Hormone Profiling and Healthful Diet

Cornerstones for Female Hormonal Health

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Even in the new millennium, with all its technology and broad dissemination and free flow of information, many busy clinicians are still performing the same diagnostic hormonal workups that have been conducted for decades. Frequently, a few specific datapoints are targeted, such as follicle stimulating hormone and luteinizing hormone (LH) or estradiol and progesterone. Yet, primary care practitioners have all been trained to realize that hormonal pathways are dependent upon homeostasis of other pathways to promote and sustain optimal health.[1] Thus, it makes sense that examining the bigger hormonal picture, the "lay of the land," so to speak, yields facts needed to maximize clinical outcomes.

The common practice of examining select and narrow hormonal indices is akin to looking at a few trees within a forest and making a judgment on the ecology of the entire forest. Until recently, affordable testing that provided a truly comprehensive look at a patient's hormonal profile was not readily available. Yet, by applying mass spectrometry more broadly in the clinical sciences, a few laboratories in the United States are providing comprehensive and affordable hormonal profiles at a fraction of the cost of previously used methods.

These tests typically provide at least 20 datapoints, including measures of estrogen metabolites, progesterone metabolites; and adrenal hormones, testosterone, and each of their respective metabolites. A steroid-hormone metabolism-profile chart illustrates, quite clearly, the clinical relevance of identifying potential highs and lows within the greater unidirectional and bidirectional pathways and the clinical relevance of using more comprehensive hormonal profiling to clarify diagnostic hypotheses. By correlating the biochemical trends of each pathway and the resultant metabolite levels, added clinical insights and understanding are gained that otherwise would require a less well-informed assumption by a treating clinician. (See box entitled A Typical Profile Yielded by Mass Spectrometry) With such insights, dietary and nutritional interventions can be prescribed more easily and have greater specificity.

There are numerous clinical considerations that come into play when one attempts to promote hormonal wellness. Many of these variables, when properly controlled, can minimize the risk of disease states, including breast cancer relative to hormonal modulation.[2]

Androgens and Breast Cancer

Although menopause is normal, the symptoms that are so commonly associated with this hormonal transition, such as hot flashes, night sweats, and many other symptoms, are only clinical indicators of a deeper problem, merely clues reflecting an underlying state of hormonal imbalance.

Current research studies are clearly demonstrating that other hormones besides estrogen potentially contribute to health problems and are, themselves, clear independent risk factors that must be measured and controlled directly and intentionally.

Postmenopausal women, for instance, can have increased risks for developing breast cancer, not only from having elevated estrogen but also from also high levels of testosterone, low levels of sex-hormone binding globulin (SHBG) and the consequential higher levels of free-steroid sex hormones.[2] Numerous other risk factors are also linked to this enhanced risk, including elevated adrenal secretions and chronic hyperinsulinemia.

A woman with elevated androgen levels is at a higher risk for developing breast cancer and other hormone-dependent diseases. Specific correlations with deleterious androgenic effects have been associated with increased levels of dehydroepiandrosterone (DHEA), DHEA sulfate,[3] androstenedione,[4] and testosterone concentrations.

Testing actively for levels of each of these specific hormones and metabolites provides the opportunity to correlate clinical presentations better and perform more focused interventions to modify hormonal dysregulation. Elevated androstenedione can arise from either ovarian or adrenal sources or from peripheral conversion of DHEA. However, increased testosterone levels are more likely to be a result of increased ovarian secretion of androstenedione and/or DHEA or peripheral conversion. Once again, seeking the source and addressing the global impact of such hormonal fluctuations is of paramount clinical significance.

When hydroxyandrostenedione (11βOHA) is elevated and the androstenedione:11βOHA ratio is depressed, the adrenal glands are the primary source of the elevated androstenedione. If the androstenedione:11βOHA ratio is elevated, the primary source of the problem is ovarian in nature. These ratios, again, illustrate that a comprehensive examination of hormonal balance and prevalence is crucial. Research findings reveal that

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women who experience a hyperandrogenic effect frequently have mixed adrenal and ovarian androgen production that has been correlated with adrenal cortical hyperplasia and ovarian stroma hyperplasia as determined by autopsies conducted on patients with breast cancer.[5–7]

