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Low Androgens, High Impact: Clinical Insights for Midlife Men and Women

Allison Smith, ND
Clinical Director
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Allison Smith, ND – Clinical Director at Precision Analytical (DUTCH)

Dr. Smith is a licensed naturopathic doctor bringing 16 years of experience including 12 years of working within the hormone lab testing space.

She provides clinical support and professional guidance to practitioners learning to apply functional endocrinology in their practices!

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Today's Agenda

1. **Describe the physiological roles of androgens** in both men and women, including their effects on metabolism, musculoskeletal health, cognition, and overall vitality.
2. **Identify typical patterns of androgen decline in midlife**, and recognize how these patterns may differ by sex and individual physiology.
3. **Interpret key androgen-related markers on the DUTCH test**, including hormone levels and metabolic patterns relevant to aging and stress physiology.
4. **Recognize stress- and metabolism-related factors** that may contribute to low androgen states and impaired anabolism.
5. **Apply DUTCH test findings to clinical case examples** involving low androgens in both male and female patients.
6. **Discuss common therapeutic options** for addressing low androgens, including hormonal and non-hormonal approaches, within a functional medicine context.

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Let's Review Androgens!

What are Androgens?

- A class of hormones and metabolites that are classically thought of as the "male" hormones as they are responsible in males to drive development of male features and secondary sex characteristics.
- They also have critical function in females!
  - Precursors to production of estrogen.
  - Critical for follicular development and egg quality in fertility.
  - Sexual function and bone health in menopause.

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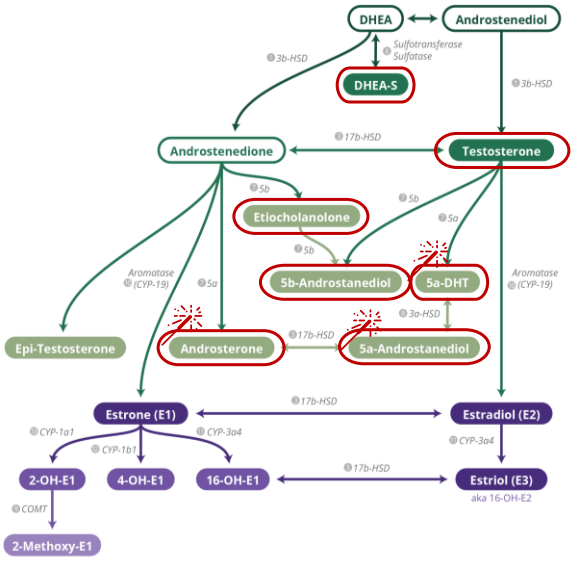
Androgens

- **DHEA-S** is the bound-up sulfated form of DHEA.
- **Etiocholanolone** is a *beta* DHEA metabolite.
- **Androsterone*** is an *alpha* DHEA metabolite.

Alpha metabolites are made in **target tissues** and are **<u>active</u>** on the androgen receptors.

Beta metabolites are made in the **liver** and are **<u>NOT active</u>** on the androgen receptors.

- **Testosterone** is converted into:
- *Alpha* metabolites in the *tissues*:
  - **5a-DHT (androgenic)**
  - **5a-Androstanediol (androgenic)**
- *Beta* metabolites in the *liver*:
  - **5b-Androstanediol (inert)**



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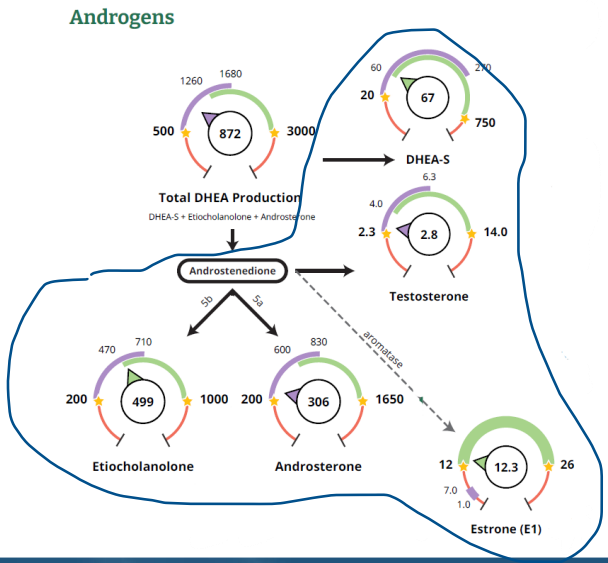
DHEA is a Pro Hormone



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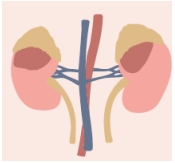
DHEA (Mostly) Made in the Adrenal Glands

- **DHEA synthesis**
  - Occurs in the adrenal cortex (zona reticularis), gonads, and brain
- **DHEA is a pro-hormone**
  - A precursor to most other steroid hormones
  - All estrogens are synthesized from androgens
- **DHEA is involved in the stress response**
  - An **immune modulator** and **anti-inflammatory hormone**
  - Acute stress biomarker (increases within 1 hour)



Dutheil F, et al. Front Psychiatry. 2021; 12: 688367.

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General Androgen Actions in Men and Women

Androgen Actions

- **Brain:** Mood, motivation, energy, sex drive, focus, sense of well-being
- **Bone density**
- **Insulin secretion**
- **Hair (body) growth**
- **Skin:** Moisture, elasticity, sebum production
- **Muscle mass:** Strength, Stamina, Recovery
- **Cardiovascular Health**
- **Immune function**
- **Sexual function:** Vasodilation, tissue elasticity, moisture
- **Fertility**: At optimal levels helps follicle growth in women and sperm production/count in men

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DHEA Levels Affect Estrogen and Testosterone Levels

Because DHEA can be converted into androgens and estrogens it can affect both androgen and estrogen activity in the body!

Estrogen's Actions

- **Brain:** Mood, cognition, memory, and focus, thermoregulation, sleep, energy
- **Hair (scalp) growth**
- **Skin:** Elasticity, collagen, repair, moisture
- **Muscle mass**
- **Nervous system:** Parasympathetic balance
- **Joint health & Bone density**
- **Breast health**
- **Liver function:** healthy cholesterol
- **Insulin sensitivity**
- **Weight management**
- **Uterine health**
- **Genitourinary system:** Elasticity, microflora, moisture
- **Fertility**
- **Cardiovascular:** endothelial function, etc.

Androgen Actions

- **Brain:** Mood, motivation, energy, sex drive, focus, sense of well-being
- **Bone density**
- **Insulin secretion**
- **Hair (body) growth**
- **Skin:** Moisture, elasticity, sebum production
- **Muscle mass:** Strength, Stamina, Recovery
- **Cardiovascular Health**
- **Immune function**
- **Sexual function:** Vasodilation, tissue elasticity, moisture
- **Fertility**: At optimal levels helps follicle growth in women, sperm development and sperm count in men

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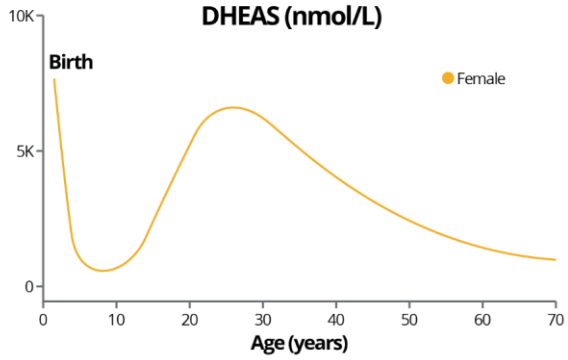
DHEA-S Declines with Age in Both Men and Women

- Androgens **peak in the 20's and 30's** and then decline thereafter.



Labrie F, et al. Front Neuroendocrinol. 2001.

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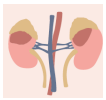
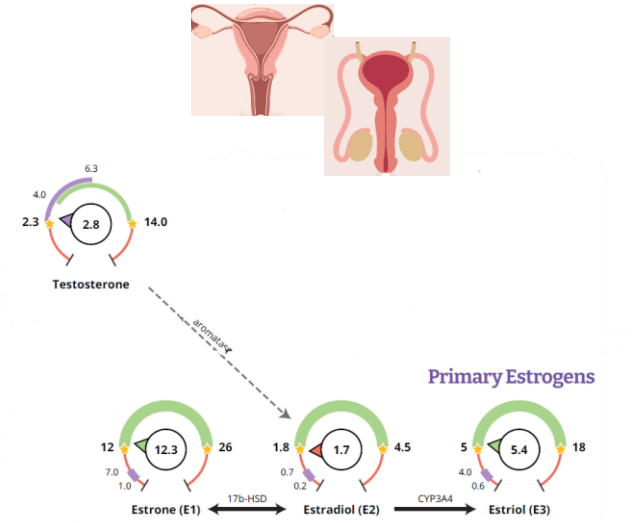
Testosterone (Mostly) Made in the Gonads in Men and Adrenal/Peripheral in Women

- **Testosterone synthesis**
  - Men: Occurs in Leydig cells in the testicles and adrenal cortex (zona reticularis)
  - Cycling women: Occurs in the theca cells in the ovaries of women and from peripheral conversion of adrenal DHEA
  - Menopausal women: Mostly adrenal source – 60% of T from peripheral conversion of adrenal DHEA plus 40% of T from theca/stroma cells in the ovaries for 10+ years after menopause
- **Testosterone forms estrogens via aromatase**
  - Adipose tissue expresses ↑ aromatase
  - All estrogens are synthesized from androgens





Laughlin GA, et al. H J Clin Endocrinol Metab. 2000.

