectrum disorder, adolescence, and home related stressors such as divorce and financial strain. ^{169,174}

↑ **Night Cortisol** – This value reflects the expected nadir of cortisol output and therefore, baseline cortisol levels. Increased levels are related to insomnia, situational stressors, inflammation, and disease conditions such as the ones in the above table. Markedly increased bedtime cortisol values, i.e., at or over 5.5 ng/ml, should prompt consideration of Cushing’s syndrome or disease.¹⁷⁵

Salivary cortisol measurements, both bedtime and midnight, have been shown to diagnose Cushing’s disease as well as plasma and urine measurements.¹⁷⁵

Causes of Elevated Cortisol -Diseases or lifestyle factors which can cause elevated cortisol are as follows:^{163,164,165}

- Cushing’s Disease/Syndrome from ACTH secreting neoplasm
- Hyperpituitarism or Hyperthyroidism
- Severe hepatic disease
- Anorexia/Hypoglycemia
- Diabetes mellitus (uncontrolled)
- Adrenal neoplastic disease
- Eclampsia
- Shock
- Pregnancy
- Glucocorticoid resistance
- Infectious disease
- Burns
- Virilism
- HIV
- Opioid Withdrawal
- Crohn’s disease
- Surgery/Post op recovery
- Chronic Renal Disease
- Hypertension
- Depression/Neuropsychiatric disease
- Stress: Heat/Cold/Trauma/Pain
- Psychological Stress
- Night Shift Work/Circadian Disruption
- Obesity
- Exercise or chronic overexercise
- Cigarette smoking
- Alcoholism and alcohol withdrawal

Drugs which can increase cortisol levels include glucocorticoids, caffeine, nicotine, corticotropin, estrogens, oral contraceptives, yohimbine, and vasopressin.¹⁶⁶ Initial or short-term use of marijuana can increase cortisol, while opposite effects may result from chronic or heavy use.¹⁶⁷

Consequences of Persistent Hypercortisolism or Hyperactivation of HPA Axis¹⁶⁸

- Bone Fragility
- Dyslipidemia
- Atherosclerosis
 - Coagulation
 - Cardiovascular Remodeling
- Increased infections
- Visceral adiposity
- Sarcopenia
- Diabetes
- Mood disorders
 - Depression
 - Anxiety
 - Bipolar Disorder
 - Memory Impairment

LOW CORTISOL

↑ Causes of Decreased Cortisol - Diseases or lifestyle factors which can cause decreased cortisol are:^{166,176,174}

- Primary adrenal insufficiency due to Addison's disease
- Primary adrenal insufficiency due to adrenal destruction from other causes (malignancy, surgery, etc.)
- Primary adrenal insufficiency due to genetic conditions (i.e., CAH - congenital adrenal hyperplasia)
- Secondary adrenal insufficiency (i.e., withdrawal from glucocorticoid therapy)
- Postpartum pituitary necrosis
- Liver Disease
- Pituitary adenoma
- Craniopharyngioma/ Hypophysectomy
- Long term use or recent withdrawal from corticosteroid therapy
- Hypopituitarism
- Rheumatoid arthritis
- Early traumatic experiences, Chronic stress, PTSD
- Hypothyroidism
- Waterhouse-Friderichsen syndrome
- Recurrent infectious processes

Drugs which can decrease cortisol levels include opioids,¹⁷⁸ ketoconazole, rifampin, phenytoin, dexamethasone, dexamethasone acetate, and dexamethasone sodium phosphate. There is some evidence that marijuana affects cortisol response, namely that heavy/chronic use can blunt cortisol response.¹⁶⁷

↓ Symptoms of Persistent Hypocortisolism or Hypoactivation of HPA axis^{179,180}

- Fatigue
- Muscle weakness
- Nausea/Vomiting
- Weight loss
- Myalgias
- Pale skin
- Hyponatremia
- Dizziness and Hypotension
- Depression
- Hyperpigmentation (in primary adrenal insufficiency)

↓ Decreased Timed Cortisol Samples (AM, NOON, EVENING, NIGHT)

- ↓ **Decreased Pooled Cortisol** -Any of the above conditions can produce a decreased pooled cortisol value. Chronic stress has been linked to a flattened or attenuated diurnal output of cortisol, however the opposite has also been shown. This discrepancy has been theorized to be related to changes in HPA axis output related to long-term exposure to chronic stress.¹⁸¹
- ↓ **Decreased AM Cortisol** – Severe exhaustion can result in a decreased AM cortisol, in addition to severe obstructive sleep apnea¹⁷² and pre-existing conditions listed above. Studies have shown morning salivary cortisol can be used to test for adrenal insufficiency (Addison's disease) and it is a "non-inferior" method as compared to serum.¹⁵⁶ Researchers proposed a value lower than 1.16ng/ml (3.2nmol/L) for salivary AM cortisol should be followed up by further stimulation testing for adrenal insufficiency.¹⁵⁶
- ↓ **Decreased Noon, Evening and Night Cortisol** – Generally, decreased values represent incomplete recovery from acute stress exposures, exhaustion from chronic stress and/or conditions related to low cortisol output as seen above.

