

# Androgen Deficiency in Women:

Understanding the *Science, Controversy* and *Art* of Treating Our Patients – **Part 2**

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*This article and Part 1, which appeared in the last issue, review the normal endocrinology of androgens in women during their reproductive and postmenopausal years, including reviews of representative literature on the therapeutic uses of androgens and a discussion of various options that compounding pharmacists have to offer.*

## Dehydroepiandrosterone Replacement Therapy

Numerous studies show the benefits of dehydroepiandrosterone (DHEA) use in women and men, particularly in those with adrenal insufficiency (Addison's disease).<sup>1,2,3,4</sup> These patients have almost no detectable DHEA and, therefore, serve as the most dramatic example of what DHEA can do when taken orally. No improvements in body composition, bone turnover and exercise capacity were demonstrated in 24 women with Addison's disease who took 50 mg/day for 4 months.<sup>4</sup> The study was double-blinded, and there was a crossover. However, a different study by the same group demonstrated significant improvements in sexual function and overall mood parameters.<sup>1</sup> These researchers also found an across-the-board drop in all lipid levels. Because DHEA raises testosterone and free testosterone in women (but not appreciably in men), it is hard to determine whether these effects are related to the increase in androgens or DHEA itself. Another group from England studied 24 women and 15 men with Addison's disease to look at the effects of 50 mg of oral DHEA on mood, fatigue and bone and body composition.<sup>2</sup> While excellent improvements in mood and fatigue scores were realized by patients, no changes in bone density or body composition could be demonstrated (possibly because of the short observation period of 12 weeks). Arlt et al published results on only the 24 women of the same study population as above and found that 50 mg of oral DHEA was associated with significant improvements in the patients' total and high-density lipoprotein cholesterol, as well as an increase into the normal range of their testosterone.<sup>1</sup> Findings of this study also showed a significant increase in the patients' frequency of sexual thoughts, level of



sexual desire and sexual satisfaction with both the physical and mental aspects of sexual activity.

A particularly interesting 1-year intervention study of 14 normal postmenopausal women with an intact uterus was conducted by Labrie,<sup>5</sup> who used a 10% DHEA cream applied to the thighs in doses of 1 g to 3 g. He was able to demonstrate vaginal epithelial maturation (just like an estrogen effect) but no effect on uterine lining using endometrial sampling. He also showed improvements in bone density and positive changes in the serum and urine biochemical markers of bone production.

## Treating the Hypoandrogenic Woman

Hopefully, this discussion has demonstrated that using bio-identical hormones to replace deficiencies in women has a sound body of scientific literature to back it up. While it is clear that more studies need to be done, particularly to address

the issues of cardiovascular safety and long-term effects, I believe that we can feel comfortable in treating patients who are seeking to optimize their health and who are not doing well.

The first requirement before treating a woman with androgens is to establish that there is a problem with low levels. This is generally accomplished by reviewing the patient's history for loss of libido, loss of energy and diminished sense of well-being. Exploring the historical background of the patient to see if there are any factors that would affect the availability of androgens is critical. For example, ask about the use of estrogen replacement therapy (ERT) in postmenopausal women, or the use of oral contraceptives in younger women, or the use of corticosteroids that would lower DHEA. It is also important to determine whether there is a surgical history of hysterectomy and/or oophorectomy, both of which lower the androgen levels. (Remember that the term *complete hysterectomy* refers to the removal of both the uterus and the cervix—it has nothing to do with the ovaries). It is also essential to rule out the presence of contraindications to androgen therapy, such as breast cancer or unexplained vaginal bleeding. Similarly, one must never forget to rule out pregnancy in a woman of child-bearing age.

Appropriate lab testing should include serum levels of estradiol, progesterone, (midluteal phase, if applicable), testosterone, free testosterone and dehydroepiandrosterone sulfate (DHEAS). It is important to note that many laboratories do not use testosterone assays and free testosterone assays designed to measure the low levels present in hypoandrogenic women. In fact, the most important test of all, the free testosterone, is usually not measured by a method using an equilibrium dialysis technique and will likely be quite unreliable. While this is not normally the responsibility of the pharmacist, some pharmacists are screening for these hormones by salivary testing. This can be quite helpful and reproducible for the initial screening but is not as reliable for following levels.

Bone-density measurements are invaluable, since low levels serve not only as an indication for intervention but also as a means of measuring the benefit over time. Other labs and hormones should be ordered, depending on the judgment of the practitioner.

How does one treat a patient in need? First of all, it is of utmost importance to treat any correctable clinical situation that is present. Lifestyle changes, while not likely to directly increase testosterone or DHEAS, may allow other systems to return to normal and, therefore, secondarily improve the situation. (For example, weight gain, rest and sleep may correct hypothalamic amenorrhea and, therefore, allow resumption of ovulatory cycles in a young athlete.) All who describe their experiences with hypoandrogenemia emphasize the importance of first addressing the presence of low estradiol and then addressing androgen replacement. It is not helpful to give a woman who is low in all hormones androgens only, as this contributes to an imbalance in the opposite direction.

Pharmacologic treatment of the low-androgen scenario is

typically addressed in current medical literature with the attendant statement: "Due to the lack of safe, convenient and available methods of androgen replacement in women, treatment options are limited..."<sup>6,7,8</sup>

Unfortunately, the mainstream medical community (particularly in academia) has failed to recognize the plethora of options provided by their local compounding pharmacists. As a result, the existing medical literature has focused on methyltestosterone, nandrolone injectable, injectable testosterone enanthate (or cypionate) and a few experimental methods, such as subcutaneous long-acting implants or testosterone undecanoate (which is taken orally but absorbed through the lymphatics). Only very recently has the US pharmaceutical industry shown any interest in androgen replacement for women; but, as of this date, it has not had any US Food and Drug Administration-approved products.