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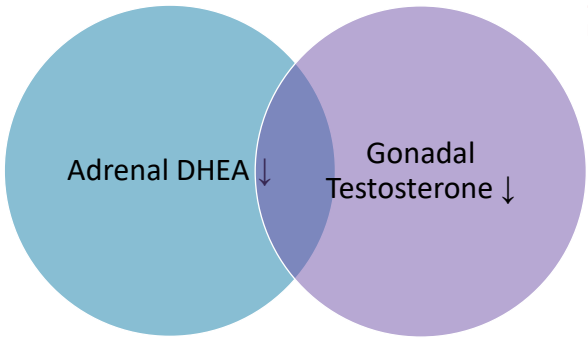
The Mid-Life Androgen Trajectory and Senescence Begins in Our 30s

In Men

Overlay of Adrenal Aging with Gonadal Aging



>95% of a man's T is gonadal sourced

Samaras N, et al. Rejuvenation Res. 2013.

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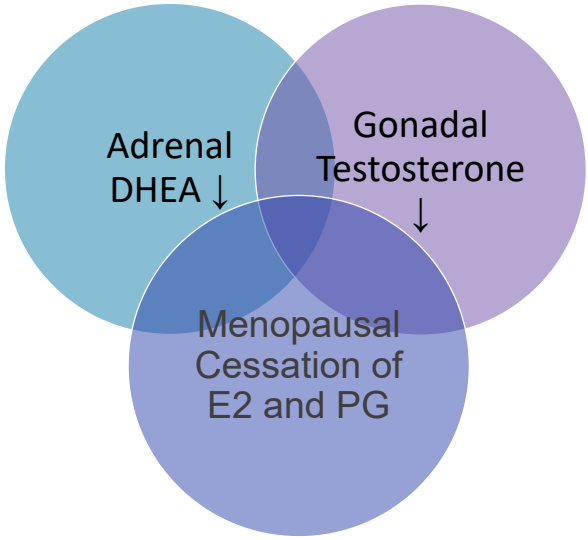
The Mid-Life Androgen Trajectory and Senescence Begins in Our 30s

In Women

Overlay of Adrenal Aging with Gonadal Aging

Added Symptom Impact of Menopause



~25% of a woman's T is gonadal sourced

Samaras N, et al. Rejuvenation Res. 2013.
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DHEA Decline is Steady

DHEA levels are dependent on:

Age
- DHEA declines gradually by 2-4% per year beginning in our 30's.

ACTH secretion through the HPA axis
- Like cortisol, DHEA (but not DHEA-S) has a diurnal pattern because it is secreted in response to ACTH signaling from the brain.
- DHEA is involved in the stress response.

Zona reticularis of the adrenal gland
- Function, hypertrophy, atrophy, etc.

Labrie F, et al. Front Neuroendocrinol. 2001.
Schiffer L, et al. Mol Cell Endocrinol. 2018.
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Testosterone Decline is Steady

In Males:

- Declines by about 1-2% per year with age
- Sexual symptoms are the most common
  - Can occur without other symptoms

In Females:

- Declines by about 50% from 20s on
- Hypoactive sexual desire dysfunction
- Body composition changes

Brzozowska M, Lewiński A. Prz Menopauzalny. 2020.

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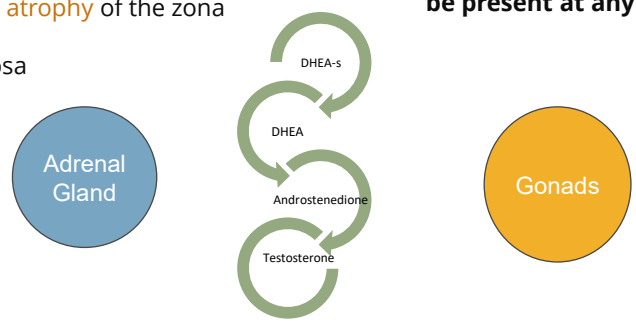
Additive Drivers to Mid-Life Decline in Androgens

Additional factors (besides aging) that lower androgen levels:

- Oophorectomy (females)
- Medications – statins, chemo, GnRH analogs
- Chronic stress/HPA axis dysfunction
- Age-related morphological changes in the adrenal cortex: atrophy of the zona reticularis
- Anorexia nervosa

Variation in androgen levels among men and women come from issues with the adrenal glands and gonads that may be present at any time in life.



Fogle RH, et al. J Clin Endocrinol Met. 2007;92(8):3040-3043.
Papierska L. Menopausal Review. 2017;2:57-60.
Sharma S, Mahajan N. J Midlife Health. 2021;12(1):3-7.

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- If >95% of a Male's Testosterone is from Gonadal Source and only 5% from Adrenal/Peripheral, Can DHEA supplementation Raise T levels?

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DHEA Supplement

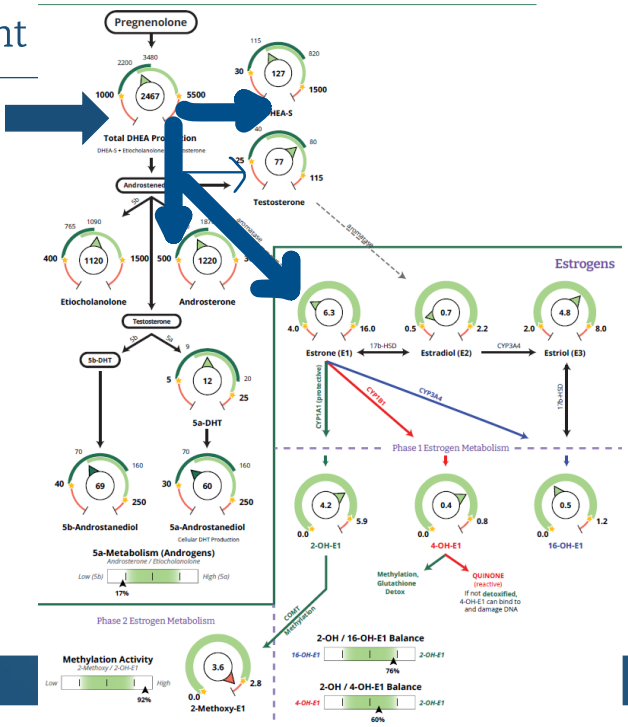
Males

Big Rises:

Estrogens
DHEA-S
Androsterone
Etiocholanolone

Small Rises:

Testosterone
DHT
5a-Androstanediol
5b-Androstanediol



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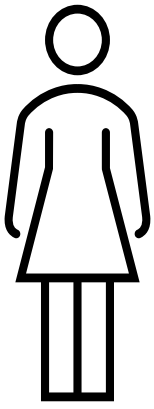
- If ~75% of a Female's Testosterone is from Adrenal/Peripheral Source, Can DHEA supplementation Raise T levels?

Yes!

Symptoms Associated with Low Androgens

Androgen (both testosterone and DHEA-S) deficiency in women is associated with:

- **Low libido**
- **Low mood**
- **Osteopenia and osteoporosis**
- **Reduced muscle mass**
- **Vaginal dryness**
- **Fatigue**
- **Vasomotor symptoms**
- **Insomnia**
- **Depression**
- **Headaches**

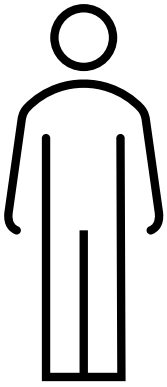


Bachmann GA. Fertility and Sterility. 2002;77:72-76.

Male Symptoms Associated with Age-Related Low Androgens

Androgen (both testosterone and DHEA-S) deficiency in men is associated with:

- **Low libido – a primary symptom and may occur in isolation esp in men > 50yo (w/o other obvious causes)**
- **Erectile dysfunction**
- **Reduced Fertility/Sperm count**
- **Cognitive issues (brain fog)**
- **Reduced muscle mass**
- **Fatigue**
- **Insomnia**
- **Depression**
- **Irritability**
- **Low motivation**



Mok SF, et al. J Gerontol A Biol Sci Med Sci. 2020.

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DHEA, Cortisol, and the Stress Response

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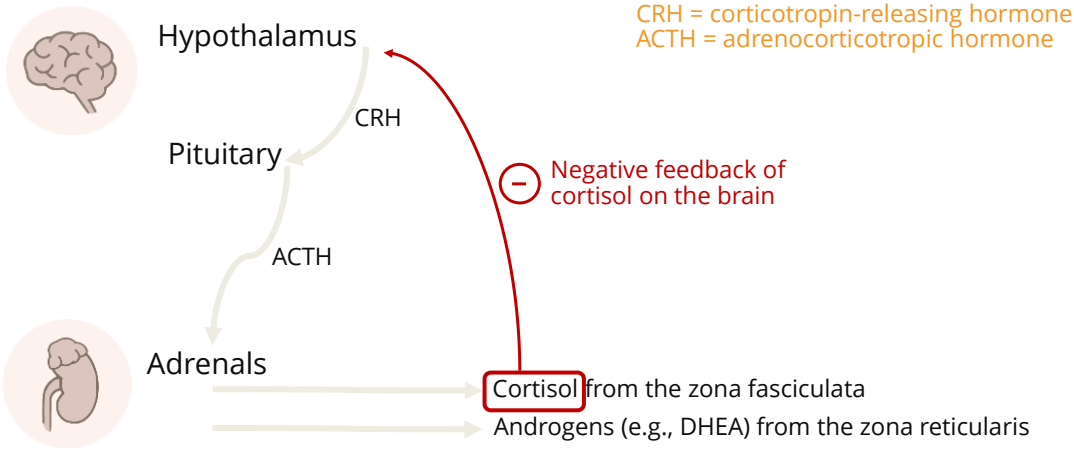
The Adrenal Stress Response

Hypothalamic-Pituitary-Adrenal (HPA) Axis Communication



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DHEA, Cortisol, and the Stress Response