Salivary Cortisone

There are specific clinical situations in which there would be expected differing results between cortisol and cortisone. In these clinical situations, cortisone may reflect a greater accuracy than cortisol.

- Systemic glucocorticoid deficiency or excess
- Use of oral glucocorticoid therapy
- Directly following acute stress

While salivary cortisone itself is an inactive metabolite, it has been shown, like cortisol, to directly compare to serum free cortisol levels.^{155,157,159} In general, salivary cortisone values tend to parallel salivary cortisol values. Thus, similar situational or condition triggers cause elevations or depressions in salivary cortisone values as cortisol values. Diurnal cortisone values have not yet been studied for normative value comparisons.¹⁵⁵ The following considerations can be applied when reviewing cortisone values.

A NOTE ABOUT 11β-HSD ENZYMES

11β-HSD1 and 11β-HSD2 enzyme activity can affect cortisol and cortisone levels. These enzymes affect local target tissues in an intracrine manner, as in 11βHSD2 upregulating in the distal nephron and 11β-HSD1 upregulating in adipose tissue and the brain. In these scenarios, the effect is intracrine, i.e. local, and does not affect systemic cortisol production.¹⁶²

However, these enzymes also work in an endocrine manner, and may affect cortisone and cortisol levels systemically as well. For example, 11β-HSD1 in the splanchnic bed generates 30–40% of the total daily production of cortisol in humans, while 11β-HSD1 in the kidney deactivates a similar percentage.¹⁶² Thus, up or downregulation of these enzymes can play a role in cortisone and cortisol dynamic levels.

↑ Increased Cortisone Relative to Cortisol

Factors which can promote actions of 11β-HSD1 Inhibition/11β-HSD1 Upregulation in select tissues

- Estrogen¹⁶²
- Progesterone¹⁶²
- Thyroid Hormone¹⁵¹
- 7-Keto DHEA¹⁶²
- PCOS¹⁸²
- Bile Acids¹⁶²
- Pravastatin
- Coffee¹⁶⁰
- Green Tea¹⁸³
- Curcumin¹⁸⁴
- Holy Basil
- Vitamin A¹⁸⁵
- Pregnancy upregulates 11βHSD²¹⁸⁶



↑ Increased Cortisol Relative to Cortisone

Factors which may have actions of 11β-HSD2 Inhibition/11β-HSD1 Upregulation in select tissues

- Licorice (pastilles)¹⁸⁷
- Grapefruit juice¹⁸⁷
- Glucocorticoids¹⁶²
- Progesterone¹⁵¹
- Proinflammatory cytokines (IL-6, TNF-α)¹⁶²
- Synthetic endocrine disruptors (phthalates, organotins, alkylphenols)¹⁶²
- Inflammatory Conditions such as osteoporosis, joint disorders, neurodegenerative diseases, diabetes, metabolic syndrome, obesity¹⁸⁸

Clinical tip:

Clinical studies have shown increased 11β-HSD1 activity associated with type 2 diabetes, adipose tissue with obesity and metabolic syndrome.

11β-HSD1 activity is theorized to increase in target tissues, i.e abdominal adipose regions, while intact HPA axis feedback loops maintain glucocorticoid homeostasis in the plasma.

11β-HSD1 is also elevated in the aging brain, where it exacerbates glucocorticoid-related cognitive decline.

INTERPRETING CORTISOL CIRCADIAN RHYTHM GRAPH – G.A.S. AND HPA AXIS DYSREGULATION

Our collective understanding of the stress response and the HPA axis largely comes from the pioneering work of Hans Selye. His theory of **General Adaptation Syndrome** described a limited, yet functional, model of stress response and adaptation to persistent stress. It is based on a stressor producing 3 stages of response.

Stage 1 – The first stage that one goes through in response to a stressor is termed “alarm” and indicates a release in catecholamines along with a transient increase in corticosteroids.

Stage 2 – The second stage of stress response is termed “resistance” and describes a heightened stress response with persistently elevated cortisol and other physiological adaptations necessary to resist the stressor.

