Urinary Hormones
by Christa Hinchcliffe, ND and Wendy Ellis, ND

Life expectancy for women in the United States is 80.1 years; for men, it is 74.8 years. As a result, most women will spend more than one-third of their lives in a postmenopausal state and face many health problems associated with reduced levels of endogenous estrogen, progesterone, DHEA, and testosterone. Men face similar challenges. Bio-identical hormone replacement therapy (BHRT) can be a safe and effective means to assist women and men at this stage in their lives.

The safety of hormone replacement therapy has been a hot topic of discussion, especially since the 2002 publication of the results of the Women's Health Initiative (WHI). In the WHI, women were using non-bio-identical hormone replacement therapy. Fortunately, the safety of BHRT has been well-researched. BHRT has fewer side effects, especially if used in a cream or gel and applied over the skin or mucous membranes. Some examples of BHRT’s benefits include the following:

• a decrease in cardiovascular risk is shown in multiple studies when estrogen is used transdermal rather than oral,
• endometrial hyperplasia is less in low-potency transvaginal estradiol or estradiol than with oral estrogen,
• the metabolism of estradiol, when used transdermally, has less tendency towards estrogen related cancers due to its end product ratios,
• if used appropriately, the combination of percutaneous progesterone with percutaneous estradiol can decrease the estradiol-induced proliferation of cyclical epithelial breast tissue; this was shown in vivo prior to breast surgery if applied to normal breast tissue.

Finally, in another review, the conclusion was made that sex hormones are not oncogenic, but mitogenic.

BHRT research is mostly lacking two aspects. First, the research is not long-term, and second, few studies are done at the cellular level. We do not know to what extent the mitogenic activity of bio-identical hormones is affecting us at a cellular level, especially if used long-term. To help allay concerns about the safe use of BHRT, we can use careful follow-up testing to monitor not only levels of the steroid hormones, but also their metabolites, relevant enzymes, and hormone ratios.

The most comprehensive and accurate testing method is the 24-hour urine test. Since serum steroid hormone levels naturally fluctuate, sometimes considerably, due to varying half-lives, pulsatile secretion, and (in the case of exogenously applied hormones) time of application, the 24-hour urine collection “averages it all out.”

Urine testing is performed with gas chromatography (GC). GC is still unsurpassed in its potential for determining a multitude of steroid metabolites simultaneously in a single steroid profile. Used together with a mass spectrometer (MS) as a detector, this technique ensures the highest specificity in determining steroid metabolites. Urine testing measures the sum of free and conjugated (sulfated and glucuronidated) hormonal steroids, not the inactive, protein-bound hormones. According to the 1999 edition of Tietz’ Textbook of Clinical Chemistry, “Urinary assays are considered to reflect the secretory activity of the endocrine glands.” The textbook also states that “urinary free cortisol and the measurement of urinary free estradiol, estrone, and testosterone have been shown to provide clinical information that can reflect the production rates of these steroids.” Moreover, 24-hour urine testing for pregnanediol (progesterone metabolite) is the best biochemical assessment of ovulation based on progesterone production. The most satisfactory alternative is plasma, and the least satisfactory is saliva.

Lastly, estriol can be more accurately measured in the urine (where estriol is routinely found to be higher than estradiol or estrone). Circulating serum levels of estriol are often found to be quite low, due to its rapid clearance from the body.

Serum testing is a direct assessment of circulating hormones. Moreover, serum levels have well-established reference ranges. Unfortunately, bio-available and non-protein-bound forms are rarely measured, with the exception of testosterone. Also, serum
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is only a one-time measurement within a 24-hour period. To be more accurate, two or more blood draws can be taken within a 24-hour period. To evaluate hormone levels via serum, different laboratories use various immunoassays. However, lack of comparability exists with the different immunoassays. Some immunoassays even lack specificity and can have detrimental effects on medical practice. For example, microparticle enzyme immunoassay has errors in estradiol measurements due to interference from unconjugated estriol.

Saliva testing measures the free, or active, form of steroid hormones via the radioimmunoassay technique. It is a convenient and non-invasive testing method. For example, monthly fluctuations in hormone levels are easily monitored so that follicular, ovulatory, and luteal phases can be determined. Moreover, four separate measurements in one day can help determine the cortisol circadian rhythm.