- **DHEA synthesis**
  - Occurs in the adrenal cortex (zona reticularis), gonads, and brain
- **Cortisol synthesis**
  - Occurs in the adrenal cortex (zona fasciculata)
- **DHEA-S**
  - DHEA-S does not follow a diurnal pattern, it is constant
  - Unsulfated DHEA is diurnal, Cortisol is also diurnal
- **DHEA is a pro-hormone**
  - A precursor to most other steroid hormones
  - All estrogens are synthesized from androgens
- **DHEA and Cortisol are both involved in the acute stress response**
  - DHEA: **immune modulator** and **anti-inflammatory hormone**
  - Cortisol: **immune suppressor, acute anti-inflammatory (chronic pro-inflammatory)**

 Dutheil F, et al. Front Psychiatry. 2021. dutchwebinars

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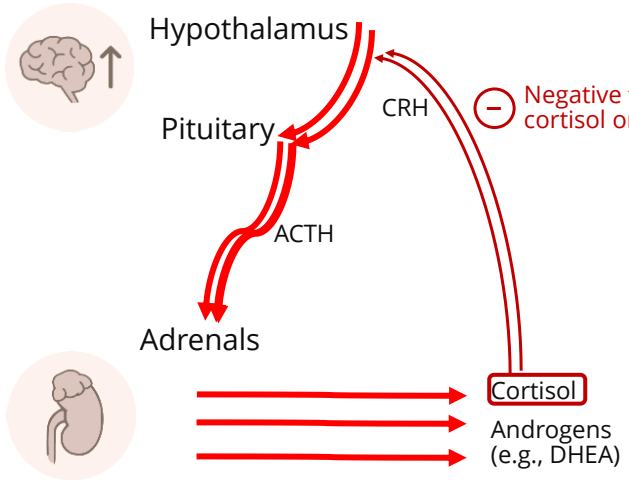
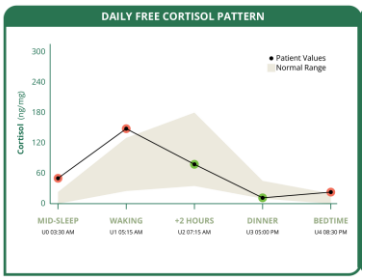
Acute vs Chronic Cortisol Effects

- Acute cortisol effects: Fight or Flight
  - Maintains glucose levels for energy
    - Gluconeogenesis: mobilizes glucose from fat and liver cells
    - Blocks insulin to maintain blood sugar for energy
  - Increased focus: mental and physical
  - Increased HR, blood pressure (vasoconstriction), muscle blood flow
  - Decreased digestive effort
  - Decreased sex hormone response
  - Decreased immune response

The Adrenal Stress Response

Over time, chronically high cortisol can lead to...



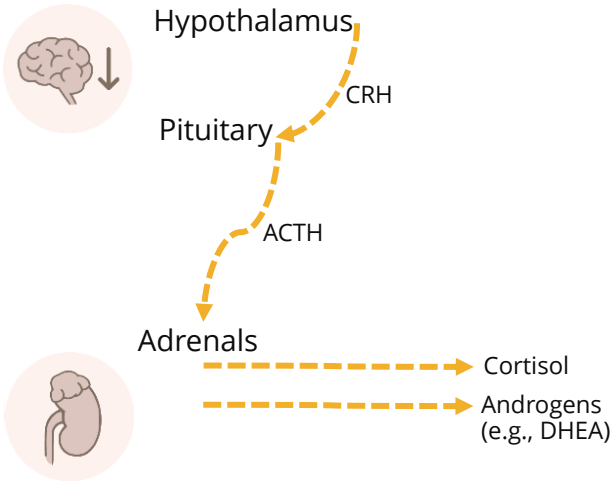


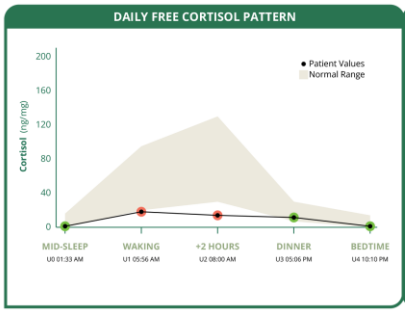
48-year-old male
Significant sleep issues

All images from http://canva.com

The Adrenal Stress Response to Chronic Stress

...low cortisol.





49-year-old female
Low libido
Fatigue that worsens throughout the day

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Chronic Cortisol Effects

- Insulin dysregulation, dysglycemia, IR/diabetes
- Central adiposity
- Muscle wasting
- Bone loss
- Immune dysregulation, immune suppression, and inflammation
- Chronic fatigue
- Gastrointestinal effects: parasympathetic nervous system suppression
- Cardiovascular effects: HTN, hyperlipidemia, endothelial dysfunction
- Sex hormone imbalance
  - Females: infertility, irregular periods, heavy periods, decreased libido
  - Males: infertility, low testosterone, decreased libido, erectile dysfunction

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Work to Normalize Free Cortisol and Cortisol Metabolism

General HPA Axis Support

- Correct insulin resistance.
- Encourage weight loss if appropriate.
- Engage in regular aerobic exercise.
- Lower inflammation.
- Lower stress and support parasympathetic activity.
- Manage acute and chronic pain.
- Manage chronic infections.
- Minerals, including magnesium and zinc (balance copper).
- Nutritional and herbal adaptogens (see next page).
- Optimize sleep and the circadian rhythm.

- Probiotics such as Bifidobacterium longum 1714 and Lactobacillus plantarum PS128
- Vitamins, including B vitamins and vitamin C

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Low DHEA vs Cortisol

Hint: #1 Reason to care about low androgens in mid-life: Cardiovascular Risk!

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Cortisol Levels Are Stable Throughout the Lifespan

With DHEA levels dropping with age, relative shift to relative cortisol dominance and favoring CATABOLISM

- DHEA is considered more *anabolic*.
- Cortisol is considered more *catabolic*.

More cortisol relative to DHEA may put a patient in a catabolic state.

- Excessive catabolism results in the body breaking down more tissue than it builds.
- It can result in fatigue, muscle loss, low bone mineral density, weakness, impaired tissue repair, poor wound healing and weakened immune function.

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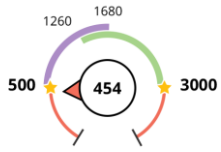
Assess Anabolic-Catabolic Balance

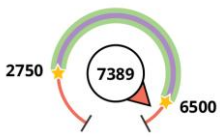
If a patient has low Total DHEA Production but high Metabolized Cortisol, they are likely in a more catabolic state. ***This is what we want to avoid!***

- It may be more difficult for this person to see gains in muscle mass, maintain muscle mass, exercise and recover from exercise, and recover from illnesses, injuries, and traumas, etc.
- They may experience immunological issues (e.g., get sick more often).



Total DHEA Production

DHEA-S + Etiocholanolone + Androsterone



Metabolized Cortisol

Total Cortisol Production (THF + THE)

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Low DHEA-S Levels are Associated with Higher CVD Morbidity and Mortality

Prognostic Value of Dehydroepiandrosterone Sulfate for Patients With Cardiovascular Disease: A Systematic Review and Meta-Analysis

Ting-Ting Wu, MD; Yuan Chen, MD; Yun Zhou, MD; Dilare Adi, PhD; Ying-Ying Zheng, PhD; Fen Liu, MS; Yi-Tong Ma, MD, PhD; Xiang Xie, MD, PhD

Background—The aim of the present study was to estimate the impact of dehydroepiandrosterone sulfate (DHEAS) on the prognosis of patients with cardiovascular disease by performing a systematic review and meta-analysis.

Methods and Results—The Embase, PubMed, Web of Science, CNKI, and WanFang databases were searched up to September 5, 2016, to identify eligible studies. The quality of each study was assessed using the Newcastle-Ottawa Scale. The association between DHEAS, either on admission or at discharge, and cardiovascular disease outcomes were reviewed. The overall risk ratio for the effect of DHEAS on all-cause mortality and fatal and nonfatal cardiovascular events was pooled using a fixed-effects or a random-effects model. The publication bias was evaluated using funnel plots. Twenty-five studies were included for systematic review. The follow-up duration ranged from 1 to 19 years. Eighteen studies were included in the meta-analysis. We found that lower DHEAS levels indicated a significant increased risk for all-cause mortality (risk ratio, 1.47; 95% CI, 1.38–1.56 [P<0.00001]), fatal cardiovascular event (risk ratio, 1.58; 95% CI, 1.30–1.91 [P<0.00001]), and nonfatal cardiovascular event (risk ratio, 1.42; 95% CI, 1.24–1.62 [P<0.0001]) in patients with cardiovascular disease.

Conclusions—Patients with cardiovascular disease who have lower DHEAS levels may have poorer prognosis than those with higher DHEAS levels. (***J Am Heart Assoc.* 2017;6:e004896. DOI: 10.1161/JAHA.116.004896.**)

Key Words: cardiovascular disease • dehydroepiandrosterone sulfate • meta-analysis • prognosis • sex hormones • systematic review

Wu, TT, et al. J Am Heart Assoc. 2017.

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Salivary Cortisol and CVD Mortality: Whitehall II Prospective Cohort Study (2011)

Association of Diurnal Patterns in Salivary Cortisol with All-Cause and Cardiovascular Mortality: Findings from the Whitehall II Study

Meena Kumari, Martin Shipley, Mai Stafford, and Mika Kivimaki

Department of Epidemiology and Public Health, University College London, London WC1E 6BT, United Kingdom

TABLE 3. HR of all-cause, cardiovascular, and noncardiovascular mortality among 4047 participants of the Whitehall II study from phase 7 (2002–2004) through to January 2010 by z-scores of measures of cortisol

	All-cause mortality	Noncardiovascular deaths	Cardiovascular deaths
Waking cortisol	0.94 (0.80–1.12)	0.93 (0.77–1.13)	0.95 (0.67–1.36)
CAR	0.94 (0.80–1.12)	0.90 (0.74–1.10)	1.12 (0.79–1.57)
Slope across the day	1.30 (1.09–1.55)	1.17 (0.96–1.43)	1.87 (1.32–2.64)
Bedtime cortisol	1.33 (1.11–1.59)	1.17 (0.96–1.44)	1.98 (1.39–2.81)

Slope across the day and CV deaths: Z-score: 1.87 ~ p = 0.03 (P < 0.05)
Bedtime cortisol and CV deaths: Z-score: 1.98 ~ p = 0.02 (P < 0.05)

- First study to document that daily salivary diurnal cortisol patterns are predictive of subsequent CV mortality in men and women
- Study: 4047 men and women, average age 61, mean FU 6.1 years
- Objective: to examine the association between cortisol patterns, CV and non-CV mortality

Kumari M, et al. J Clin Endocrinol Metab. 2011; 96(5): 1478-1485.