Stage 3 – The third stage is termed “exhaustion” and results in persistent hypocortisolism and depletion of other biological resources needed to maintain the stress response.¹⁸⁹

As research evolves it can be said that numerous factors influence the stress response and subsequent HPA axis result, and the issue is more complex than originally modeled. Selye and others have noted,¹⁹⁰ timing is a critical element. Hormonal activity is elevated at stressor onset but reduces as time passes. However, how much time passes, and how much the cortisol response is affected, is widely variable among persons. This heterogeneity may relate to HPA axis linked genetic variation among other factors.¹⁸¹ Second, ongoing stressors that threaten physical integrity, involve trauma, and are uncontrollable can elicit a high, flat diurnal profile of cortisol secretion.¹⁹⁰ However, it is demonstrated that this is not the case in every situation. For example, it is lower in people with posttraumatic stress, and it may be lower after many years of persistent stress. Thirdly, regarding hypocortisolemia, situations that provoke repeated or sustained cortisol elevations may lead to a breakdown in the negative feedback system of cortisol secretion, ultimately resulting in low flattened slopes.¹⁹⁰

Clinical tip:

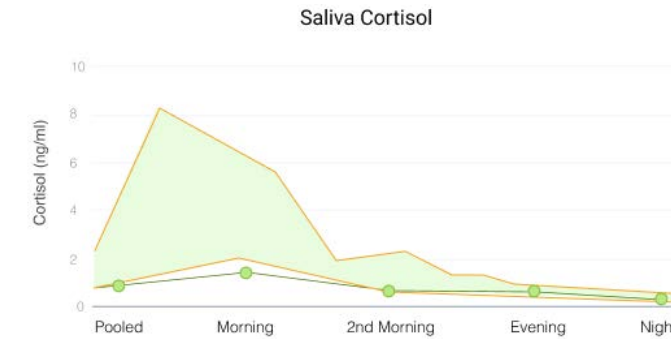
Circadian Rhythm Graph at a Glance

1. Does the Diurnal rhythm look normal from AM to PM?
2. Is there a single elevation only, that can be explained by a situational trigger or chronic condition? (Reflects more need for stress trigger and condition support).
3. Is there a combination of either high or low elevations with loss of diurnal rhythm? (Reflects more need for condition, trigger and HPA axis support)

Normal HPA Axis Function

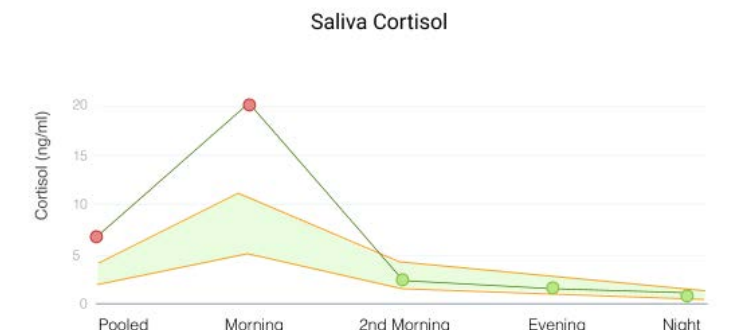
A normal cortisol circadian rhythm is that cortisol is elevated in the morning, peaks within 30-45 minutes following waking, known as the cortisol awakening response or CAR, then begins a steady downward trend until it reaches its nadir at bedtime.¹⁸¹

In the sample below, the circadian rhythm of this sample demonstrates intact HPA functionality, i.e., a smooth pattern from highest in the morning to lowest in the evening. One can observe the second morning cortisol is trending slightly high, but overall axis function and pooled cortisol value remains within the normal range.



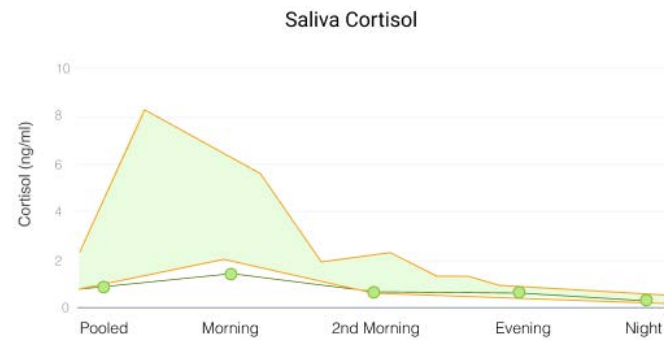
HPA Axis Dysregulation

HPA dysregulation generally infers some loss of diurnal rhythm throughout the 12-hour waking period. This can be from a blunted diurnal rhythm or from more than one out of range elevation or depression in the diurnal sample. In the graphs below there is obvious HPA axis dysregulation. In both, there is an over-elevation of cortisol upon waking followed by a noticeable loss of HPA axis circadian rhythm after mid-morning. In the graph on the left, a nighttime spike in cortisol shows further dysregulation.