Dr. John Lee was a strong advocate of salivary hormone testing, particularly for monitoring transdermal progesterone. He wrote that transdermal progesterone is highly lipophilic, absorbed through the skin into the fat layer, taken up gradually by red blood cell membranes, and made readily available to all target tissues and saliva. However, this may not be completely accurate, as the serum content of progesterone has been shown to be higher than the red blood cell membrane content. In one study, after transdermal application, plasma progesterone and pregnanediol-3-glucuronide (progesterone metabolite) excretion showed small increases, red cell progesterone never exceeded plasma levels, and salivary levels were very high and variable compared to placebo.

This study also indicates the possibility of false representation of overdose with salivary testing after the use of progesterone cream. Another small study on saliva testing, published in 2003, found variation in results within each laboratory for each participant. The researchers concluded that at-home saliva testing was not reliable. However, this needs to be repeated with a larger sample size.

Saliva is a difficult matrix to deal with experimentally. The presence of both sex hormone-binding globulin and corticosteroid-binding globulin in uncontaminated saliva casts doubt on the reliability of salivary steroids to accurately reflect circulating free steroid levels. Lastly, caution should be exercised in androgen assays, as well as in assays to assess ovarian function. The use of salivary cortisol for measuring endogenous cortisol is the most encouraging.

As mentioned above, 24-hour urine testing for steroid hormones is extremely valuable, due to the many metabolites that are measured. This is especially true for estrogen and adrenal hormone metabolites. There are more than 20 circulating estrogens in the body; however, estrone, estradiol, and estriol are generally cited as the main players. Estrone and estradiol are potent estrogens, whereas estriol is a relatively weak estrogen. All these values are measured in urine steroid hormone testing, whereas serum testing usually incorporates only estradiol, although estrone can be ordered as well. Urine testing provides free and conjugated values for estrone, estradiol, and estriol, as well as many downstream metabolites for each of these hormones, while serum testing incorporates protein-bound estradiol only.

To further complicate matters, each of these hormone metabolites has actions of its own. Some estrone is metabolized to 4 OH estrone, which may encourage the growth of breast or prostate cancer. Yet another metabolite of estrone, 16 alpha OH estrone, is considered an "unsafe" estrogen metabolite, as it is a potent estrogen with uterotopic effects similar to estradiol. This estrogen metabolite forms covalent bonds with amino groups of macromolecules and is genotoxic. Estrone is also metabolized to 2 OH estrone, a relatively weak metabolite that may be anti-estrogenic. Other metabolites, 2-hydroxyestrone and 2-hydroxysteradiol, offer protection against the estrogen-agonist effects of 16-alpha-hydroxyestrone.

However, 16 alpha OH estrone appears to play an important role in maintaining bone density.

As this very brief discussion of estrogen metabolites demonstrates, monitoring how patients metabolize their hormones and what factors may modify hormone metabolism is important. Many patients are taking diindolylmethane (DIM) or indole 3 carbinol (I3C) for "safe" estrogen metabolism. These substances improve the "2/16" ratio, which is known to decrease the risk of breast cancer. But not all patients need DIM or I3C, as they may already have a healthy 2/16 ratio, and using these substances may overly decrease the 16 alpha hydroxyestrone fraction, increasing risk for osteoporosis.

Adrenal hormone values and their metabolites, which are measured in the 24-hour urine test, may point toward significant adrenal dysfunction. Here are some examples:

- Elevated levels of pregnanetriol indicate congenital adrenal hyperplasia. This is a disorder most often caused by a 21-hydroxylase deficiency and can lead to cortisol and aldosterone deficiencies, as well as progesterone and androgen excess.
- The cortisol/cortisone should be ~0.7/1. Elevated cortisol/cortisone ratios can be a sign of "Apparent Mineralocorticoid Excess." Elevated ratios are also indicative of licorice excess. Hypertension can occur in either case, as cortisol has an aldosterone-like activity and cortisone does not.
- The cortisol metabolites tetrahydrocortisone, tetrahydrocortisol, and allo-tetrahydrocortisol account for approximately 50% of daily cortisol biosynthesis. If these metabolites add up to 5 mg,
then the body is producing about 10 mg of cortisol daily. This is useful in determining adrenal excess or deficiency. In an unpublished study by Patrick N. Friel, BS, at Meridian Valley Labs, all patients who failed the 250mcg ACTH (2/10) stimulation test had low cortisol metabolites in the baseline 24-hour urine.