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- Slope across the day and CV deaths: Z-score: 1.87, p = 0.03 (P < 0.05)
- Bedtime cortisol and CV deaths: Z-score: 1.98, p = 0.02 (P < 0.05)

- Results: A flattened cortisol curve was SS associated with increased CV mortality; elevated PM cortisol was an independent predictor of subsequent CV mortality
  - No association between waking cortisol, CAR, and mortality

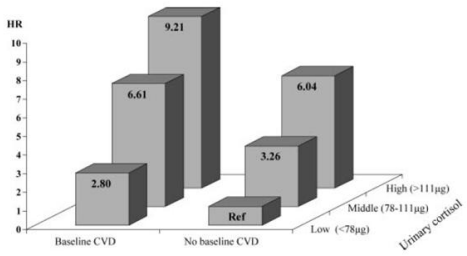
- **Conclusion: A flattened cortisol curve and elevated PM cortisol levels are robust CV mortality**

Kumari M, et al. J Clin Endocrinol Metab. 2011; 96(5): 1478-1485

Urinary Cortisol and CVD Mortality: InCHIANTI, a Prospective Cohort Study (2010)

Urinary Cortisol and Six-Year Risk of All-Cause and Cardiovascular Mortality

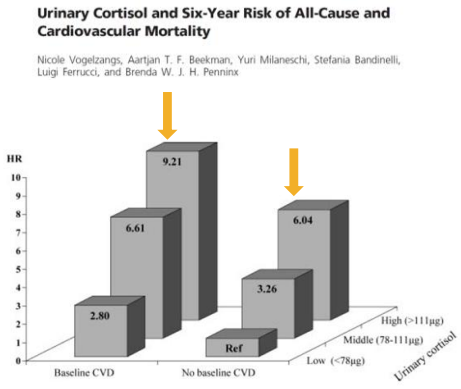
Nicole Vogelzangs, Aartjan T. F. Beekman, Yuri Milaneschi, Stefania Bandinelli, Luigi Ferrucci, and Brenda W. J. H. Penninx



- First urine study to document that 24-hour urinary free cortisol (UFC) levels predict CV mortality
- Study: 862 older individuals, mean age 74, 55% women; 6-year study; samples at baseline
  - UFC divided into 3 terciles: low < 78μg; moderate: 78-111μg; high: > 111μg
- Objective: To determine whether 24-hour UFC levels predict all-cause and CV mortality

Vogelzangs N, et al. J Clin Endocrinol Metab. 2010; 95(11): 4959-4964

Urinary Cortisol and CVD Mortality: InCHIANTI, a Prospective Cohort Study (2010)



- Results: UFC strongly predicts CV mortality, not non-CV mortality in persons with and without baseline CVD
  - Risk increased with increasing UFC levels
  - Those in the highest tercile had a 5x increased CVD mortality risk over 6 years
    - No baseline CVD: 6x increased risk of dying from CVD
    - Baseline CVD: 9.2x increased risk of dying from CVD

- **Conclusion: UFC is a strong CVD mortality predictor in persons with and without baseline CVD**

Vogelzangs N, et al. J Clin Endocrinol Metab. 2010; 95(11): 4959-4964.

Cortisol Key Points re: Cardiac Risk

- Cortisol production is a sign of inflammation
- Chronic stress is significantly associated with HPA axis dysfunction and with MI risk
- Cortisol is a strong predictor of CVD risk, events, and mortality
  - **Salivary** flattened diurnal cortisol pattern and/or high PM cortisol
  - **Urinary Cortisol**: elevated 24-hour UFC strong predictor of CVD mortality in persons with and without preexisting CVD

- **How do we measure this risk?**
  - Saliva and cortisol awakening response (CAR)
  - Urine free cortisol and cortisol/cortisone metabolites
  - For Anabolic/Catabolic balance, we assess Total DHEA Production against Total Cortisol Metabolites

Kumari M, et al. J Clin Endocrinol Metab. 2011; 96(5): 1478-1485.
Vogelzangs N, et al. J Clin Endocrinol Metab. 2010; 95(11): 4959-4964

Low DHEA and High Cortisol – 35 Year-Old Female

Catabolic or Anabolic?

What if salivary cortisol looks like this?

More worried or less worried now?

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Low DHEA + Low Cortisol – 43 Year Old Male (baseline before TRT 2x weekly)

Catabolic or Anabolic?

If we improve his HPA axis activity, will his testosterone level increase?

41

Assessing Androgens and Cortisol in Mid-Life Men and Women using DUTCH

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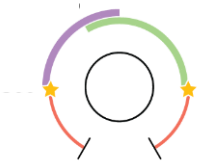
Range-Embedded Androgen Dials - Women

- Female androgen dials have reproductive stage-related reference ranges.
- "Optimal Premenopausal" is regarding women **age 20+.**
- **Women aged 41-55 may fall within or below the optimal pre-menopausal androgen range.**



Key to Reading the Dial

- Optimal Premenopausal
- Postmenopausal Range
- Out of Range
- Edge of Range

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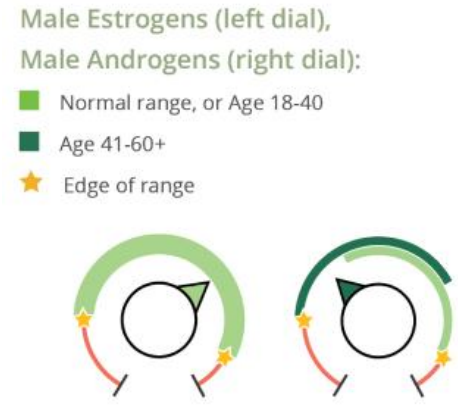
Range-Embedded Androgen Dials - Men

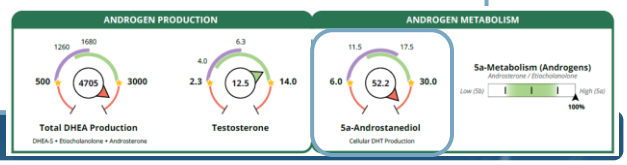
- Male androgen dials have age-related reference ranges.
- Optimal Age 18-40 range in light green
- Optimal Age 41-60+ in dark green



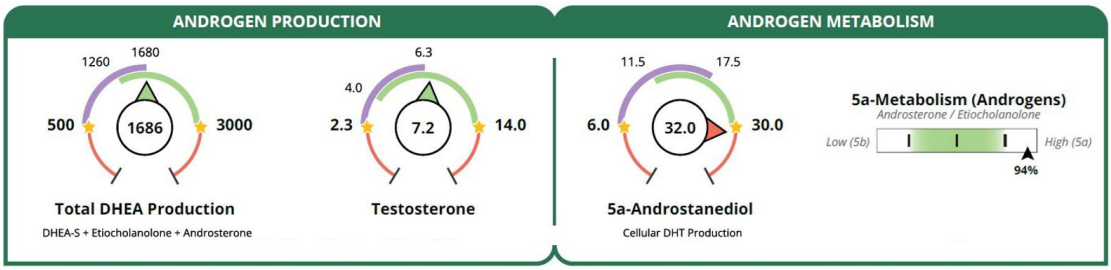
Testosterone's Metabolites – 5a-R Metabolites Do Testosterone's Work

- 5a-DHT – high impact at androgen receptor
  - Primarily in target tissues by the enzyme 5a-reductase
  - **3x more potent than testosterone**
  - When DHT is robust, it can help with skeletal muscle turnover
  - , increasing muscle development and improving strength.
  - DHT damages hair follicles, increasing body hair and decreasing scalp hair growth.
  - DHT can cause cystic acne development.
  - DHT can act as a neuro-steroid and increase agitation.

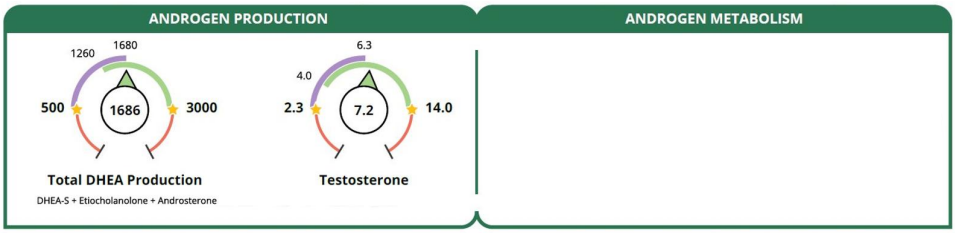
- 5a-Androstanediol – **marker of DHT formation, intact/unaffected by UGT deletion**
  - Primarily formed from DHT in target tissues
  - Weakly binds androgen receptors
  - More persistent marker for TISSUE 5a-DHT activity than urinary 5a-DHT itself
  - Correlates with high androgenic symptoms such as acne, body hair, oily skin, irritability, and scalp hair loss.



