Yams for breakfast, lunch, and libido? A critical look at bioidentical hormone therapy

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Background

It has only been in the recent past that the Women’s Health Initiative (WHI) changed how physicians and consumers viewed postmenopausal hormone therapy (HT). The estrogen-progestin arm of the study, involving over 16,000 women, was stopped prematurely due to findings suggesting an associated increased risk of stroke, breast cancer, and dementia without a reduction in cardiovascular risk.2

Subsequently, women have been searching for “safer” alternatives to treating their climacteric (menopausal) symptoms — including hot flashes, decreased libido, vasomotor changes, urogenital atrophy, skin changes, increased body weight and abdominal fat, and psychophysiological changes like mood changes, insomnia, and anxiety.2 One alternative that has been offered to women is “bioidentical hormone” therapy (BHT), which is purported to be safer, natural, and more efficacious compared to standard post-menopausal HRT.

Defining bioidentical hormone therapy

BHT is a term used to describe plant-derived precursor compounds (eg. diosgenin from Mexican yam, stigmasterol from soy), which have been synthesized in the laboratory to be structurally identical to endogenous human hormones such as estrogen (estrone, estradiol, estriol), progesterone, testosterone and dehydroepiandrosterone (DHEA).2 Perhaps a more accurate name for bioidentical hormones should be native synthetic hormones, as these hormones are not found naturally in any plants.3 Proponents of BHT claim that it is capable of restoring a balance between hormone levels, and yet due to similarity to human hormones along with individualized dosing, it is able to provide symptom relief with minimal side effects.4

Those who favour BHT affirm that the first step in determining the usefulness of BHT is a salivary hormone profile, looking for deficiencies in sex hormones. Steroids easily diffuse into the saliva and in some cases may accurately reflect free hormone levels. For instance, midnight salivary cortisol is an evidence-based, validated test for Cushing’s syndrome. However, BHT proponents expand their diagnostic range and offer an entire panel of various hormone testing through mail-order kits. Interested consumers can mail in a saliva sample (collected by chewing on a cotton ball, placed in a plastic receptacle) and then they will receive an extensive computer print-out with their results as well as an explanation of findings and possible correlated symptoms.5 The inexpensive nature of the test and the relative ease of obtaining samples make this test particularly popular with consumers and BHT advocates.

Once the salivary results are obtained, the BHT practitioner will prescribe a course of bioidentical hormones, and tailor the dosage specifically to the individual’s hormone profile. In some cases, special preparations can be created by pharmacists5. BHT comes in creams, gels, pills, patches, self-injectors and pellet therapy. Within the various treatments are hormones such as estrogen, progesterone, cortisol and “women testosterone.”6

According to one company’s website, the cost of BHT can exceed $5000USD per year. An initial consult is $400, follow-up consults $185 (of which you need three), and the cost of treatment may range from $75-350 per month. Further costs come with the treatment itself and laboratory tests.7 Because insurance companies do not cover the cost of these treatments, this may be a limiting factor for many patients. Keeping this in context, daily Premarin 0.625 mg along with Provera 2.5 mg would be around $700USD per year, even with the 80% increase in price in 2009.8,9

Currently, there are numerous commercial as well as individually prepared “natural” products. Formulations are created by pharmacies according to prescriptions written by referring practitioners, and cannot all be purchased commercially. One such product is Biest (bioestrogen) which is a combination estrogen containing 20% E2 (estradiol) and 80% E3 (estriol), expressed in a milligram per milligram basis.10 Another such formulation used frequently is Triest (triestrogen) which contains 10% E2, 10% E3, and 80% E3. It is important to note the relative potencies of the estrogens: E1 (estrone) is the most potent, followed by E2, and E3 is the weakest of the three, being the final end product of E2 and E1 metabolism. The presence of such a high proportion of E3 in these mixtures is advertised as the key to reducing adverse side HRT effects while still conferring symptom relief.10

What is the evidence from medical literature?

There have been few evidence-based trials looking at the safety, efficacy, and durability of BHT. According to proponents, because the steroids are found in nature, are not extensively manufactured, and are dosed in a way that is individualized, there is no need to research these compounds and therefore submit data to FDA for approval and regulation.5 In addition, pharmacies can mix their products differently, which makes it difficult to standardize and determine the risks associated with BHT.

