

## Testosterone Therapy and Women's Sexuality

a report by

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The relative contribution of androgen and estrogen to female sexual function is controversial. Low libido, decreased wellbeing, blunted motivation, and fatigue are listed as major features of the proposed syndrome of female androgen deficiency.<sup>1,2</sup> However, defining and elucidating this syndrome has been problematic. First, the symptoms are vague and difficult to objectify, and can all occur in other syndromes such as major depressive disorders. Second, there is no consensus on the definition of low testosterone (T) levels. This lack reflects assay difficulties and insufficient studies establishing the normal range of androgen levels in different phases of life. In fact, T levels reach an apparent peak in the early reproductive years (early 20s) and decrease with age. Women in their 40s have approximately half the level of circulating total T as that of women in their 20s.<sup>3</sup> The rate of the age-related decrease in total T then seems to slow, and is not specifically related to menopause. Dehydroepiandrosterone sulphate (DHEA-S) shows similar changes to those described for T, but has an even more pronounced age-related decrease after the early reproductive years that continues through to later life.<sup>4</sup>

Diurnal- and menstrual-cycle-linked changes in T and androstenedione (A) also occur. T (and A) levels are highest in the morning before 10am and in the middle third of the menstrual cycle, although one small study found that the mid-cycle ovarian increase in free T level did not occur in older menstruating women (those aged 43–47 years).<sup>5,6</sup> There have been conflicting reports concerning post-menopause. Some studies reported that T, A, and sex-hormone-binding globulin (SHBG) levels remain unchanged, whereas others reported a small yet significant difference in the first six months after menopause.<sup>7</sup>

However, after spontaneous menopause the ratio T/SHBG did not show any change,<sup>8</sup> even though in surgical menopause both T and A decrease by about 50%, suggesting an important role of ovaries in T secretion after menopause. On the other hand, in post-menopause the principal source of circulating T is derived from the peripheral conversion of A and DHEA(S).<sup>9</sup> In addition, independently of menopausal transition, circulating delta5-androgens fall linearly with age, beginning in the 20s as a result of the age-related reduction of 17,20 desmolase activity, the enzyme that rules the biosynthesis of the delta5-adrenal pathway.<sup>10</sup>

### Androgens in Women

The biological activity of an androgen depends on its ability to bind to androgen receptors in target tissues and regulate gene transcriptional activity, the production rate, the metabolic clearance rate (which includes various metabolic conversions and excretion), and the quantitative

amount that is available to the target tissues. The metabolic clearance rate and amount of androgen that is bioavailable in the blood to be transported into cells is dependent to a great extent on the degree of binding of the low capacity and high affinity to SHBG, and the high capacity but low affinity to albumin.<sup>9,11,12</sup> If the quantity of androgen in the blood that is not bound to serum proteins or weakly bound to albumin is considered to be bioavailable, every pathological status that could influence SHBG metabolism also could influence free T levels. For example, SHBG levels are decreased in obesity, hyperinsulinism, glucocorticoid or growth hormone excess, hypothyroidism, and hyperandrogenic states. On the other hand, SHBG levels are increased with oral estrogen therapy, hyperthyroidism, cirrhosis, and some antiepileptic medications.<sup>13,14</sup>

Androgens are directly secreted into the circulation by the ovaries and adrenals. In addition, various peripheral tissues such as adipose tissue, muscle, and fat convert androgens and androgen precursors from the ovaries and adrenals into androgens, which then enter the circulation as part of the androgen pool (see *Table 1*). The circulating concentrations of androgens may not reflect androgen action at a specific target tissue. For instance, the expression of the levels of 5 $\alpha$ -reductase, the enzyme that catalyzes the conversion of T to dihydrotestosterone (DHT), varies in different target organs and at different sites. Indeed, the term 'intracrinology' has been used to describe hormone production, metabolism, and effect occurring in the same local target tissue.<sup>15</sup>

Androgen production and serum levels decrease with age, and both T and A levels decrease before menopause. There are conflicting data as to whether T levels decrease further during the menopause transition. Some studies suggest that an approximate decline of 15% occurs.<sup>11,16</sup> In contrast, the large longitudinal Melbourne Women's Midlife Health Project, which studied women throughout the menopausal transition, did not demonstrate a decline in total serum T. Indeed, a decrease in SHBG levels resulted in an increase in the calculated free androgen index.<sup>17</sup> On the contrary, there is no controversy surrounding the observations that production of the major androgen precursor from the adrenal glands, DHEA (and its sulphate), peak during a woman's 20s and then sharply decline between the ages of 30 and 60 years.<sup>18,19</sup> Between the ages of 20 and 80 years, serum DHEA levels steadily decrease by an average of 44% in association with a decrease of between 48 and 72% in various conjugated metabolites. Thus, the relatively low androgen levels found in women after menopausal transition compared with women in the fertile age range (20s–30s) reflects an age-related decrease rather than a specific menopausal effect.

