Urine Steroid Hormones

Clinical Information for Professionals

What are the benefits of urine steroid hormone testing?

The urine steroid hormone profile measures hormones and hormone metabolites in a 24-hour urine specimen. The information gathered from a 24-hour urine steroid hormone profile has some distinct advantages over other hormone tests:

Averages fluctuating hormone levels
Steroid hormones are secreted in a pulsatile fashion, throughout the day. The amplitude of the pulses also varies in a circadian rhythm. When point samples are collected in either serum or saliva, the results can vary significantly depending on whether hormone release is at its peak or trough at the time. In a 24-hour urine collection, these pulsatile variations are smoothed out, and a picture of total daily hormone output may be obtained.

Provides a view of overall hormone output
Any examination of hormone balance must take into account all the hormones – including hormone metabolites. Focusing solely on the ‘parent’ hormone is to potentially miss out on critical information. For example, a low salivary cortisol with no clinical signs or symptoms of adrenal insufficiency may be better explained by a urine steroid hormone profile. In this case, the 24-hour urine collection, these pulsatile variations are smoothed out, and a picture of total daily hormone output may be obtained.

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Measures unique and important metabolites
Some estrogen metabolites can be measured in urine, but not in saliva or serum. These metabolites (e.g. 4-hydroxyestrone) may be important for assessing risk of estrogen-sensitive cancers.

Assesses important biochemical processes
Several important physiologic and biochemical processes can be assessed via a 24-hour urine hormone profile:

- anabolic/catabolic balance - looks at the balance of anabolic (growth and healing) metabolites over catabolic (wear and tear) metabolites.
- methylation capacity - assesses ability to attach methyl groups to hormones, which may be important for reducing cancer risk.
- 5-alpha reductase activity - levels of hormones metabolized by 5-alpha-reductase can be used to measure enzyme activity and help understand high androgens signs and symptoms.

How do urine steroid hormones compare to saliva and serum?

Urine steroid hormone levels cannot be directly compared to saliva or serum because unlike saliva, they represent the sum of conjugated and free hormone.

Specifically, steroid hormones are excreted in urine in two different non-protein bound forms. The most abundant are conjugated hormones, which are steroid hormones with sulfate and/or glucuronide functional groups attached to increase water solubility. Also found in urine are unconjugated, or free urine steroid hormones, usually in much lesser quantities.

Measuring steroid hormones in urine requires hydrolysis of conjugates (sulfate, glucuronides). Once these conjugates have been cleaved off, the measured hormone levels reflect the combined value of previously conjugated hormone plus free hormone, and are therefore not comparable to saliva or serum hormone levels, which do not generally reflect conjugates.

Which is better: urine or saliva?

A toolbox normally contains many different tools, each suited to a particular task. The same is true for your testing toolbox - the test you choose depends on the question you are trying to answer. Urine steroid hormones reflect hormone production and metabolism, while saliva testing is excellent for mapping out hormone levels over time.

Test Limitations

The urine steroid hormone profile is not appropriate for patients with impaired renal function or on diuretic medication. If mapping the diurnal rhythm is important, a salivary diurnal cortisol could be recommended.

Reference Ranges

When endogenous hormones are being measured, the reference range used is specific to cycle (luteal, follicular or post-menopausal). The range applied for the supplemented hormones is the luteal range.
### Clinical Considerations

#### Metabolite

<table>
<thead>
<tr>
<th>Adrenal Glucocorticoids</th>
<th>LOW levels of total 17-hydroxysteroids</th>
<th>HIGH levels of total 17-hydroxysteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible causes</td>
<td>B vitamins, vitamin C, zinc</td>
<td>Cushing’s disease, excessive exercise, stress, inflammation, infection, dysbiosis, visceral fat, metabolic syndrome, hypoglycemia, hypothyroidism</td>
</tr>
<tr>
<td>Supplements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adaptogenic Herbs</td>
<td>Siberian ginseng, Panax ginseng, ashwagandha, astragalus, rhodiola, schisandra, licorice</td>
<td>Siberian ginseng, ashwagandha, astragalus, rhodiola, schizandra, magnolia, skullcap, passionflower</td>
</tr>
<tr>
<td>Lifestyle Changes</td>
<td>stress management, decrease intake of high glycemic index foods, reduce intake of stimulants (e.g. caffeine), improve sleep</td>
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#### Anabolic/Catabolic Balance

Excessive cortisol contributes to catabolism, a state of tissue breakdown and poor recovery from stress or illness - while DHEA contributes to anabolism, a tendency toward tissue growth and repair. The ratio of total 17-ketosteroids to 17-hydroxysteroids is generally taken to reflect the balance between anabolic and catabolic steroid hormones. A ratio greater than 1 reflects anabolism whereas a ratio below 1 reflects a tendency toward catabolism.

