Oxytocin/Melatonin / hGH

Human Growth Hormone (hGH)

Secreted from the anterior pituitary gland, hGH is a key anabolic mediator of tissue repair and regeneration. It plays a role in many metabolic functions such as reducing visceral adiposity, maintaining lean muscle mass, minimizing inflammation, improving bone mineral density, decreasing cardiovascular disease mortality and enhancing the overall quality of life.[58-61] General strategies to improve hGH include lifestyle changes, nutrients, and optimizing thyroid and sex hormones. High endogenous levels may occur due to diabetes, renal disease or extended fasting. Other causes may require additional testing for IGF-1 and pituitary function

Melatonin

Melatonin assists in the body's sleep/wake cycle and is also a very powerful antioxidant.[62] Primary production is in the pineal gland. The GI mucosa is a significant source of secondary production, with retina, bone marrow, platelets, skin, and lymphocytes all producing smaller amounts. GI-produced melatonin has paracrine effects and does not enter general circulation. Urinary 6-sulfatoxymelatonin (MT6s) is the main metabolite of melatonin. MT6s itself has no physiologic activity, but is a good indicator of whole body melatonin production.[63] Low urinary MT6s is an indication for melatonin supplementation. It is common to see elevated urinary values with supplemented doses higher than 1mg. Such elevated levels should not discourage recommending melatonin when its use is clinically indicated.

Oxytocin

Beyond its actions in pregnancy and lactation, oxytocin modulates the HPA axis[64,65] and helps attenuate the stress response. Oxytocin may mitigate chronic pain and has been used experimentally in chronic pain syndromes.[66] Oxytocin may also influences trust, sociability, intimacy and sexual function.[67-69] Oxytocin declines with age and is also important for muscle regeneration and maintenance.[70]

What Affects hGH?

↑	↓
Good quality sleep	Sedentary lifestyle
Vigorous exercise	Excess weight
Resistance training	Inadequate protein
Adequate protein	Poor sleep
Glutamine (older people)	Low endogenous hormones
Arginine (younger people)	
Melatonin	
Optimizing thyroid function	
Optimizing sex hormones	

Low Melatonin

Insomnia
IBS
Peptic ulcers
Breast cancer
Colorectal cancer
Ulcerative colitis
Acute pancreatitis

High Melatonin

Pregnancy
Narcolepsy
Functional dyspepsia
Extended exercise

Thyroid

Thyroid Hormones

Free thyroid hormones are readily measured in the urine and are an effective screening tool for thyroid gland dysfunction. Research suggests that 24-hr urinary T3 has good correlation with thyroid symptoms.[71]
A high or low urinary thyroid hormone measurement may suggest the need for additional serum tests, such as thyroid auto-antibodies and reverse T3 (RT3).

Nutrients to Support Thyroid Function

Selenium
Iodine
Tyrosine
Zinc

Organic Acids

Xanthurenic and Kynurenic Acids

High levels of the tryptophan metabolites xanthurenic (XA) and knyurenic (KA) acid occur during subclinical B6 deficiency (excess estrogen, chronic illness), and may be an early warning sign of blood sugar dysregulation.[72] High levels can damage the pancreas, trigger an autoimmune response towards insulin and result in type II diabetes. XA binds to insulin and prevents it from entering cells.[73] High levels of KA may worsen mood disorders or cognition.[74] Elevated levels of XA and KA may inhibit catechol-O-methyltransferase, important for estrogen detoxification. Levels increase during menopause or due to chronic inflammation.

Treatment Considerations:

High KA may indicate low NAD+ synthesis or a B2/B3 deficiency.

High XA may indicate a sub-clinical B6 deficiency, blood sugar dysregulation or chronic inflammation.

Correct nutritional deficiencies, improve antioxidant status and consider evaluation of blood viscosity and the Kraft Prediabetes Profile.

Minerals

Na^+, K^+, Na^+/K^+ Ratio

Sodium has significant effects on the blood pressure and cell to cell communication. Values just within or outside of reference range indicate mineral imbalance and are correlated with kidney and adrenal function. High levels may contribute to high blood pressure and may be related to low aldosterone levels.

Potassium is important in the prevention of hypertension, in muscle contraction, and in cell to cell communication. High levels are uncommon and are usually due to over-supplementation or use of a diuretic. Low levels may indicate low vegetable intake, use of a potassium-sparing diuretic, or poor GI absorption.

