

# The Role of Androgen Therapy in Postmenopausal Women

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## Physiology of Androgens in Women

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Recent evidence indicates that androgens play an important but underestimated and underrealized role in female physiology. A crucial aspect of androgen physiology in women is that most androgens in women are not of direct ovarian or adrenal origin. In fact, following menopause, nearly all androgens and estrogens are produced locally in peripheral tissues that contain the enzymes required for the transformation of dehydroepiandrosterone (DHEA) into dihydrotestosterone (DHT) or estradiol.

Androgens are inactivated by specific glucuronyl transferases in the same cells where androgen synthesis occurs. The active androgens testosterone and DHT are first transformed into androsterone (ADT) and androstane 3-alpha, 17-beta-diol (3-alpha-diol), which are then transformed into the glucuronide derivatives ADT-G and 3-alpha-diol-G.

Since the active androgens diffuse poorly to the extracellular compartment, in order to ascertain true androgen activity in tissues, it is necessary to measure their metabolites in the blood instead of or in addition to measuring testosterone and DHT. Plasma concentrations of ADT-G and 3-alpha-diol-G are the only accurate parameters.

### Androgen Levels in Women

As estimated from the circulating levels of the DHT metabolites ADT-G, 3-alpha-diol-G and androstane-3-beta, 17-beta-diol-G (3-beta-diol-G), women produce approximately two-thirds of the androgens found in men (Table 1).<sup>1</sup>

Because nearly 100% of estrogens and androgens are synthesized in peripheral target tissues, the plasma concentrations of the

active sex steroids have limited value in estimating intracellular androgen and estrogen concentrations and activity.<sup>2</sup> This makes it difficult to ascertain androgen levels in women. Moreover, because of the lack of specificity, precision and accuracy, most information derived from radioimmunoassays of serum steroids must be re-examined with new technology using liquid or gas chromatography and mass spectrometry.

The rate of formation of each sex steroid depends on the level of expression of each steroidogenic enzyme in each cell of each tissue.<sup>3,4</sup> Such a specialized and highly specific intracrine system permits each target tissue to: (1) make its own sex steroids according to its needs, and (2) regulate their intracellular concentrations by controlling the level of activity of both the steroidogenic and steroid-inactivating enzymes.

**Table 1**  
Comparison of Serum Androgen Metabolites (nM) in Men and Women, 20-80 Years<sup>1</sup>

	Men	Women (% compared with men)
ADT-G	87.5	32.5 (37%)
3-alpha-diol-G	8.6	4.3 (50%)
3-beta-diol-G	30.2	17.3 (57%)
Total	76.2	54.1 (71%)

**Table 2**  
**Intracrinology: Tissue-Specific Effects of DHEA**

<b>Androgenic effects</b>
• Bone formation
• Sebaceous gland stimulation
• Mammary gland inhibition
• Muscle mass increase
<b>Estrogenic effects</b>
• Vaginal mucosa maturation
• Insulin resistance decreased
<b>No Effect</b>
• Endometrium

\* demonstrated in postmenopausal women  
† possibly also androgenic

In premenopausal women, the origin of the serum levels of androstenedione is split equally between the adrenals and the ovaries. In postmenopausal women, 80% of the serum androstenedione concentration is from the adrenals' serum. Testosterone levels in both pre- and postmenopausal women are divided equally between the adrenals and the ovaries.<sup>5</sup>

**Androgen Therapy**

By menopause, the serum concentration of the androgen metabolites is greatly diminished.<sup>1</sup> DHEA levels decline markedly from age 30 to 60, and by age 75 they are at only 20% of their maximum

level. Thus, it is not surprising that androgen therapy is beneficial for this age group. The loss of bone that occurs before menopause is most likely a consequence of the decrease of DHEA and androgen formation in the bone (Table 2).