<table>
<thead>
<tr>
<th>LOW Anabolic/Catabolic Ratio</th>
<th>HIGH Anabolic/Catabolic Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible causes</td>
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</tr>
<tr>
<td>aging</td>
<td>excessive exercise</td>
</tr>
<tr>
<td>lack of growth hormone</td>
<td>adrenal tumors</td>
</tr>
<tr>
<td>excessive exercise</td>
<td>polycystic ovarian syndrome and/or hirsutism</td>
</tr>
<tr>
<td>chronic or acute illness</td>
<td>high dose androgens</td>
</tr>
<tr>
<td>chronic stress</td>
<td>congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>use of glucocorticoids</td>
<td>metabolic syndrome/insulin resistance</td>
</tr>
</tbody>
</table>

#### Mineralocorticoids

Mineralocorticoids include aldosterone and its metabolites, which help regulate renal sodium reabsorption and water balance.

<table>
<thead>
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<tbody>
<tr>
<td>Possible causes</td>
<td>Possible causes</td>
</tr>
<tr>
<td>medications: prednisone and other potent glucocorticoids, beta blockers, ACE inhibitors, high sodium intake, low potassium intake, licorice</td>
<td>medications: lithium, spironolactone, diuretics, hypertension, excessive exercise (dehydration, sodium depletion), sodium restricted diet, obesity, metabolic syndrome</td>
</tr>
<tr>
<td>Interventions</td>
<td>Interventions</td>
</tr>
<tr>
<td>Identify and treat underlying cause, e.g. reduce sodium intake</td>
<td>Identify and treat underlying cause, e.g. increase sodium intake if patient currently voluntarily self-restricts.</td>
</tr>
</tbody>
</table>
### Estrogens and Breast Cancer

- Increased risk of breast cancer in overweight women is related to elevated estradiol levels.\(^1\)

  - The **Estrogen Quotient** is calculated by dividing the estriol level by the sum of estrone plus estradiol\(^2\):
    \[
    EQ = \frac{E_3}{E_2 + E_1}
    \]
    - non-Caucasian populations with a low incidence of breast cancer generally have EQs above 1.
    - Caucasian North American women have an EQ closer to 0.5\(^2\).
    - Iodine supplementation may increase EQ.

- The **4-hydroxyestrone** (4-OHE1) metabolite is implicated in breast cancer. 4-OHE1 covalently bonds to DNA, forming DNA adducts which are considered biomarkers of exposure to carcinogens. 4-OHE1 also generates free radicals, which damages DNA as well. Prevention of adduct formation via improved methylation and glutathionation is desirable. Supplementing with antioxidants may also help ameliorate damage.

  - RMA database analysis found the highest levels of 4-OHE1 in women with a current diagnosis of breast cancer. It is important to note that this finding does not prove that high levels of 4-OHE1 are predictive for future development of breast cancer.

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### Metabolite

<table>
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<tr>
<th>Estrogens</th>
<th>LOW Estrogens</th>
<th>HIGH Estrogens</th>
</tr>
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<tbody>
<tr>
<td><strong>Possible causes</strong></td>
<td>Identify &amp; treat underlying problem</td>
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</tr>
<tr>
<td>- low percent body fat (e.g., endurance athletes)</td>
<td>• consider hormone supplementation if no reversible cause can be found.</td>
<td>• modify estrogen dose if supplementing</td>
</tr>
<tr>
<td>- decreased synthesis</td>
<td></td>
<td><strong>Supplements</strong></td>
</tr>
<tr>
<td>- low cholesterol</td>
<td></td>
<td>• supplement with fish oil, antioxidants, MSM to decrease inflammation</td>
</tr>
<tr>
<td>- low testosterone</td>
<td></td>
<td>• supplement with zinc, progesterone to regulate aromatization</td>
</tr>
<tr>
<td>- excessive supplementation with progesterone</td>
<td></td>
<td>• decrease visceral fat (increase growth hormone)</td>
</tr>
<tr>
<td>- excessive zinc supplementation suppresses aromatase (aromatase converts testosterone to estrogen)</td>
<td></td>
<td>• liver detoxification</td>
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### Clinical Considerations