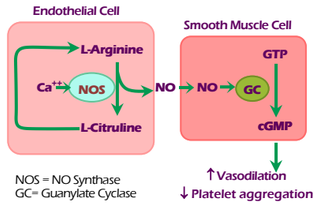
The **Na^+/K^+ Ratio** in urine is optimal at 1.5. Higher levels are associated with an increasing risk of hypertension.[75]

Optimal Urine Na+/K+ Ratio =1.5

Nitrates

Nitrates

Urinary nitrates are a good indicator of the level of the nitric oxide production in the body. Nitric oxide synthesized from the diet or supplements promotes vasodilation via cell signaling pathways. Poor nitric oxide production is thought to play a role in the pathogenesis of both erectile dysfunction and ischemic heart disease.[76-80] Values < 2,000 mmol/24 hr. may require intervention . High levels are found with specific amino acid therapies or consumption of foods high in nitrates. Nitric oxide production declines after age 40. Supplementation of arginine and citrulline, consumption of healthy nitrate-containing foods, such as beets and arugula, and exercise have been shown to improve low nitric oxide production. [81, 82-87]



Enzyme Activity

5α-Reductase

5a-reductase [SRD5A2; B3] converts testosterone into DHT. The reactions are irreversible and activity is measured by metabolite ratios, which provide context for androgen excess or deficiency symptoms. Supplemental androgen dosages may require adjustments based on enzyme activity.

High SRD5A2 is associated with insulin resistance and central adiposity.[88] Increased enzyme activity is also associated with BPH and male pattern hair-loss (men) and hirsutism, acne and PCOS (women).[89-91] Enzyme activity increases with excess circulating androgens or thyroid hormone.

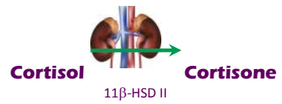
Low ratios may occur due to lower androgen levels and coincide with symptoms of androgen insufficiency in men, while lower ratios are common in women and rarely require action. SRD5A2 activity may be reduced due to niacin (B3) insufficiency, which may correlate with higher kynurenic acid levels.[92]

11β-Hydroxysteroid Dehydrogenase II

11b-HSD II is predominantly a renal enzyme, which also has activity in the placenta, fetus, and some glandular tissues. It functions to inactivate cortisol in order to prevent competitive binding to mineralocorticoid receptors. 11b-HSD II activity is best measured by the ratio of urinary cortisol/cortisone. An increased ratio suggests suppressed enzyme activity, and may be clinically related to a heightened stress response, hypertension, high dose licorice, or cortisol administration.

Natural 5a-Reductase Inhibitors

Zinc
y-linolenic acid (GLA)
Saw Palmetto
Progesterone



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Hormone Interpretation Guide

Leader in preventive medicine since 1976

Estrogens

Estrone (E1)
A moderately potent estrogen. Binds primarily to estrogen receptor alpha (ERα).[1] Estrone is metabolized into 2-hydroxy estrone (2-OH E1), 16α-hydroxy estrone (16α-OH E1), and 4-hydroxy estrone (4-OH E1).

Estradiol (E2)
The most physiologically active estrogen. Binds to both to ERα and estrogen receptor beta (ERβ).[1] Estradiol rapidly converts to estrone. Poor symptom control with estrogen replacement may suggest the need for improving absorption or increasing estradiol.

Estriol (E3)
Has weak estrogen activity. Considered to be a protective estrogen.[2,3] Most prevalent estrogen in pregnancy. Binds to ERb.[1,4] Estriol is metabolized from 16a-OH estrone; low iodine levels may alter CYP45 activity and decrease estriol levels.[5]

Total E1, E2, E3
High, out-of-range estrogens are commonly seen with oral or sub-lingual supplemental estrogen. High levels are also seen in pregnancy. Non-bioidentical hormones, such as birth control pills and other hormone-based contraception usually result in suppressed estrogen levels. Individual estrogen requirements vary widely and levels that result in estrogen deficiency symptoms in some women may be adequate for others.