Diet, Lifestyle, Hormones, and Breast Cancer

Chronic hyperinsulinemia is intimately linked to diet, lifestyle, and the development of a hormonal profile that correlates with increased breast cancer and hormone-related disease risk. What is noteworthy is the ability of insulin to inhibit hepatic synthesis of SBHG and enhance ovarian production of androgens.[8–10]

Addressing the cause of hyperinsulinemia is a significant clinical intervention, thus, lowering the adverse risk associated with this hormonal disturbance. Overweight women with high intra-abdominal fat stores have a particular risk for developing breast cancer as a result of hormone-modifying factors, including insulin resistance, increased insulin levels and insulin-like growth factor-I, low serum levels of SBHG, and high sex-hormone levels.[11–14]

Consuming a low-carbohydrate diet, while focusing on high-fiber and antioxidant-abundant vegetables is a must for these patients. Increased fiber intake helps to ensure more regular bowel movements, with the goal being 2–3 bowel movements per day to increase elimination of toxic digestive products, hormones, and deleterious metabolites. Equally important is the ability of fiber-rich foods to prevent reabsorption of hormonal metabolites back into circulation.

Dietary Interventions for Hormone Modulation

Isoflavone- and Indole-Rich Foods

Dietary interventions, particularly phytoestrogen-rich foods,[15,16] can help to control and modulate the availability of sex hormones. These plant-derived diphenolics have both estrogenic and antiestrogenic properties that can help to diminish breast-cancer risk.[17,18] Classical phytoestrogen sources include soy (*Glycine soja*) isoflavones, lignans from flax (*Linum usitatissimum*) and other seeds and fiber-rich vegetables, and coumestrol from legumes and alfalfa sprouts.[19–21] (See box entitled Phytoestrogen-Rich Foods.) Indole-3-carbinol (I3C)–abundant foods, such as cruciferous vegetables, are equally worth integrating into a hormone-modifying regimen because of these foods' estrogen-modulating activity.[22] It is advisable for patients to consume organic produce (and organic food in general) whenever this is possible, to minimize exposure to lipid-soluble pesticides and herbicides that can have numerous adverse effects in the body.* What is noteworthy is that several agricultural chemicals can have hormone-like effects within the body, thus, introducing another risk factor into the health equation.*

There is a significantly lower prevalence of cancer risk in Asian populations whose diets are high in soy products, which have 20–50 percent lower estradiol and testosterone levels than the foods consumed by Western women.[23] Studies on this reinforce the need to look at more than the common factors, such as estrogen or testosterone, when determining the state of a patient's hormonal health. In approximately 50 percent of the current studies available on this topic, Asian women have higher serum levels of SBHG.

Fats and Fatty Acids

One of the most intriguing studies, commonly referred to as the DIANA study, was conducted by Berrino et al.[1] This study demonstrated that the plasma insulin-lowering effects of low-fat intake decreased insulin resistance as a result of reduced body mass index and waist circumference.[1,24,25] Additional benefits were obtained by increasing omega-3 fatty acid and monounsaturated fatty acids while decreasing refined carbohydrate intake, with the goal of improving insulin sensitivity.[26–28]

Low-fat diets have been thoroughly tested. Diets that limit fat intake to 10–25 percent of total calories significantly reduce plasma estradiol concentrations. Nine studies showed a mean 7.4 percent estradiol decrease in premenopausal women and, in four of the studies, a dramatic 23 percent after menopause.[29] Most participants in these studies also had increased intakes of fiber-rich foods. In the DIANA study, a serum estradiol reduction of 18 percent was achieved with fat reduction from 37–31 percent of total calories as a result of shifting consumption from animal to vegetable fats and focusing on low glycemic-index foods.[1]

*EDITOR'S NOTE: For more on the toxic effects of chemicals, see Russ Mason's article entitled "Chemical Toxins and Obesity: Paula F. Baillie-Hamilton, M.B., B.S., D.Phil., Explains the Link" in this issue 218–223.

Maintaining and restoring intestinal microflora can augment the effects of isoflavone consumption.