Androgen plays several important therapeutic roles for women:

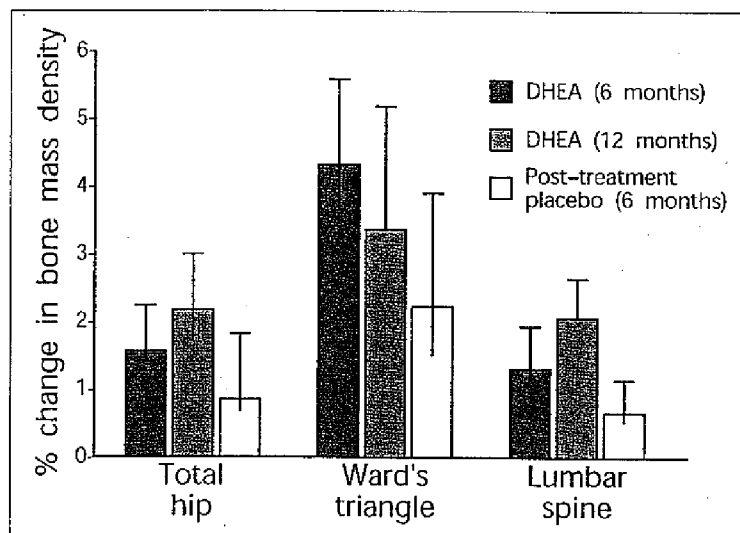
**Bone mineral density.** Androgens increase bone mineral density (BMD) in postmenopausal women. Need et al<sup>6</sup> found that injections of the anabolic steroid nandrolone decanoate caused a significant increase in bone mineral content. In a trial measuring the effects of estradiol and testosterone on BMD, women on the combined therapy had more rapid increases in BMD of total body, lumbar vertebrae and hip area than women on estradiol alone.<sup>7</sup> Postmenopausal women who received DHEA percutaneously had increased BMD (Figure).<sup>8</sup>

**Skin.** DHEA increases sebum secretion and epidermal thickness and improves the papery appearance of postmenopausal skin.<sup>8,9</sup> The epidermis, dermis, sebaceous glands, hair follicles and sweat glands all make androgens from DHEA.<sup>10</sup>

**Hot flashes.** In a placebo-controlled study of parenteral administration of estrogen and androgen for their effect on hot flashes, surgically menopausal women who were given a combined estrogen-androgen preparation reported a significantly reduced frequency of hot flashes compared with estrogen alone.<sup>11</sup>

**Libido and sexual satisfaction.** Androgens given with hormone replacement therapy (HRT) improve libido and sexual satisfaction to a greater degree than HRT alone. Women who received an estrogen-androgen preparation reported higher rates of sexual desire and sexual arousal than those who were given estrogen alone.<sup>12</sup> These responses correlated with higher levels of plasma testosterone.

Leiblum et al<sup>13</sup> investigated the effects of sexual activity on vaginal atrophy and the role of hormones. Sexually active women had less vaginal atrophy compared with sexually inactive women. In addition, women with less vaginal atrophy had significantly higher mean levels of androgens (androstenedione and testosterone).



**Figure.** Percent change in bone mineral density in total hip, Ward's triangle and lumbar spine with DHEA. Increases in all three areas were seen at 6 and 12 months with administration of DHEA.<sup>8</sup>

**Conclusions**

It is now recognized that androgens are an important, yet underappreciated, constituent in the physiology of women. Better appreciation of their role, and the place of androgens in therapy for women—including the areas of BMD, skin, vasomotor symptoms, libido and sexual satisfaction—is a necessary component in providing quality health care to women of menopausal age.