Estrogen Quotient (EQ)
Women with an EQ>1 have a higher survival rate after breast cancer[6], and may be at decreased risk for developing breast cancer. EQ in pre-menopausal women is typically >1.[7] EQ often declines as women enter menopause. An EQ < 1 may improve with iodine supplementation.[5]

Estrogen in Male Profiles
Estrogens are an important part of male hormone balance that contribute to bone density, libido, cognition and cardiovascular health.[8-10] Estrogens in men are always evaluated in relationship to testosterone levels. In general, the 24-urine testosterone should be at least four times greater than the total of E1, E2, and E3. (T:E ≥ 4.0) A lower ratio may signal over-aromatization of testosterone to estrogen, which is associated with insulin resistance.[11-14] Pharmaceutical aromatase inhibitors will suppress estrogen levels in men and may result in very low levels.

Estradiol (E2) ⟷ **Estrone (E1)**

E2 readily converts to E1.
A lesser amount of E1 converts to E2.

Estrogen Metabolites

2-Hydroxyestrone (2-OH E1)
This Phase I liver metabolite of estrone is considered protective.[15,16] A comparison with 2-methoxyestrone, its Phase II metabolite, may help with assessing adequacy of methylation processes. (See below.)

16α-Hydroxyestrone (16α-OH E1)
16α-OH E1 is a Phase I metabolite of estrone that has some duality: it is both carcinogenic[17] and important for building bone.[18,19] Therefore, very high levels and very low levels are simultaneously undesirable. High levels suggest a need for measures to improve estrogen detoxification. Low absolute levels may increase risk of osteopenia and may indicate a need for supplemental estradiol, especially in women with other risk factors for osteoporosis.

2/16 α ratio
Optimal ratio is between 2-4. Ratios <2 may indicate increased breast cancer risk.[20-24] This may be less significant when overall levels are low. Consider nutrients that push estrogen metabolism toward 2-OH E1. Ratios > 4 may indicate increased risk for osteopenia, especially when absolute level of 16α-OH E1 is low.[18,19]

4-Hydroxyestrone (4-OH E1)
High levels of this Phase I metabolite have been shown to damage DNA and increase cancer risk.[25] Additional magnesium[26], liver support, and methylation support may help decrease 4-OH E1 levels.

2 Methoxy-Estrogens
The 2-methoxy estrogens (Phase II metabolites) are considered to be protective.[27-29] Low levels are usually a reflection of overall low estrogens and may be improved with supplemental estrogen.

2 Methoxy-Estrone (2-MeOH E1)
Metabolized from 2-OH E1. A comparison of 2-MeOH E1 with 2-OH E1 allows insight into methylation pathways. In healthy, cycling women the 2-MeOH E1 value usually at least 50% of 2-OH E1 value, methylation is probably adequate.[30] If <25% consider adding methyl donors.

2 Methoxy-Estradiol (2-MeOH E2)
2-MeOH E2 may be the most protective of the estrogen metabolites and is produced endogenously in small amounts. It is showing promise in a number of animal and human trials as an adjunctive treatment for several types of cancer. Current scientific understanding suggests it does not bind to estrogen receptors.[31-34]

Estrogen Detoxification

Increase	Decrease
Soluble fiber	Excess weight
Calcium D-glucarate	High fat diet
Cruciferous vegetables	Pesticides
Exercise	Alcohol
Flax	Cimitidine
Ω-3 Fatty Acids	
Progesterone	
DIM	
I3C	
Thyroid Function	

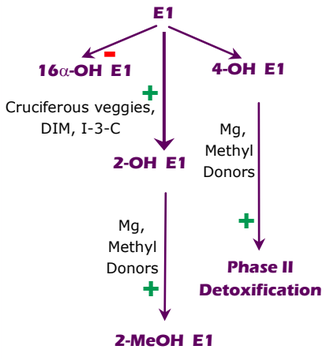
$$EQ = \frac{E3}{E1 + E2}$$

Optimal ratio > 1

T:E ≥ 4

Optimal ratio for men

Phase I Liver Metabolites	Phase II Liver Metabolites
2-OH E1	2-MeOH E1
16α-OH E1	2-MeOH E2
4-OH E1	

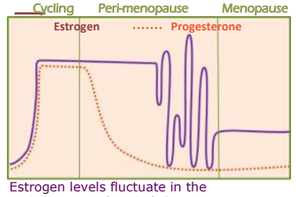


Progesterons

Progesterone
Progesterone metabolites are derived from progesterone, which is produced in the ovaries, placenta and adrenal gland. It is a precursor for adrenal hormones and androgens. Low progesterone levels may contribute to mood changes and insomnia. Circulating progesterone levels are highest after ovulation (luteal phase) in cycling women or with direct hormone replacement. There is limited evidence that bio-identical progesterone (with estrogen) replacement contributes to breast cancer risk.