The Androgen Story in Dried Urine



Tissue Androgenic Activity

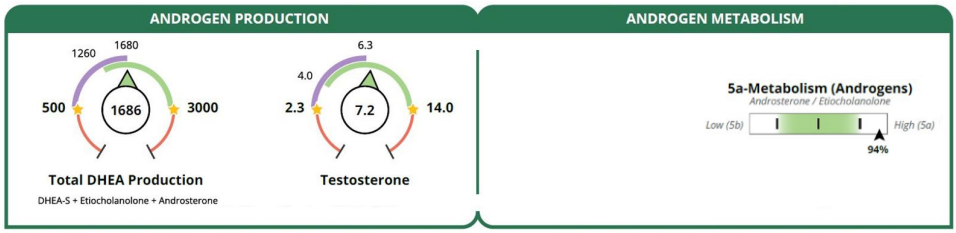


Circulation

Free T

Target Tissue

Tissue Androgenic Activity



Target Tissue

T → 5aR → DHT

Androgenic impact

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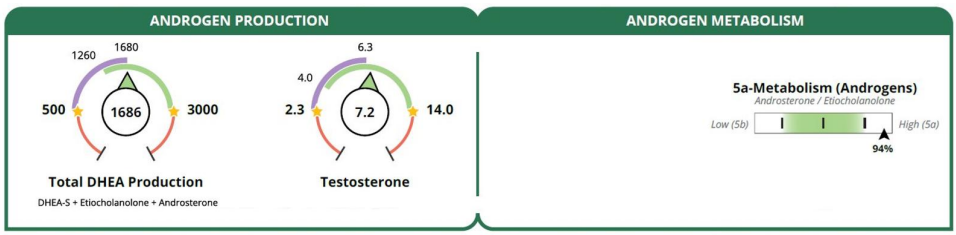
Tissue Androgenic Activity



Target Tissue

5a-Androstanediol ← DHT

AR

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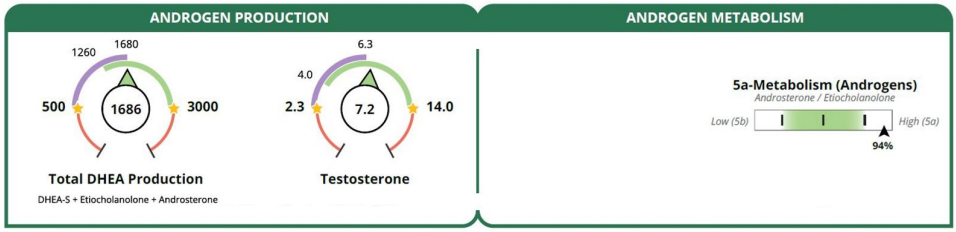
Tissue Androgenic Activity



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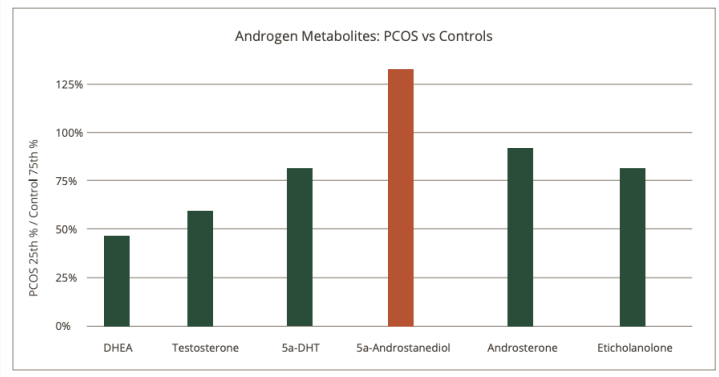
5a-Androstanediol is the most differentiating androgen metabolite

Figure 2: *An analysis of androgen metabolites in 24-hour urine (nmol/24h) in women with or without PCOS shows that, for 5a-androstanediol, the 25th percentile value for PCOS patients is more than 125% of the 75th percentile value for normal controls. Essentially, even the lower end of the PCOS range (25th percentile) exceeds the upper end of the normal range (75th percentile) for healthly controls, suggesting no overlap between the normal range and the PCOS range for 5a-androstanediol.* [98]



Dhayat NA, Marti N, Kollmann Z, et al. Urinary steroid profiling in women hints at a diagnostic signature of the polycystic ovary syndrome: A pilot study considering neglected steroid metabolites. PLOS ONE. 2018; 13(10):e0203903. doi:10.1371/journal.pone.0203903

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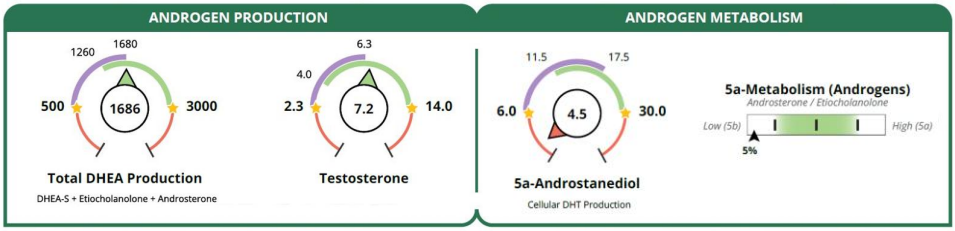
Urine Captures Tissue Androgen Activity



The ISSUE is the TISSUE

- 5a-Androstanediol best represents tissue DHT
- Parent hormones AND metabolites matter

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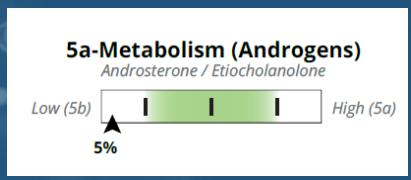
Low 5a-Reductase Activity Can Worsen Symptoms of Declining Androgens



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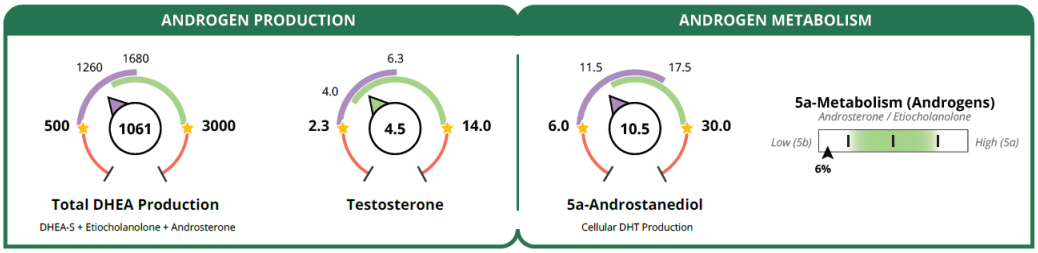
What is the androgen status? 46 Yr Old Cycling Female



- This 46 yo perimenopausal female has irregular cycles and struggles with low libido and vaginal dryness.
  - Testosterone level is normal but 5a-Androstanediol is low
    - Low tissue DHT-driven androgenic activity
  - DHEA is low for cycling status and 5a-Reductase Activity Slider shows low 5aR
    - DHEA metabolism favors 5b-Reductase, low tissue androgen activity

- Assessment: Mildly low adrenal androgens and impaired 5a-Reductase activity at the tissue level both contributing to low libido and vaginal dryness, perhaps even irregular cycles.

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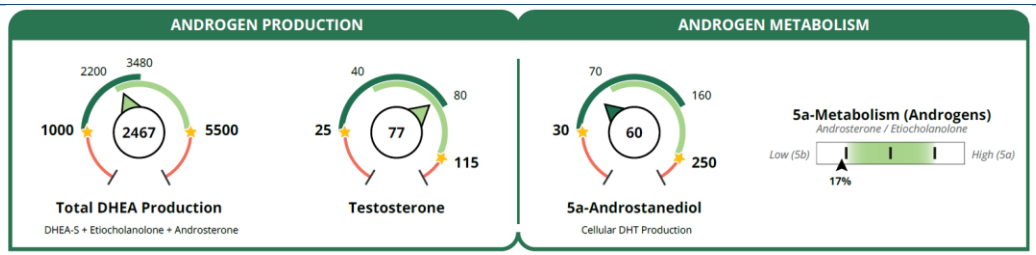
What is the androgen status? 57 Yr-Old Male on TD TRT



- This 57yoM struggles with continued fatigue, low libido, and low mood since starting transdermal testosterone 3 months ago. Why is he not responding?
- DHEA and Testosterone both look great for his age but….
  - 5a-Androstanediol
    - Testosterone's formation of DHT is low compared to testosterone consistent with 5b preference
  - 5a-Reductase Activity Slider shows low 5a-R activity
    - 5b preference confirms a low tissue androgenic activity

- Assessment: Normal DHEA and T on therapy but low tissue activation of androgens (low 5a-Metabolism)

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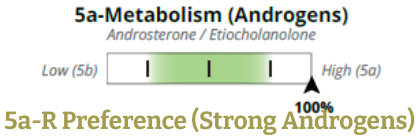
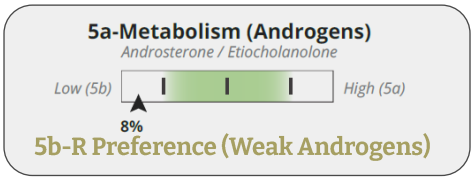
5a-Metabolism Summary

- **5a-reductase** is the enzyme that metabolizes DHEA and testosterone into their **active, androgenic metabolites**.
  - DHEA → Androsterone (~ 7x weaker than testosterone)
  - Testosterone → DHT (3x more potent than testosterone)
  - 5a-Androstanediol = end-clearance of ALL 5-alpha metabolites
- Low 5a-reductase activity may be associated with:
  - **Autoimmune disease**
  - **Thyroid disease**
  - **Medications (ie: Finasteride, Dutasteride, Saw Palmetto, Reishi, EGCG, Nettle Root)**
- 5b-reductase preference may lead to low androgen symptoms even when DHEA and Testosterone are within normal ranges.