Flattened Diurnal Slope

A flattened diurnal slope is found when there is a pattern of blunted response to stress throughout the day, typically with hypocortisolemia. This flattened diurnal slope pattern represents a more advanced state of HPA axis dysregulation. This pattern has been studied in relationship to chronic stress, early childhood adversity, burnout, etc. and has associations with many clinical conditions as seen on the right.¹⁹¹



CLINICAL KEY



The most studied variation in diurnal cortisol slope pattern is a flattened or blunted slope. The following conditions have been associated with a flatter diurnal cortisol slope:

- Immune dysregulation
- Inflammatory Dysregulation
- Chronic Fatigue Syndrome
- Chronic Stress
- Breast cancer mortality
- Obesity/BMI/adiposity
- Depression and negative affect
- Cardiovascular disease
- Recent withdrawal from corticosteroid therapy

Lifestyle Treatment Considerations for Glucocorticoids

HYPERCORTISOLISM – TRANSIENT OR PERSISTENT

Treatment Objectives: Consider which of the following single or combination of therapeutic approaches is the best fit for the patient with hypercortisolism. Transient elevated cortisol values may be corrected by remediation of situational triggers. Further modifiable HPA axis triggers for persistent hypercortisolism include dysglycemic and inflammatory conditions as listed below.

- Identify stressful situational triggers and offer lifestyle remediation
 - ✓ long commutes, caffeine, jet lag, stressful life event, hypoglycemia, insomnia
- Identify and treat glycemic dysregulation
 - ✓ diabetes, hypoglycemia, stress/comfort eating, eating disorder
- Identify and treat chronic inflammatory conditions which may promote hyper signaling of HPA axis
 - ✓ Autoimmune disease, arthritis or chronic MSK pain, chronic sinusitis, CVD, GI inflammation

HOLISTIC TREATMENT CONSIDERATIONS FOR HIGH CORTISOL EFFECTS

Lifestyle Considerations	To Aid Cortisol Reduction/Mitigate Effects of High Cortisol
Supplements	<p>Ashwagandha 300mg/ BID KSM-66 brand (Chandrasekhar), also positive studies for Sensoril and Shoden brands ¹⁹²</p> <p>Phosphatidyl serine/phosphatidic acid 400mg ¹⁹³</p> <p>L-theanine 200mg¹⁹⁴anti-stress and cortisol lowering effect</p> <p>Curcumin 500mg BID – lowered AM cortisol¹⁹⁵</p> <p>Curserin brand - Phosphatidyl serine/curcumin blend -800mg/BID – lowers AM cortisol¹⁹⁶</p> <p>Panax Ginseng 1.5g/ Korean ginseng BID reduced cortisol in metabolic syndrome¹⁴⁹</p> <p>Rhodiola 300mg/BID¹⁹⁷</p> <p>Relora – Magnolia/phellodendron 250mg BID¹⁹⁸</p> <p>DHEA* 10-450mg/d in meta-analysis of multiple studies - reduces cortisol, considered safe under doctor monitoring (avg. dose 50 or 100mg), moderate's effects of high cortisol in target tissues¹⁹⁹</p>
Diet	<p>Low sucrose diet/carbohydrate restriction– May modulates 11β-HSD enzyme activity to reduce truncal obesity²⁰⁰</p> <p>Prebiotics, high fiber diet may reduce cortisol levels, anxiety, and related cognitive function²⁰¹</p> <p>Cherry juice (Jerte Valley Brand) 125 ml/BID²⁰² enhances mood, reduces cortisol</p> <p>In Cushing's syndrome and prolonged hypercortisolism consider the following dietary measures: Low sodium diet, (excess cortisol can lead to hypertension), higher calcium diet (to offset osteoporosis), higher protein diet (offset muscle wasting)</p>
Exercise	<p>Yoga – heterogenous mix of styles, is associated with decreased evening and/or waking cortisol, improved regulation of HPA axis system²⁰³</p> <p>Habitual exercise (low or moderate intensity) regulates HPA axis function, buffers anxiety response and rumination time ^{204,205} however extreme exercise is associated with prolonged cortisol elevations and decreased immunity.</p> <p>Weight bearing exercise – to offset bone loss from chronic hypercortisolism</p>
Stress Management	<p>Meditation - Numerous styles of meditation are associated with decreases in salivary cortisol and anxiety, rumination^{203,204}</p> <p>Forest Bathing – Decreases cortisol after forest walking, anticipation of stress relief is also helpful²⁰⁷</p> <p>Biofeedback – 5 minutes once a day decreases stress and cortisol levels²⁰⁸</p> <p>QiGong – Reduces cortisol, raises serotonin and brain derived neurotropic factor (BDNF)²⁰⁹</p> <p>Sleep - Maximize sleep – at least 7 hours each night for prevention of high cortisol</p>