Pregnanediol
Progesterone itself is not readily found in the urine. Instead, this test measures pregnanediol (a progesterone metabolite). Pregnanediol is well-established in research literature as a reliable marker for progesterone levels.[35] Low or low-normal levels of pregnanediol signal less than optimal progesterone. This commonly results in an increase in symptoms occurring in the luteal phase. In the perimenopausal years, progesterone levels tend to fall faster than estrogens, resulting in a relative estrogen dominance. Botanicals or supplemental progesterone can be useful for managing symptoms. Low levels are commonly associated with sleep disturbances, anxiety, stress, and edema. High levels are usually due to high doses of oral progesterone.

3a-dihydroprogesterone (3aHP), 20a-dihydroprogesterone (20aHP)
3aHP and 20aHP are non-proliferative metabolites and are found in normal breast tissue. Low levels may result from low levels of the progesterone precursor, or diversion of progesterone down the 5a-reductase pathway.



Estrogen levels fluctuate in the perimenopausal period. Progesterone levels often drop rapidly.

5a-dihydroprogesterone (5aP)
5aP is a proliferative metabolite produced by the 5a-reductase enzyme [SRD5A2; B3]. Low levels are found in normal breast tissue. High 5aP levels are found in breast tumors. Local changes in enzyme activity may or may not be reflected in circulating hormone levels. Inhibition of 5a-reductase may decrease 5aP levels and improve progesterone metabolism. SRD5A2 activity may be decreased by zinc, *Serenoa repens*, gamma-linolenic (GLA) and eicosapentaenoic (EPA) fatty acids. SRD5A2 activity may be increased due to excess androgens or thyroid hormone.

Consider if androgens are high:

Women: PCOS, especially if coinciding with estrogen dominance, low progesterone and high 5α-Reductase activity.

Men: Check blood viscosity, especially if hematocrit is high-normal or high out-of-range. The most common side effect of exogenous testosterone is an increase in hematocrit.

Menopause Symptoms: ♀
Fatigue
Low libido
Vaginal dryness
Loss of Muscle mass
Osteopenia
Mood or memory changes

Andropause Symptoms: ♂
Fatigue
Apathy
Loss of muscle mass
Loss of strength
Memory changes

Treatment Considerations:

Elevated cortisol with an elevated sum of THE+5α-THF+THF suggests excessive cortisol secretion. Stress management interventions along with calming botanicals and nutraceuticals may be indicated.

Values low in or below the reference range suggest suboptimal cortisol secretion. Nutrients and adrenal adaptogenic herbs may be of value in this scenario. Hydrocortisone supplementation may be indicated in certain cases.

THE
5α-THF
+ THF
Total

Optimal:
5000-7000 (Women)
8000-10,000 (Men)

Androgens

Dehydroepiandrosterone (DHEA)
DHEA is produced in the adrenal glands and is a precursor to both testosterone and estrogen. DHEA also affects bone density, response to stress, mood and cognitive function, improves insulin sensitivity, and is associated with decreased cardiovascular and cancer risk.[36-41] It peaks in the mid-20s and begins to decline after 30. Longevity is associated with higher than age-normal levels of DHEA.[42] Low levels may be a sign of adrenal stress and/or reduced androgen production. Adrenal support and meditation can increase DHEA levels, or supplementation may be appropriate. High levels are common with PCOS or may be a sign of over-supplementation.

Testosterone
Testosterone is derived from DHEA and converted into estrogens via the aromatase enzyme, or DHT via 5a-reductase. Low levels of DHEA may result in low levels of testosterone and its metabolites. Testosterone levels often decrease with age and have been associated with symptoms common to menopause and "andropause". In younger men particularly, low levels may indicate exposure to environmental toxins. Higher levels of endogenous testosterone may occur during hormone replacement, may be associated with PCOS (women), or (rarely) indicate an androgen-producing ovarian or adrenal tumor.[43] High testosterone from hormone replacement may increase blood viscosity.