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Interventions To Help Activate Androgens at the Tissue Level

Decreasing a 5b-Reductase Preference

In addition to treating the underlying cause (see the DUTCH Interpretive Guide), other potential support considerations for decreasing a 5b-reductase preference (by supporting more 5a-reductase activity) in females and males include:

Lifestyle and Diet

- Forskolin
- High intensity interval training (HIIT)
- Pine pollen
- Weight resistance exercises

Avoid 5a-Reductase Blockers

- Beta-sitosterol
- Epigallocatechin gallate (EGCG) from green tea
- Polyunsaturated fatty acids
- Pygeum
- Reishi
- Saw palmetto
- Stinging nettle root
- Zinc (balance copper)
- Rx: Finasteride[6]

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Important Caveat to Interpreting Testosterone in Urine Tests

UGT2B17 Deletion

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UGT2B17 Gene Deletion

- For those carrying this deletion, urinary testosterone will not correlate with circulating testosterone levels.
- It also diminishes DHT and 5b-Androstanediol in urine.

→	Testosterone	Below range	1.04	ng/mg	2.3 - 14
→	5a-DHT	Within range (But low edge)	0.4	ng/mg	0 - 6.6
	5a-Androstanediol	Within range	11.5	ng/mg	6 - 30
→	5b-Androstanediol	Below range	8.3	ng/mg	12 - 75
	Epi-Testosterone	Within range	13.0	ng/mg	2.3 - 14

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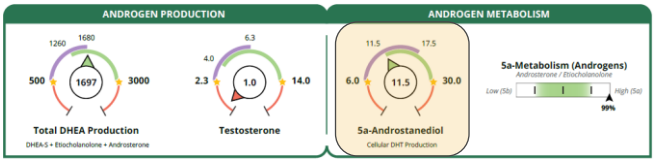
UGT2B17 Gene Deletion

- 5a-Androstanediol is unaffected, so use it to assess tissue DHT in UGT del carriers.



Testosterone	Below range	1.04	ng/mg	2.3 - 14
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→ 5a-Androstanediol	Within range	11.5	ng/mg	6 - 30
5b-Androstanediol	Below range	8.3	ng/mg	12 - 75
Epi-Testosterone	Within range	13.0	ng/mg	2.3 - 14

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62 Year Old Female on Oral Prednisone

Fatigue, sleep disturbed, low libido

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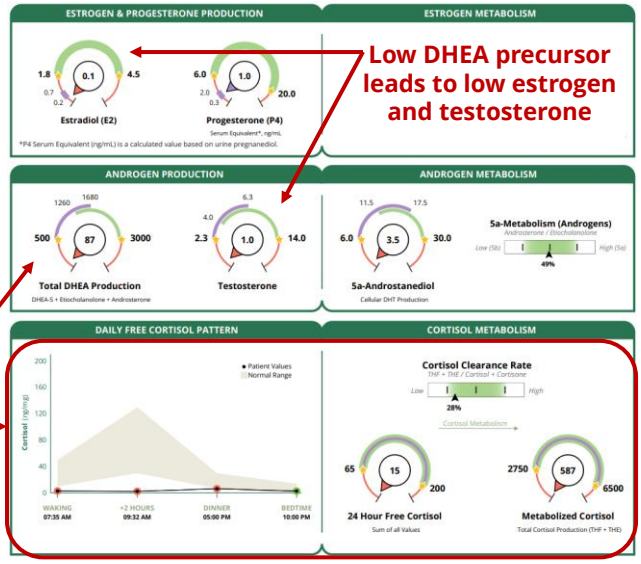
62-Year-Old Postmenopausal Female on Oral Prednisone



Low DHEA precursor leads to low estrogen and testosterone

Adrenal Suppression

What hormone might she need to replace while she's on prednisone?

DHEA!

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49 Year Old Female in Late Perimenopause

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Case: Late Perimenopause

49 Year Old Female

LMP > 6 months prior to collecting samples

Has been using Equol to control hot flashes but it has stopped working well

Difficulty getting to sleep and staying asleep due to hot flashes, feels restless nightly and wakes tired x 1 year

Libido has decreased significantly x 5 years

Weight gain 3-5 pounds per year over the past x 2 years

BMI is normal

Late Perimenopause Baseline

Pertinent Baseline serum labs:

- FSH (day 3): 18 mIU/L

All other findings within healthy norms including thyroid panel, CBC, CMP, lipids, and hs-CRP.

Late Perimenopause Baseline – Let's use the D12 to make a plan!

Hot flashes and sleep issues likely due to low Estrogen and Progesterone

Rx ideas?
- **E2 Patch 0.0375 mg**
- **OMP 100 mg**
- **Phase One Support w/ glucoraphanin**

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Late Perimenopause Baseline – Let's use the D12 to make a plan!

Hot flashes and sleep issues likely due to low Estrogen and Progesterone

Rx ideas?
- **E2 Patch 0.0375 mg**
- **OMP 100 mg**
- **Phase One Support w/ glucoraphanin**

Low libido and weight gain could be stemming from low androgens and 5B preference

Rx ideas?
- **DHEA 10 mg**
- **Resistance Training 3x week**

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Late Perimenopause Baseline – Let's use the D12 to make a plan!

Hot flashes and sleep issues likely due to low Estrogen and Progesterone

Rx ideas? **E2 Patch 0.0375 mg**
OMP 100 mg
Phase One Support w/ glucoraphanin

Low libido and weight gain could be stemming from low androgens and 5B preference

Rx ideas? **DHEA 10 mg**
Resistance Training 3x week

Poor sleep is probably the chronic stressor leading to flattening of the cortisol pattern and low cortisol production

Low neurotransmitter metabolites common with low adrenal function – same drivers

Rx ideas? **Adaptogen Botanical Complex w/ Rhodiola and Maca**

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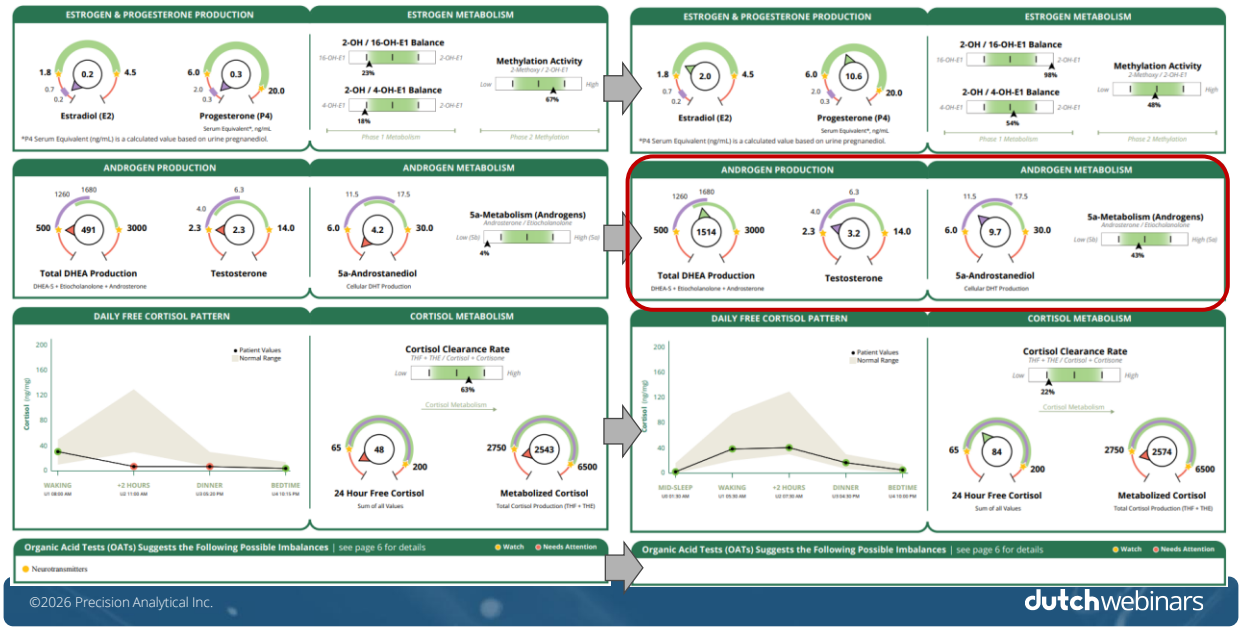
Late Perimenopause Baseline vs Retest at 6 Months on Therapy



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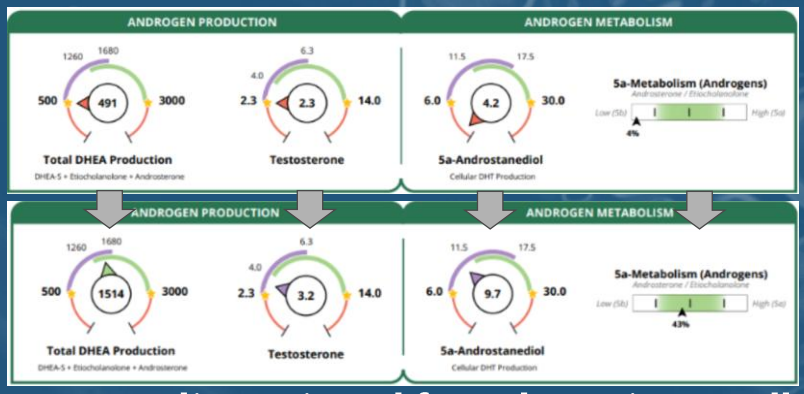

Oral DHEA was discontinued for 72 hrs prior to collecting samples.

Q: How does that information affect your assessment?

A: DHEA therapy isn't responsible for the rises in DHEA, T, 5-Andro, or the shift in 5a-R. Does she still need to take it?