A Typical Profile Yielded by Mass Spectrometry

Estrone (E1)
2-Hydroxyestrone
16-α-Hydroxyestrone
2 OH:16 OH estrone ratio
Estradiol (E2)
Estriol (E3)
Estrogens ratio
Total estrogens
Testosterone
Androstanediol
Androstenedione
Dehydroepiandrosterone (DHEA)
Androstenetriol
Androsterone
Etiocholanolone
Prenanediol[a]
5-Pregnenetriol
Pregnenolone
Cortisone
Cortisol
Tetrahydrocortisone
Tetrahydrocorticosterone
5-α-Tetrahydrocorticosterone
Tetrahydro-11-dehydrocorticosterone
Tetrahydrocortisol
5-α-Tetrahydrocortisol

Adapted from Rhein Consulting Laboratories, Portland, Oregon.

[a]This metabolite is a marker used to measure progesterone levels indirectly because progesterone is not typically excreted via the urine.

Phytoestrogen-Rich Foods

- Berries
- Cruciferous vegetables
- Flax (*Linum usitatissimum*) seed (lignan-rich)
- Legumes
- Miso soup
- Seaweed
- Seeds
- Soybeans (*Glycine soja*)
- Soy milk
- Tempeh
- Tofu
- Whole-grain cereals

NOTE: Organic foods are recommended to minimize exposure to organotoxins.

Fiber

Supplemental fiber may be of clinical value in the absence of sufficient dietary intake; yet, it is not a substitute for a diet that is rich in fiber. Studies that have examined specific types of fiber supplements found no significant increases in plasma SBHG levels, although estradiol levels were frequently lower and attributable to fiber inhibition of steroid reabsorption from the gut. [30–32] Measurement of postprandial and fasting plasma insulin levels has consistently shown that specific single-fiber supplementation has less effect on plasma SHBG than consumption of whole-grain food.[33] In short, consuming fiber-rich foods provides broader health benefits than swallowing fibers via supplements.

Nutraceutical Interventions

Calcium D-glucarate

This unique calcium nutraceutical is derived from fruits and vegetables. Within the liver, hormone residues and other fat-soluble toxins are bound by glucaronic acids so that they are increasingly eliminated by means of glucuronidation via the β-glucaronidase enzyme pathway. Calcium-D-glucarate has been shown to support β-glucaronidase activity aiding in the detoxifying pathway.

Chromium

This critical trace mineral can be particularly helpful for balancing insulin response directly and for reducing body fat and weight, thereby reducing the hyperinsulinemia and elevated sex-steroid levels that are associated with an increase risk for developing diseases.[34, 35]

Indoles

Men and women should be told to add cruciferous vegetables to their diets but consistent dietary intake of these vegetables can be hard to achieve. Extracted indole-3-carbinol can provide significant protection by shunting estrogen metabolism away from the 16-α hydroxylation pathway to the 2-hydroxylation pathway. This shunting produces a predominance of 2-hydroxy and 2-methoxy estrogens. These active "good" metabolites serve as antioxidants and decrease the likelihood of cell division, whereas 16-α-hydroxy compounds promote cellular division and, thus, can enhance cancer risk. Cruciferous vegetables, which are high in indoles, have significant amounts of folic acid, a vitamin that is also essential for the methylation of estrogen metabolites.

When cruciferous vegetables are chewed or macerated, glucobrassicin is hydrolyzed with the assistance of myrosinase to create indole-3-carbinol. In turn, IC3 is transformed in the stomach into various indole compounds, including indole (3´3´-di-indolymethane; DIM). Typical supplemental dosing of DIM is in

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the range of 100–300 mg per day. (See box entitled Specific Nutraceuticals for Promoting Hormonal Health.)

Isoflavones

Isoflavones, such as genistein and daidzein, are abundant in soy and numerous other botanicals including red clover (*Trifolium pratense*). There are numerous isoflavones in soybeans and soy products, such as tofu and tempeh, including the two more widely recognized, genistein and daidzein, and in genistin, glycitin, glycitein, and daidizin. These flavones are potent antioxidants that help to support immune function and help to protect DNA integrity from exogenous and endogenous stressors. The phytoestrogen properties of isoflavones produce weaker estrogenic activity than human estrogens. The isoflavones compete with the human estrogens for the same cell-receptor sites, thus decreasing total the estrogenic effect on the body. These phytoestrogens have been shown to increase growth hormone and prolactin while decreasing LH and cholesterol.[36] Additional health benefits may be gained from the unique phytoestrogens, including biochanin A and formononetin, that are found in red clover.