Despite salivary hormone testing (SHT) developing a medical literature showing usefulness in certain areas of clinical practice, it is often criticized for its lack of reliability and inability to correlate symptoms and hormone levels. Standard HRT prescribes estrogen and progestins in doses...
that provide symptom relief. In the BHT approach, SHT test results may persuade asymptomatic women to take doses they may not need and symptomatic women to take excessive doses.\textsuperscript{11}

**In theory, saliva is similar to ultrafiltrate and should correlate with free/unbound serum concentrations.** However, it has been shown that these correlations vary depending on the time of day, diet and the specific hormone tested.\textsuperscript{10} Many hormone levels vary during the day, week, month, season and therefore a one-time SHT may be inadequate for diagnosis or monitoring dose adjustments, particularly unless greater than 5 samples are taken daily.\textsuperscript{2}

Traditional medicine uses individualized dosing for drugs which have a narrow therapeutic index, as described by population-based pharmacokinetic studies (eg. cyclosporine, digoxin). According to Jelliffe, true individualized dosing must be predicated upon a known target serum concentration, at a desired target time after the dose, for each patient.\textsuperscript{12} However, proponents of BHT have no studies dealing with important pharmacokinetics of their drugs such as volume of distribution, protein binding, route of elimination, among other factors.\textsuperscript{10} Without a predictable relationship between dose and response of the drug, it becomes impossible to know how much medication to prescribe.

As mentioned previously, the BHT hormones typically used for menopausal symptoms are estrogen and progesterone. But how much estrogen is really in these compounds? In addition to inter-pharmacy differences of product formulation, there appears to be another underlying problem—ratios may not be what they seem. Biest, an 80:20 ratio of E\textsubscript{2} to E\textsubscript{3}, is not based on the estrogen potency of each compound, but rather is based on the milligram quantity of different agents added together. For example, if a woman takes 2.5 mg of Biest (2.0 mg E\textsubscript{2}, 0.5 mg E\textsubscript{3}), and the potency of E\textsubscript{3} is 1/80\textsuperscript{th} of E\textsubscript{2}, the equivalent content of E\textsubscript{2} is actually 0.525 mg.\textsuperscript{10} Some women may take 2.5 mg Biest twice daily, increasing the E\textsubscript{3} equivalent to 1.05 mg per day which is a dosage exceeding most prescribed estrogen therapies. The same applies for Triest, which is a combination of estriol, estradiol, and estrone.\textsuperscript{2}

With E\textsubscript{3} being the least potent of the estrogens, its high percentage in BHT formulations is believed to decrease the incidence of breast cancer and endometrial hyperplasia. However, past studies have shown equal endometrial stimulation from estradiol and estriol medications.\textsuperscript{13} Estriol was also found to partially overcome antiestrogen inhibition from Tamoxifen, even when Tamoxifen is present in 1000-fold excess. Therefore, estrogen does not have a protective role in human breast cancer, and all estrogens bind to an equal number of sites when saturating concentrations are used.\textsuperscript{14} It can be deduced that despite being the least potent estrogen, E\textsubscript{3} still carries risks of cancer that BHT tries to avoid.

Much has been written about progesterone in BHT. Although that extensive literature will not be reviewed here, it should be noted that many of the health claims from BHT practitioners have not been substantiated, but rather have been overshadowed by evidence-based medicine. For example, BHT practitioners claim progesterone increases metabolism and causes weight loss. However, no studies are identified to support those claims. Indeed, weight gain, rather than loss, has been shown with progestin therapy in cancer-related anorexia.\textsuperscript{15}

**Practice guidelines for the physician**

In view of the evidence, how should the physician respond to BHT practitioners and claims? The North American Menopause Society, the American Association of Clinical Endocrinologists, and the Endocrine Society have all published positional statements expressing concern for the safety of women using these products.\textsuperscript{16-18} These groups are currently advocating for FDA oversight in the standardization of drug purity, the need for mandatory reporting of adverse events, as well as uniform labeling of precautions on BHT formulations.

The bottom line from these groups involves strong recommendations that BHT not be used in the treatment of menopausal symptoms. It is argued that both "bioidentical" and "traditional" hormone replacement treatments will carry essentially the same risks and benefits if dosage and

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Table 1. A comparison of traditional and bioidentical hormone therapy.
purity are equal. Therefore, no matter the source or hormone regimen, the “individualized” dosing must be carefully controlled.

A summary of the Endocrine Society's comparison of BHT and HT is shown in Table 1. Overall, further research and an evidence-based scientific approach must be applied to BHT to validate or debunk its proposed health benefits. Until then, it might be best to keep the yams on the Thanksgiving table instead of using them to treat human conditions.

References