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Female - Non-Hormonal Therapies for Low Testosterone

LOW TESTOSTERONE IN FEMALES

In addition to treating the underlying cause (see the DUTCH Interpretive Guide), other potential support considerations for low testosterone in females include:

HPO Axis Support (Cycling Females)

- Treat energy deficit from anorexia, low calorie intake, low body weight, and/or extreme exercise.
- Optimize nutrition: B vitamins, choline, inositol, vit. D, and Zn.
- Reduce stress and support parasympathetic activity.
- Optimize sleep and the circadian rhythm.
- Treat hyperprolactinemia.
- Treat hypothyroidism.
- In cycling females, if estrogen and progesterone are also low, consider phytoestrogen and phytoprogestogen support. See
- Avoid endocrine disrupting chemicals (EDCs).

Androgen Supportive

- **Ashwagandha (A)**
- Damiana
- Epimedium
- Fenugreek
- Indian coleus
- **Korean Ginseng (A)**
- **Maca (A)**
- Mucuna[3]
- Sarsaparilla
- **Shatavari (A) (Females)**
- Tongkat Ali
- Tribulus
- Yohimbe

(A) Indicates an Adaptogen

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Activate Androgens at the Tissue Level

Decreasing a 5b-Reductase Preference

In addition to treating the underlying cause (see the DUTCH Interpretive Guide), other potential support considerations for decreasing a 5b-reductase preference (by supporting more 5a-reductase activity) in females and males include:

Lifestyle and Diet

- Forskolin
- High intensity interval training (HIIT)
- Pine pollen
- Weight resistance exercises

Avoid 5a-Reductase Blockers

- Beta-sitosterol
- Epigallocatechin gallate (EGCG) from green tea
- Polyunsaturated fatty acids
- Pygeum
- Reishi
- Saw palmetto
- Stinging nettle root
- Zinc (balance copper)
- Rx: Finasteride[6]

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Low Libido and Metabolic Syndrome in a 49 yo Male

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Case 2: 49-Year-Old Male Libido/Weight

Chief Complaints

- Low libido, erectile dysfunction
- Trouble losing weight
- Low mood, motivation
- Difficulty falling asleep, wakes
- Daytime fatigue

PMHx

- Prediabetes dx 2022
- Has gained 20 lbs. over the past 3 years
- Offered but refused to take statins

Baseline labs

- CBC & CMP: WNL except fasting glucose = 112
- HbA1c: 5.9
- Fasting insulin: 35
- Lipids: TG: 180, LDL: 120, HDL: 35
- TSH, fT4, fT3, TPO, rT3, anti TG: all WNL
- hs-CRP 2.7 (goal <1)
- SHBG: <15

Physical Exam

- 5'9"
- 202 lbs.
- BMI 29.8 (overweight)
- BP 138/87 mm Hg
- Pulse 82

Medications

- None

KEY = High end | Low end

DUTCH Test Results

Male Libido/Weight: DUTCH Hormone Testing Summary Page

DUTCH Complete

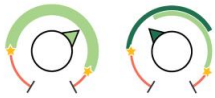
Androgen Story

Estrogen Story

Cortisol Story

OATs Abnormals

Male Estrogens (left dial),
Male Androgens (right dial):
- Normal range, or Age 18-40
- Age 41-60+
- Edge of range



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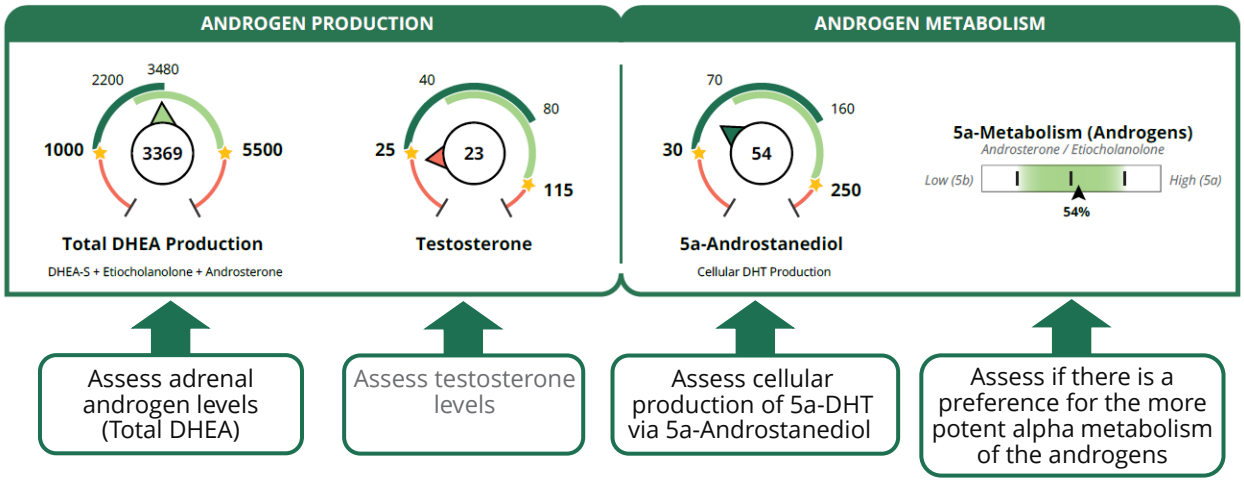
Male Libido/Weight: Androgens



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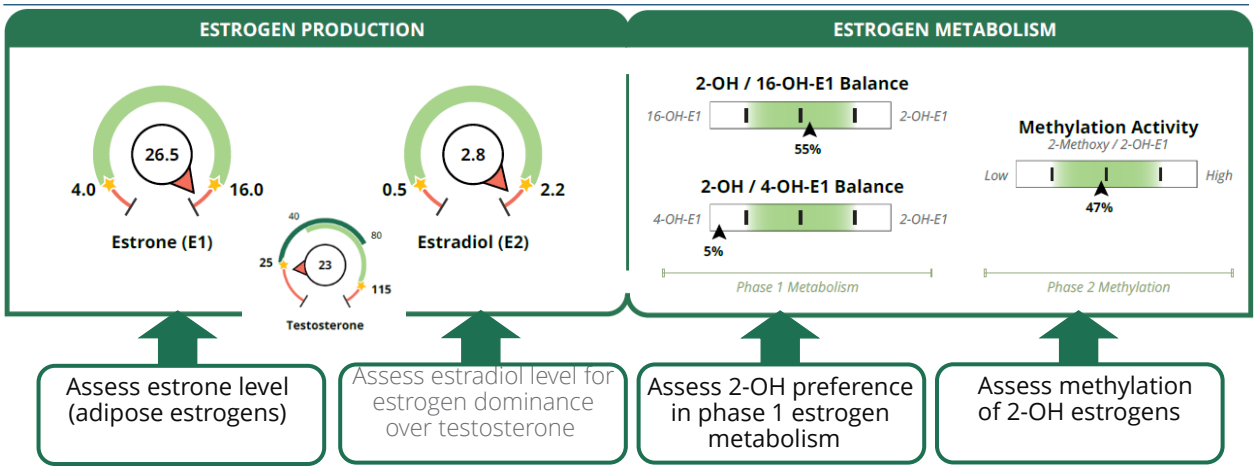
Male Libido/Weight: Estrogen



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Non-Hormonal Options for Promoting Androgen Function in Men

Downregulate Aromatase

Slow aromatase activity if estrogen is high.

- Apigenin
- Chrysin
- Damiana
- Enterolactone
- Genistein
- Grape seed extract (GSE)
- Normalize body fat percentage
- Red wine procyanidin dimers
- Resveratrol
- White button mushroom
- Rx: Anastrozole

Improve Androgen Deficiency Symptoms

Note that these may improve androgen deficiency symptoms without necessarily increasing androgen levels.

- Exercise performance:
  - Korean ginseng
  - Maca
- Erectile function:
  - Arginine
  - Korean ginseng
  - Tribulus
  - Yohimbe
- Muscle mass:
  - Optimal protein consumption
  - Weightlifting

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Male - Non-Hormonal Therapies for Low Testosterone

LOW TESTOSTERONE IN MALES

In addition to treating the underlying cause (see the DUTCH Interpretive Guide), other potential support considerations for low testosterone in males include:

HPT Axis Support

- Herbal and nutrient support:
  - Fenugreek
  - Indian coleus
  - Korean ginseng
  - Mucuna[3]
  - Shilajit
  - Tongkat ali
  - Tribulus
  - Vitamin D
  - Zn (balance Cu)
- Metabolic support:
  - Correct insulin resistance.
  - Eat a low glycemic and whole foods diet.
  - Exercise regularly.
  - Maintain healthy body weight.
- Lower stress and increase parasympathetic activity.
- Optimize sleep and the circadian rhythm.
- Decrease inflammation.
- Treat thyroid disorders if present.
- Treat hyperprolactinemia if present.

Avoid endocrine disrupting chemicals (EDCs).

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Non-Hormonal Supports for Dopaminergic Tone and Androgens

Dopamine Support

Testosterone supports dopamine production. If symptoms of low dopamine are present, consider:

- Adequate dietary protein intake
- B vitamins
- D,L-phenylalanine (DLPA)[3]
- Mucuna[3] (contains L-DOPA)
- Tyrosine
- Vitamin C

Consider when HVA is low!