Probiotics

Maintaining and restoring intestinal microflora can augment the effects of isoflavone consumption. The DIANA study suggested that the bioavailability of phytoestrogens may have been higher as a result of the enhanced microflora balance produced by a more vegetarian diet that promoted beneficial flora growth. Phytoestrogens are in foods, in the form of glycosides that must be hydrolyzed by gut bacteria to produce aglycones. Studies comparing Western microflora versus the flora of vegetarians or people who consume macrobiotic diets demonstrate that the latter subjects typically have more lactobacilli and bifidobacteria, which hydrolyzes glycosides to aglycones.[37]

Specific Nutraceuticals for Promoting Hormonal Health

Calcium-D-glucarate	1000 mg, 2–3 times per day
Indole (3´3´-di-indolymethane; DIM)	100 mg, 1–3 times per day
Isoflavones	1000 mg, 2–3 times per day
Red clover (*Trifolium pratense*) (8% isoflavones)	500 mg, 1–3 times per day

General Herbals

Other herbal products that modulate hormone function include *Angelica sinensis* (dong quai), *Glycyrrhiza glabra* (licorice root), *Leonurus cardiaca* (motherwort), *Vitex agnus-castus* (chaste tree), *Dioscorea villosa* (wild yam), *Cimicifuga racemosa* (black cohosh), and many more. The key is understanding how each herb acts on hormonal pathways, how it can be applied best relative to a given patient's comprehensive hormonal profile and induce specific modulation of hormonal pathways. Licorice, for instance, can affect estrogen directly via the herb's isoflavone content and can also help to support adrenal function and its resultant hormonal production, illustrating the versatility of potential botanical interventions and the need to understand how each pathway is functioning to avoid creating disturbances in an otherwise balanced pathway.

Case Discussion

As a physician in family practice, my patient base is comprised of approximately 70 percent adult women who experience the spectrum of hormonal wellness. Over the years, certain common clinical patterns have emerged from these patients, providing increased clinical insight that has helped to yield improved patient outcomes.

Recently, a 57-year-old menopausal patient presented with numerous hormone-related symptoms, including hot flashes, night sweats, irritability, and vaginal dryness, that had not responded to standard hormonal treatment provided by her previous physician. After having the patient complete a 24-hour urine collection for a hormone-profile analysis, her clinical picture became substantially clearer. Her laboratory values reflected low progesterone metabolites, pointing to low progesterone levels. She had low normal testosterone and androgen levels and substantially lower-than-optimal cortisone and cortisol levels.

This correlated well with her previous experience, when she had taken progesterone, either orally or transdermally, and felt better. However, her severe atopic vaginitis with ulcerations strongly correlated with an effect caused by lower-than-normal estrogen. Thus, she had taken a

Examining a patient's full hormonal picture provides the basic foundation needed to achieve rapid, clear, and specific diagnosis and treatment for patients with hormonal imbalances.

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preparation consisting of estradiol, estrone, and estriol. However, she experienced symptoms of estrogen dominance even with small and varied dosing regimens.

Her comprehensive steroid-hormone profile helped to solve the riddle by showing that her adrenal pathways reflected dramatic adrenal-insufficiency trends. She had a history of experiencing improved energy, decreased aches and pains, less irritability, and improved sleep/wake cycles when she took a progesterone supplement alone. This made sense because her body was probably shunting progesterone via 17-hydroxyprogesterone to cortisol. And the estrogen-dominance symptoms she experienced when she took the triple-hormone preparation probably were the result of shunting her insufficient dose of progesterone to the cortisol pathway and, thus, producing symptoms of relative estrogen dominance.

Considering these factors, her treatment protocol was adjusted and her short- and long-term health goals were accomplished successfully. These extra datapoints, thus, were the key to solving this patient's problem. A growing number of laboratories, nationwide, are beginning to offer comprehensive hormone profiles to choose from, thus, providing the flexibility to choose one that meets an individual patient's needs best. (See box entitled Representative Analytical Laboratories for a list of four laboratories that offer female hormone profiling.)

Conclusions

Clinicians are challenged daily when diagnosing hormonally related disease states. Often preceding actual pronounced signs of hormonal imbalance, symptoms arise that can alter the quality of a patient's life dramatically. These symptoms can be typical premenstrual syndrome, menopausal problems, or more subtle conditions, such as depression, anxiety, and fatigue.

Examining a patient's full hormonal picture provides the basic foundation needed to achieve rapid, clear, and specific diagnosis and treatment for patients with hormonal imbalances.

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