**Dr. Labrie reports no significant financial relationships.**

## References

1. Labrie F, Bélanger A, Cusan L, et al. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. *J Clin Endocrinol Metab* 1997;82:2396-402.
2. Labrie F, Bélanger A, Cusan L, et al. Physiological changes in dehydroepiandrosterone are not reflected by serum levels of active androgens and estrogens but of their metabolites: Intracrinology. *J Clin Endocrinol Metab* 1997;82:2403-9.
3. Labrie F. Intracrinology. *Mol Cell Endocrinol* 1991;78:C113-8.
4. Labrie F, Luu-The V, Lin SX. Intracrinology: Role of the family of 17 $\beta$ -hydroxysteroid dehydrogenases in human physiology and disease. *J Mol Endocrinol* 2000;25:1-16.
5. Judd HL, Judd GE, Lucas WE, et al. Endocrine function of the postmenopausal ovary: Concentration of androgens and estrogens in ovarian and peripheral vein blood. *J Clin Endocrinol Metab* 1974;39:1020-4.
6. Need AG, Horowitz M, Morris HA, et al. Effects of nandrolone therapy on forearm bone mineral content in osteoporosis. *Clin Orthop* 1987;225:273-8.
7. Davis SR, McCloud P, Strauss BJ, et al. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. *Maturitas* 1995;21:227-36.
8. Labrie F, Diamond P, Cusan L, et al. Effect of 12-month DHEA replacement therapy on bone, vagina and endometrium in postmenopausal women. *J Clin Endocrinol Metab* 1997;82:3498-505.
9. Baulieu EE, Thomas G, Legrain S, et al. Dehydroepiandrosterone (DHEA), DHEA sulfate and aging: Contribution of the DHEAge Study to a socio-biomedical issue. *Proc Natl Acad Sci* 2000;97:4279-84.
10. Labrie F, Luu-The V, Labrie C, et al. Intracrinology and the skin. *Horm Res* 2001;54:218-29.
11. Sherwin BB, Gelfand MM. Effects of parenteral administration of estrogen and androgen on plasma hormone levels and hot flushes in the surgical menopause. *Am J Obstet Gynecol* 1984;148:552-7.
12. Sherwin BB, Gelfand MM. The role of androgen in the maintenance of sexual functioning in oophorectomized women. *Psychosom Med* 1987;49:397-409.
13. Leiblum S, Bachmann G, Kemmann E, et al. Vaginal atrophy in the postmenopausal woman. The importance of sexual activity and hormones. *JAMA* 1983;249:2195-8.

# Is There an Androgen-Deficiency Syndrome?

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The need for testosterone replacement is being increasingly diagnosed among surgically and naturally menopausal women. There are two fundamental questions, however: (1) What are we treating? and (2) Is there an androgen-deficiency syndrome?

Testosterone is an important compound for women. In addition to its direct androgenic actions, it is a prohormone for estradiol in the brain and other tissues. In the human female brain, there is much more testosterone in the important behavioral areas than there is estradiol. In contrast to the abrupt decline in estradiol at menopause, testosterone levels drop gradually with age from the midreproductive years and do not change acutely across the menopause transition (Figure).<sup>1</sup> Consequently, testosterone levels can be insufficient in the late premenopausal years. (Women who undergo surgical menopause experience a sudden drop in both testosterone and estradiol levels.)

Testosterone circulates in the bloodstream highly bound to sex-hormone-binding globulin (SHBG). Total androgen production is best reflected by total testosterone, but the free testosterone value determines whether deficiency is present. The gold stan-

dard for measurement of free testosterone is equilibrium dialysis. Because non-SHBG-bound testosterone is indicative of the free testosterone level, the SHBG levels can guide the management of the patient with low testosterone levels.

## Causes of Androgen Deficiency in Women

A clinical or biochemical definition of androgen deficiency in women does not exist, and no large cross-sectional study has been conducted that correlates proposed symptoms with circulating levels. Consequently, clinicians must manage androgen deficiency without a defined syndrome to treat. Androgen deficiency in women has both endogenous and exogenous causes:

*Aging.* Between the ages of 20 and 40, total circulating testosterone in women decreases by 50%. This reduction predates menopause. It occurs because of a reduction in dehydroepiandrosterone (DHEA) and a loss of cyclical ovarian production of testosterone.

*Ovarian insufficiency unassociated with natural menopause.* Ovarian dysfunction before menopause can result in a 50% reduction in androgen and testosterone production.