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<tr>
<td><strong>Estrogens</strong></td>
<td><strong>Androgens</strong></td>
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<td>Possible causes</td>
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<tr>
<td>• low percent body fat (e.g., endurance athletes)</td>
<td>• decreased synthesis</td>
</tr>
<tr>
<td>• decreased synthesis</td>
<td>• stress</td>
</tr>
<tr>
<td>• decreased sleep</td>
<td>• decreased sleep</td>
</tr>
<tr>
<td>• men with increased visceral fat, metabolic syndrome</td>
<td>• very low cholesterol</td>
</tr>
<tr>
<td>• very low cholesterol</td>
<td>• low tissue activity of thyroid T3 hormone (↑Cd, Hg; ↓iodine)</td>
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### Lifestyle Changes

- **LOW Androgens**
  - • resistance exercise
  - • weight loss increases androgens in men

- **HIGH Androgens**
  - • associated with metabolic syndrome, visceral obesity in woman
  - • supplementation with DHEA, 7-keto-DHEA
  - • supplementation with testosterone

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### Interventions

- **LOW Progestogens**
  - • identify & treat underlying problem
  - • progesterone given cyclically sometimes ‘kickstarts’ natural progesterone production

- **HIGH Progestogens**
  - • excessive progesterone supplementation
  - • adrenal tumor

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### Supplements

- **LOW Androgens**
  - • naltrexone

- **HIGH Androgens**
  - • licorice
  - • Adapagenic Herbs
  - • Other
  - • naltrexone

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### Other

- • naltrexone
### Ratios

#### Clinical Considerations

**Cortisol Ratios**

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\frac{\text{allo-THF} + \text{THF}}{\text{THE}})</td>
<td>11(\beta)-HSD Type I converts cortisone and its metabolites to cortisol and metabolites</td>
</tr>
<tr>
<td>(\frac{\text{allo-THF}}{\text{THF}})</td>
<td>11(\beta)-HSD Type II isoenzyme converts cortisol and its metabolites to cortisone and its metabolites</td>
</tr>
</tbody>
</table>

Manipulation of the balance of the enzymes has been studied as a target to achieve weight loss, as the type I isoenzyme has been associated with obesity.

### Lower Ratio

- means more cortisone produced relative to cortisol
- lowered ratio may be beneficial to patients with clinical signs/symptoms of elevated cortisol
- may be associated with weight loss

### To Increase the Ratio

- licorice supplementation

### Higher Ratio

- means more cortisol produced relative to cortisone
- a higher ratio may be beneficial to patients with clinical signs/symptoms of low cortisol
- associated with visceral obesity a greater proportion of cortisol metabolites relative to cortisone metabolite often occurs in situations where there is visceral obesity and increased waist circumference

### To Decrease the Ratio

- increase growth hormone
- reduce inflammation
- adequate sleep

#### Androgen Ratios

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<tbody>
<tr>
<td>(\frac{\text{Androsterone}}{\text{Etiocholanolone}})</td>
<td>(\frac{\text{DHT}}{\text{Testosterone}})</td>
</tr>
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Hormones metabolized by 5\(\alpha\) reductase can provide useful information on its activity. High levels of androsterone, allo-THF, allo-THB and/or a high ratio of allo-THF to THF may suggest increased 5\(\alpha\) reductase activity.

**Low 5\(\alpha\) reductase activity**

- genetic mutation causing 5-ARD (5-alpha-reductase deficiency)
- medication use: e.g. finasteride

**Strategies to Increase 5\(\alpha\) reductase activity**

- reduce dose of 5-alpha reductase inhibitor

**High 5\(\alpha\) reductase activity**

- complaints of excess facial hair growth and/or acne
- associated with male pattern baldness

**Strategies to Reduce 5\(\alpha\) reductase activity**

- saw palmetto
- progesterone supplementation can regulate ovarian function and normalize testosterone production.

#### Estrogen Ratios

Some 2-hydroxyestronne is methylated to 2-methoxyestronne. A ratio close to or above unity indicates a relative excess of the methylated product, relative to the precursor.

**Low ratio of 2MeOE1 to 2OHE1**

- may be associated with decreased capacity to methylate due to faulty SNP or deficiency in methyl donor, magnesium, pyridoxine

**Ratios >1 are not thought to be problematic.**

**Low ratio of 4OHE1 to 2OHE1 is generally preferable**

- 75% of women supplementing with hormones have a ratio of less than or equal to 0.15.

**High ratio** may indicate increased flow down the 4-OH pathway, not simply increased total estrogen production.

### References