Further Testing Considerations for Elevated Cortisol

- **DEXA** scan for osteoporosis
- **Blood pressure** monitoring
- **Vibrant America Cardiovascular Panel and Diabetes Panel**
- **hs-CRP** for inflammation
- **Thyroid Panel**
- **Methylation Panel**
- Extreme elevations of cortisol require a more **extensive endocrine workup** including workup for Cushing’s syndrome, adrenal tumor/hyperplasia and/or pituitary tumor etc. Endocrinologist referral is advised.
- **Tickborne or Infections** tests to explore occult infections
- **Chronic Inflammation Panel, Gut Zoomer** for inflammation if cause of persistent inflammation is unknown or clinical symptoms correlate

LOW CORTISOL – TRANSIENT OR BLUNTED

Treatment approach to low cortisol

- Differentiate low to moderate hypocortisolism, which is more common, from adrenal insufficiency which is more uncommon.
 - Hypocortisolism, sub-optimal adrenal output, and/or HPA axis dysregulation are all terms which indicate maladaptation to chronic stress and are associated with conditions such as burnout, PTSD, impacts of early life trauma, chronic fatigue syndrome, etc.
 - Adrenal insufficiency (Primary, secondary or tertiary) is extreme hypocortisolism; it can lead to life threatening events and necessitates glucocorticoid and possibly mineralocorticoid replacement therapy. Researchers proposed a value lower than 1.16ng/ml (3.2nmol/L) for salivary AM cortisol should be followed up by further stimulation testing for adrenal insufficiency¹⁵⁶ Similarly, a blunted or flattened circadian release of cortisol should prompt a workup for adrenal insufficiency.
- Maximize sleep – at least 7 hours each night for restoration and repair
- Address chronic life/job stressors/major depression and provide relevant support
- Re-establish circadian rhythm through morning light, early, daytime exercise and sleeping in total darkness
- Consider nutrient and herbal support for adrenal nourishment and stress buffering
- Regular macronutrient balanced meals to stabilize blood glucose levels

HOLISTIC TREATMENT CONSIDERATIONS FOR LOW CORTISOL EFFECTS

Lifestyle Considerations	Improve Low Cortisol/Re-establish Diurnal Rhythm
Supplements	<p>Phosphatidyl serine/omega 3 fatty acid blend 300mg normalization of blunted cortisol response²¹⁰</p> <p>St John’s Wort 600mg/d – increased cortisol at 600mg/d in 2 studies, null cortisol effect in others at varying doses¹⁹⁷</p> <p>Licorice –Inhibits 11βHSD2 – increases cortisol: cortisone ratio in target tissues. dosage varies based on glycyrrhizin content of product, genetics, gut flora, blood pressure. Licorice may promote pseudoaldosteronism effects if dose is too high – monitor BP. ²¹¹</p> <p>Adaptogens such as Rhodiola rosea, Eleutherococcus senticosus and Schisandra chinensis show benefits for fatigue, endurance and cognitive performance in several studies, however, no evidence found for increased cortisol with use.²¹²</p> <p>Hydrocortisone (Cortef) for adrenal insufficiency*</p>
Diet	Grapefruit Juice – inhibits 11BHSD2 – can increase cortisol: cortisone ratio
Exercise	Conflicting studies - Low intensity exercise only, to patient tolerance
Stress Management	Mindfulness meditation – 12-minute meditation scan - Reduces blunted cortisol in cancer patients ²¹³

*Hydrocortisone/Cortef is a prescription glucocorticoid replacement used for adrenal insufficiency. Lower doses (2.5-10mg qd) are sometimes used by integrative physicians for low or moderate hypocortisolism or HPA axis dysregulation with blunted cortisol levels. Risk reward considerations, frequent cortisol/DHEAS monitoring, evaluation for side effects and established tapering program is advised with any glucocorticoid replacement plan.

Further testing considerations for Low Cortisol

- Neurotransmitter testing
- Total Tox Burden (Heavy Metals, Environmental Toxins, and Mycotoxins tests)
- Thyroid Panel
- Inflammation Panel
- Vibrant America Cardiac Health Panel
- Extreme hypocortisolism requires a more extensive endocrine workup including ACTH stimulation test, etc., for adrenal insufficiency. Endocrinologist referral is advised.

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