5a-Dihydrotestosterone (DHT)
Testosterone is converted into DHT by 5a-reductase or 3b-hydroxysteroid dehydrogenase enzymes and DHT has higher affinity for androgen receptors, making it a more potent androgen. High levels of DHT contribute to BPH and androgenic alopecia (hair loss); testosterone, etiocholanolone, androsterone, and 5a-reductase levels may also increase.[44-45] Hyperthyroidism may increase DHT levels. Use of 5a-reductase inhibitors decreases levels of DHT.[46]

5a-Androstane-3a,17β-diol (3a-Adiol) and 5a-Androstane-3b,17β-diol (3b-Adiol)
Testosterone is converted into 5a-dihydrotestosterone DHT by the enzyme 5a-reductase. DHT is further metabolized by niacin-dependent 3a-hydroxysteroid dehydrogenase enzymes into the metabolites 3a-Adiol and 3b-diol.[47] 3a-diol, in excess may contribute to hirsutism.[48] This metabolite is considered pro-inflammatory and in some studies, 3a-diol has been associated with prostate cancer risk.[49] 3b-diol is found in normal tissues and is considered cell-protective in the prostate and breast tissue where it binds to estrogen receptor b. Low levels may occur during hypothyroidism or the use of 5a-reductase inhibitor medications.[50]

5α-Androstanediol , 5β-Androstanediol, Androsterone , Etiocholanolone
5α-Androstanediol and 5β-androstanediol are metabolites of testosterone via 5α- and 5β-DHT. Androsterone and etiocholanolone are DHEA metabolites via androstenedione and the 5α- and 5β-reductase pathways. These androgens allow assessment of 5α-reductase activity. Normal metabolites may be a better indicator of androgen status in a patient with low DHEA and/or testosterone. Low or low-normal metabolites can help confirm low androgen levels. High levels are often seen in PCOS and with over-supplementation.

Glucocorticoids

Pregnanetriol
Pregnanetriol is a marker for the precursor leading into the cortisol pathway. Very high values may indicate an accumulation from a rate-limiting 21-hydroxylase enzyme deficiency (rare), if androgens are also high and mineralocorticoids are low.[51] Low levels with low glucocorticoids may reflect inadequate precursors as a potential etiology of adrenal hypo-function.

Cortisone
The inactive or "storage form" of adrenal glucocorticoid. Can be reversibly transformed to cortisol. Clinically, cortisone may reflect a measure of adrenal reserve when compared to cortisol. The middle of the reference range generally indicates adequate adrenal function. Given sufficient precursor cortisone may be up to 30% higher than cortisol.[52] Values at the high end or low end of the reference range are generally not optimal.

Cortisol
The active form of adrenal glucocorticoid. Plays a role in gluconeogenesis, maintaining blood pressure and modulating immune function. Can be reversibly transformed to cortisone. When compared to cortisone, can provide clinical information about adrenal reserves and any present state of adrenal compensation or decompensation. The middle of the reference range generally indicates adequate adrenal function.

Tetrahydrocortisone (THE), Allo-tetrahydrocortisol (5α-THF), Tetrahydrocortisol (THF)
These three cortisol and cortisone metabolites reflect approximately 50% of the total endogenously produced cortisol. The sum of the three therefore gives an indication of total cortisol production.[53-55] A total of < 5000 (women) or 8000 (men) may indicate low adrenal function. A total >7,000 (women) or 10,000 (men) may indicate an excessive cortisol response.

11β-Hydroxyandrosterone, 11β-Hydroxyetiocholanolone
These end-products can help confirm an overall high or low trend in adrenal corticosteroid health.

Mineralocorticoids

Aldosterone
Aldosterone, the primary mineralocorticoid, contributes to sodium balance and blood pressure. As a product of the adrenal cortex, aldosterone can reflect adrenal health status. Low levels (<10) may be due to high sodium, dehydration, or stress. High levels may be seen with salt-restricted diets[56] and spironolactone use.[57]

Allo-tetrahydrocorticosterone (5α -THB), Tetrahydrocorticosterone (THB), 11-dehydrotetrahydrocorticosterone (THA)
When low, these mineralocorticoid metabolites are a strong indicator of chronic adrenal fatigue. High levels are associated with acute stress. Together with DHEA and the glucocorticoids, these metabolites afford a comprehensive assessment of adrenal-cortical health.

Numbered references are available on the MeridianValleyLab.com practitioner portal.