Clinical Pearl: HVA is often low in mid-life males with low androgen symptoms

Gonadal Support

- Indian coleus
- Mucuna[3]
- Treat nutrient deficiencies

Androgen Supportive

- **Ashwagandha (A)**
- Damiana
- Epimedium
- Fenugreek
- Indian coleus
- **Korean Ginseng (A)**
- **Maca (A)**
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- Sarsaparilla
- **Shatavari (A) (Females)**
- Tongkat Ali
- Tribulus
- Yohimbe

(A) Indicates an Adaptogen

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Treat ALL Imbalances That Contribute to Low Androgen Symptoms

- Estrogen/Progesterone Imbalance
- High and Low Cortisol
- Hypothyroid
- Gut Dysbiosis
- Metabolic Syndrome
- Chronic Inflammation
- Neurotransmitter imbalances

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DUTCH TESTING & HT GUIDE - WOMEN

	Why	Common Dosing Strategies	How to Monitor with DUTCH
Oral Progestrone	Effective at balancing ET, but clinical effects are due largely to metabolites formed in the gut. A good option when postmenopausal women struggle with sleep. A different ROA may be better for premenopausal women. 100-200mg has been shown to balance concurrent ET in postmenopausal women. Perimenopausal women may benefit from higher dosing (100-400mg) especially in the early menopausal transition when estrogen excess may occur.	**Low:** 25 - 50 mg **High:** >200 mg **Most Common:** 100 - 200 mg **Premenopausal dosing:** 50-400 mg *Consider taking sequentially or continuously.*	DUTCH results only show which metabolites are preferred. Evaluate which pathway is dominant (alpha or beta).
Estradiol Patch	Patches offer consistent hormone dosing over time and are very effective at managing hot flashes. Even low doses may increase bone mineral density (BMD) in some women.	**Low:** 0.014 - 0.025 mg **High:** 0.1 mg **Most Common:** 0.05 mg *Usually used continuously. Typically changed 1-2 times per week.*	**Monitoring Estrogen Therapy (ET)** Typical on-therapy values between the top of the postmenopausal range (0.7ng/mg for estradiol) and within the first third of the premenopausal range (about 2.4ng/mg). The specific target for a patient depends on the patient's history and symptoms as well as the patient and provider's comfort level with the risks for too much (breast cancer, etc.) and too little (osteoporosis, etc.) estrogen. It is recommended to closely monitor phase I metabolites to ensure that too many 4-OH metabolites are not formed. Methylation should also be evaluated and supported if inadequate. DUTCH OATs may also be helpful to ensure that a nutrient deficiency is not present. ET may induce vitamin B6 deficiency. Proper metabolism requires B6, B12, and glutathione. For testosterone pellets, premenopausal levels are often targeted and patient symptoms monitored. Evaluate 5a-reductase activity before dosing with testosterone to ensure there isn't excessive 5a metabolism.
Estradiol Cream/Gel	Increases serum and urine levels and may improve hot flashes and BMD at the right dose. Transdermal E2 is attractive because it is easy to use and bypasses first pass metabolism. Estriol often given in doses 1 - 4 times higher than estradiol.	**Low:** 0.1 - 0.25 mg Estradiol 0.1 - 1.0 mg Estriol **High:** 1.0 - 2.5 mg Estradiol 2.0 - 5.0 mg Estriol **Most Common:** 0.25 - 0.5 mg Estradiol 0.25 - 2.5 mg Estriol *Usually taken continuously.*	
Testosterone or Estradiol Pellet	Pellets offer consistent hormone dosing over time for testosterone and estradiol. Research is limited on effects on hot flashes and BMD. Because serum/urine E2 levels match or exceed those seen in patches, E2 pellets are likely to help with hot flashes and BMD.	**Low:** <5 mg Estradiol 20 - 50 mg Testosterone **High:** >12 mg Estradiol >125 mg Testosterone **Most Common:** 5 mg Estradiol 100 mg Testosterone *Inserted every 3 - 4 months*	
Vaginal Estrogen or Testosterone	Low doses increase local tissue levels while higher doses also increase systemic levels. Placing in the top 1/3 of the vagina significantly increases uterine levels. Estriol often given in doses 1 - 4 times higher than estradiol. Studies have found that some FDA-approved low dose vaginal E2 formulations (e.g., 0.01 mg E2 insert) may be safe to use without progesterone in a woman with a uterus. Doses higher than this may require concomitant progesterone therapy to prevent endometrial hyperplasia and cancer.	**Low:** 0.01 mg Estradiol 0.25 mg Testosterone **High:** 0.5 mg Estradiol 2 mg Testosterone **Most Common:** 0.1 mg Estradiol 0.25 - 1.0 mg Estriol 0.25 - 1.0 mg Testosterone *Usually used 2-3 times per week at night but may be used nightly.*	Levels above the postmenopausal range imply systemic uptake. For localized (vaginal) effects only, results should not exceed the postmenopausal range.
Testosterone Cream/Gel	Transdermal testosterone can be used to correct low T and improve sex drive and muscle mass.	**Low:** 0.5 - 2.0 mg **High:** 10 - 20 mg **Most Common:** 1 - 5 mg *Taken daily, at waking or bedtime*	It is optimal if levels of T (as well as metabolites) are in range. A lower dose may be needed if the 5a-reductase pathway is favored. Monitor patient for excess androgen symptoms (e.g., scalp hair loss, facial/body hair growth, acne, etc.)
DHEA	Sublingual or oral DHEA will increase systemic levels and also contribute to downstream androgens (testosterone) and estrogens.	**Low:** 1 - 5 mg **High:** 25 - 50 mg **Most Common:** 5 - 10 mg *Usually taken daily*	Monitor conversion to testosterone, E2 and metabolites of both. DHEA and testosterone metabolites may be artificially elevated if the patient doesn't skip the dose of DHEA the day of and day before the test (as described in the test instructions).

ET, especially with an intact uterus, should be balanced with adequate progesterone (vaginal or oral preferred).

Transdermal progesterone, oral estrogen and sublingual hormones are not well monitored by DUTCH and are not represented on this form along with a few other less commonly used HT options.

DUTCH TESTING & HT GUIDE - MEN

	Why	Common Dosing Strategies	How to Monitor with DUTCH
Testosterone Pellets	Testosterone pellets offer consistent hormone dosing over time. Most pellet doses tend to suppress endogenous testosterone production. They can be given with aromatase inhibitors if conversion to estrogen is a concern.	**Low:** 400 mg **High:** 1600 - 2000 mg **Most Common:** 800 - 1200 mg *Inserted every 4-6 months*	Urine testosterone levels are often supraphysiological in the days following an injection and in the first three months of pellet therapy. With 1200 mg testosterone pellets, results are expected to be 90-220ng/mg over this period (reference range 25-115ng/mg). Monitor testosterone along with its metabolites to assess 5a-DHT production and evaluate potential need for blocking 5a-reductase. Patients on TTh should also be evaluated for aromatization of testosterone to estradiol by monitoring estradiol and its metabolites.
Testosterone Injections	The most frequently used testosterone injections are testosterone cypionate (8 day half-life) and testosterone enanthate (4-5 day half-life). Injections provide robust testosterone levels for 1-2 weeks typically. Bi-weekly dosing (with lower dosing than weekly injections) may offer improved steady state and less highs and lows.	**Low:** 25 - 100 mg **High:** >300 mg **Most Common:** 100 - 250 mg *Administered biweekly, or every one to two weeks*	In men who are not on TTh, epi-testosterone is expected to be found in similar concentrations as testosterone. When gonadal production of hormones is suppressed by TRT, epi-testosterone may be a good indicator of this suppression. Typically levels below 10ng/mg indicate suppression (and especially if <5ng/mg). While correlating data has not been generated, these levels may parallel serum LH levels. Both LH and epi-testosterone are suppressed by most doses of injections and pellets.
Transdermal Testosterone	Testosterone creams and gels are the most popular TRT formulation but can be challenging to dose and monitor effectively. Doses between 50 and 150mg are commonly used in studies in order to see improvements in muscle mass and other clinical parameters. Application is convenient, but patients must also be careful to avoid transference (to partners, children, or pets).	**Low:** 25 - 75 mg **High:** 150 - 250 mg **Most Common:** 50 - 100 mg *Typically applied daily*	Doses proven to increase muscle mass (25-100mg) in most recipients typically push DUTCH testosterone levels to levels matching the reference range for young, healthy men (50-115ng/mg). Monitoring 5a-DHT and its metabolite will assist in evaluating if 5a-blockers may be appropriate. Epi-testosterone levels will often be only partially suppressed (not below 10ng/mg), which implies that endogenous production (and likely pituitary LH secretion) is only partially suppressed. Monitor estrogen conversion and metabolism as well.
DHEA	Even though testosterone is downstream from DHEA, very little testosterone is made from circulating DHEA. The testes make testosterone directly (from cholesterol), so do not give DHEA expecting significant increases in testosterone. Oral or sublingual DHEA is often used. The latter may absorb directly in the mouth and bypass gut/liver metabolism, which may result in less estrogen production.	**Low:** 5 - 10 mg **High:** >100 mg **Most Common:** 10 - 25 mg *Typically taken daily*	Oral DHEA must be stopped 48 hours prior to DUTCH sample collection to avoid hormone elevations from 1st pass metabolites. Monitor androgen metabolism pathways (alpha vs beta), conversion to estrogens, along with estrogen metabolism. Be aware that DHEA can form testosterone metabolites without necessarily making testosterone itself. Transdermal DHEA may be used on the day of testing and overall DHEA levels can be monitored by looking at the total DHEA (DHEA-S + Androsterone + Etiocholanolone).
HCG or Clomiphene	Human chorionic gonadotropin (hCG) acts as an LH analog and stimulates the Leydig cells to produce testosterone. Clomiphene citrate, a selective estrogen receptor modulator (SERM) can also be used for secondary hypogonadism. By blocking negative feedback of estrogen receptors, it increases gonadotropin levels, indirectly increasing testosterone production. These two options are not advised for primary hypogonadism.	**HCG:** 100 - 250 ug (2000 - 5000 IU) *Taken 2 - 3 times/week* **Clomiphene:** 25 mg *Taken every other day*	Providers may want to target young, healthy testosterone levels (50-115ng/mg) with these therapies. 50-150% increases are common in (non-primary) hypogonadal men. Metabolites of testosterone (including DHT production) should all be monitored along with estrogen production and metabolism. Estradiol conversion will often exceed physiological levels with hCG use. Clomiphene citrate and hCG will not compromise fertility in a male patient, unlike testosterone therapy.

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