- 11-dehydrotetrahydrocorticosterone is an inactive metabolite of corticosterone. Compared to cortisol, corticosterone has approximately one-third the anti-inflammatory action but 15 times the sodium-retaining action.
- Allo-Tetrahydrocorticosterone and tetrahydrocorticosterone are sensitive markers for monitoring adrenal stress. Both respond to ACTH stimulation with greater "vigor" than even cortisol. Allo-tetrahydrocorticosterone is elevated in young female patients with eating disorders. Levels of tetrahydrocorticosterone are elevated in depressed women, yet significantly decreased in depressed men. Both are useful in evaluating hypoaldosteronism.28,29

Enzyme activity, pre-determined by genetics or influenced exogenously by medications or supplements, can play a very important role in determining hormone safety in individuals. We are often hearing about supplements and medications for improving clinical conditions such as weight loss and hair loss, for improving estrogen metabolism, and for aiding post-cancer treatment (aromasin, tamoxifen). By altering metabolic pathways and up- or down regulating enzyme activity, what are we affecting on a cellular level?

Urine testing not only measures the activity of specific enzymes, but also gives information about downstream metabolites that are influenced by various endogenous hormones. By measuring downstream metabolites, we can better determine the enzyme activity associated with each hormone. For example, if a patient is taking saw palmetto, we can determine the effectiveness of the medication by seeing a shift in the testosterone metabolized down the 5 beta DHT pathway vs. the 5 alpha DHT pathway. Women who suffer from PCOS very frequently have an upregulation in the 5 alpha reductase pathway - which is seen as an increase in the downstream metabolites driven by this enzyme. This is pertinent information and may help guide your diagnosis of this condition.

Urine testing additionally determines activity of 11 beta hydroxysteroid dehydrogenase (11 β HSD), an enzyme with two isoenzymes (I and II) and bidirectional activity. The isoenzyme, 11 β HSD1, facilitates the regeneration of active cortisol and corticosterone (both 11 hydroxy glucocorticoids) from their inactive forms, cortisone and 11 dehydrocorticosterone by oxidoreductase (11 β reductase) action.30 The reverse reaction facilitating inactivation of cortisol to cortisone is affected by the 11 β HSD2 enzyme through 11 β dehydrogenation.31

Leptin-resistant Zucker obese rats have impaired 11 β HSD1 in the liver with increased activity in the omental adipose tissue.32 Dysregulation of 11β HSD1 in human obesity has been recognized and appears to be tissue-specific. An increase in BMI is associated with impaired 11β HSD1 activity, the degree of impairment correlating with visceral fat mass.33 This downregulation of 11 β HSD1 activity in the obese could be protective against development of insulin resistance. Like the genetically obese Leptin-resistant Zucker rats, obese humans also demonstrate impairment of hepatic 11 β HSD1 activity.
resulting in decreased reactivation of corticosteroids, while 11 β HSD1 activity in subcutaneous abdominal adipose tissue is increased. This increase in 11 β HSD1 in adipose tissue might explain the proliferation of fat tissue and adverse metabolic effects in obesity. Growth hormone replacement in growth hormone-deficient patients results in reduction of body fat along with lowered ratio of cortisol to cortisone in keeping with 11 β HSD1 inhibition. With the increase in insulin resistance in the population, it is useful to have this added information via urine testing when addressing the approach to treatment.

In women, 24-hour urine testing sometimes finds lower levels of estrone than the sum of estrone and estradiol, which many population-based studies have shown to be associated with increased breast cancer risk. Administration of Lugol’s iodine (six to eight drops daily and tapered according to response) most frequently increases estradiol and diminishes estrone and estradiol. Urine testing can also help explain failure of BHRT to relieve menopausal symptoms. In this circumstance, much higher than anticipated levels of all estrogens are frequently found in the urine, a situation termed “hyperexcretion” or “failure of hormone retention.” Treatment with physiologic-dose (300-600 micrograms) of cobalt chloride almost always corrects this situation, gradually reducing urinary estrogen excretion towards normal, while menopausal symptoms gradually fade.

**Notes**


31. Ibid.

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