Testosterone is clearly the best androgen to use if the adrenals are intact, and the percutaneous route is the most physiologic method of administration.<sup>9,10</sup> Micronized testosterone is easily incorporated into gels and creams. I have had no trouble getting excellent testosterone levels by applying 1 mL of a 0.5% to 1% gel in any of a number of lipophilic gels or cream preparations. Topical products can be applied to the trunk, abdomen, buttocks, inner arms or thighs. I do not see the benefit of using labial or vulvar application, and I am concerned that this will result in 5- $\alpha$ -reduction to dihydrotestosterone (as scrotal application does in men) and, therefore, cause more skin problems, such as acne and hirsutism (abnormal hairiness).

When testosterone is applied to the skin, the stratum corneum serves as a reservoir of steroid storage and slowly releases testosterone into the blood stream. The kinetics of this after several days of application ends up looking like a straight line with regards to delivery over time.<sup>11</sup> In this regard, it resembles the delivery of steroid by patch but without the skin irritation or cost.<sup>10-12</sup>

Testosterone can be incorporated into troches for sublingual application. Recall that this method uses the venous plexus and lymphatics in the oral mucosa to absorb steroids directly into the circulation without sustaining first-pass degradation. The pharmacokinetics of this method, however, are not ideal since there is rapid absorption of testosterone into the system with resulting high levels, followed by a quick drop of the levels to baseline after about 2 hours.<sup>13</sup> This route may be useful for a woman looking for an occasional boost in her testosterone levels to boost libido. This, in fact, could mimic the ovulatory spike that a menstruating woman experiences midcycle.

Hargrove, who is considered a pioneer in the field of bio-identical hormone replacement therapy (HRT), offers the use of micronized testosterone as an orally effective replacement hormone in women who prefer an all-oral format. He recommends a 1-mg starting dose of micronized testosterone in conjunction with estradiol and estriol if desired. Whether or not this route results in some deleterious effects on the lipid

profile remains to be established, as there are virtually no data on this method of testosterone replacement.

DHEA is easily absorbed by the oral route and is inexpensive. I advise my patients to obtain only high-grade DHEA from compounding pharmacists and to avoid that sold from grocery or health-food stores.<sup>14,15</sup> Doses of 15 mg to 50 mg per day appear to be more than adequate in most women. The creams are well absorbed, and 10% concentrations of 1 mL to 3 mL applied to the trunk give the desired results. Androstenedione does not appear to be necessary as a separate supplement, since DHEA raises the levels of androstenedione to physiologic in most cases.<sup>2</sup>

Patients should be monitored periodically by reviewing how they feel, asking about side effects and recommending that they see their physicians to have their blood levels checked to document

physiologic replacement ranges. I strive to raise a woman's testosterone level to between 40 to 80 ng/dL. DHEA levels vary widely, but levels from 150 to 300 ng/dL are consistent with a healthy young adult. Remember, the labs are a guideline; they are not meant to be the final say on dosage.

### Conclusion

Clearly, there is ample evidence that women produce and require androgens as part of their normal physiology during reproductive years. Many scenarios cause the production of androgens to be reduced, including the administration of estrogens; the surgical removal of the ovaries; and, to a lesser extent, the surgical removal of the uterus. These scenarios apply to both pre- and postmenopausal women. Therefore, the thoughtful approach to caring for women needs to consider that many

women benefit from the addition of testosterone and/or DHEA to any hormonal regimen that may be prescribed. With our careful attention to dosage and method of administration, these women patients can realize improvements in moods, libido and feelings of well-being. They are also likely to develop stronger bones and better muscle tone. Side effects, such as acne, hair growth and voice changes, can be eliminated or minimized by careful attention to dosage and by monitoring serum levels.

In August 1998, Hulley et al published the preliminary data of the Heart and Estrogen/Progestin Replacement Study (HERS) and changed the perception of HRT forever.<sup>16</sup> Their data, using a prospective, double-blind approach to study postmenopausal women, compared HRT (esterified equine estrogens, with and without medroxyprogesterone) with placebo. The results contradicted the long-held view that estrogens had cardioprotective effects. It was not until 4 years later that the full data were released, which showed that the estrogen that was used caused more heart disease, strokes and breast cancer than placebo, and that those results worsened with the addition of a synthetic progestin.<sup>17</sup> Almost no attention was paid to the fact that under the worse-case scenario, only 23 additional cases of heart attacks, strokes and breast cancer occurred out of 10,000 women. This had the unfortunate effect of convincing millions of women to question or even quit their prescribed HRT, many without even consulting their healthcare providers. In effect, the idea of using hormones to improve the quality of life and health for postmenopausal women was given a huge setback; and many women were left confused and suffering.

Most people reading this journal understand that the HRT used by the HERS group has been under suspicion for years. That is why the idea of bio-identical HRT was advanced in the first place. We understand that there is a body of literature that supports the use of human estrogens and progestins (estradiol, estriol, estrone and

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progesterone) as a safe and effective method of sustaining health in women. The next step in this evolution is the use of testosterone and DHEA supplementation as a way of reaching the ideal, balanced BHRT. Hopefully, the information in this discussion has helped readers understand a safe and scientific rationale for this goal. The improvements that patients realize after persisting with this therapy are often dramatic. Our ability to help our patients through yet another evidence-based intervention is a great source of personal and professional satisfaction.

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