### Role of Androgens in Female Sexuality

The predominant role of estrogens or androgens in female sexuality is still controversial. In fact, it is important to note that estrogens clearly decrease the vasomotor symptoms that can lead to sleep disorders (i.e. insomnia), which can affect mood, energy, and general quality of life. Estrogens also improve vaginal trophism, thereby reducing dyspareunia and the avoidance of sexual intercourse due to pain. These effects increase sexual receptivity but do not improve libido. Arousability, libido, and frequency of sexual intercourse have been correlated strictly with the mid-menstrual cycle increase in T.<sup>20</sup>

Several cross-sectional studies performed on women at various ages have shown positive correlations with androgens levels (in particular T levels) and sexual desire, arousal, initiation, responsiveness to sexual activity, and frequency of orgasm.<sup>21,22</sup> A longitudinal study<sup>22</sup> that followed women from approximately two years before the menopause until two years after demonstrated a decline in coital frequency, sexual thoughts, or fantasies and an increase in dyspareunia and sexual dissatisfaction. In this study, estradiol and T levels both showed significant ( $p < 0.002$ ) declines, whereas T demonstrated closer correlation with coital frequency. In contrast, other literature data have described no correlation between androgen levels and sexual function.<sup>23–25</sup> The variables that are most problematic in attempts to correlate androgen levels to sexual function include insufficiently sensitive androgen assays. Even in the studies showing a positive association between androgens and parameters of sexual function, the correlations have generally not been very robust, indicating that in addition to androgens other factors such as relationship issues, attitudes, and general health, as well as medication use by the patient and partner, contribute to sexual function/dysfunction.

### Androgen Insufficiency Syndrome

Androgen insufficiency syndrome (AIS) has been well documented in four conditions: hypopituitarism, adrenal insufficiency, oophorectomy/premature ovarian failure, and after use of oral estrogen replacement therapy (ERT) due to elevations of SHBG. The symptom complex of AIS has been empirically derived from observations of patients who developed symptoms after an event such as an oophorectomy that can precipitate a decrease in T. The frequently described symptoms are fatigue, low energy, decreased or absent sexual motivation and desire, and a generalized decrease in wellbeing. These symptoms, which are consistent with the diagnosis of hypoactive sexual desire disorder (HSDD), often result in considerable distress in women. Signs of androgen insufficiency such as thinning or loss of pubic hair and decreased muscle mass may be seen (see *Table 1*). Reduction of bone mineral density may be present on bone densitometry testing.<sup>26</sup> In women who have hypopituitarism or hypoadrenalism or who have undergone oophorectomy and present with symptoms of androgen insufficiency, free T levels and the free T index are low. According to the recent Princeton Consensus Conference, it is reasonable to consider a menopausal woman to have AIS if she suffers typical symptoms and has a free T or free T index level in the lowest quartile of the normal range or below the normal range for reproductive-age women.<sup>27</sup>

During a clinical evaluation of a woman who is suffering from suspected AIS, it is important to investigate other causes of the same symptoms such as depression, hypothyroidism, anemia, and drug use (in particular glucocorticoids and selective serotonin re-uptake inhibitors [SSRIs]). It is very important to make sure that the women is adequately estrogenized to

**Table 1: Plasmatic Levels of Some Sexual Steroids in Fertile Life, in Natural Menopause, and in Surgical Menopause**

|                        | Fertile Life | Natural Menopause | Surgical Menopause |
|------------------------|--------------|-------------------|--------------------|
| Estradiol (pg/ml)      | 40±3         | <20 pg/ml**       | <20 pg/ml**        |
| Testosterone (pg/ml)** | 400±30       | 200±20 (↓50%)     | 100±20 (↓75%)      |
| DHEA (pg/ml)**         | 4,200±210    | 1,970±430 (↓53%)  | 1,260±360 (↓70%)   |

\*\* 1 ng/dl = 10 pg/ml.

eliminate dyspareunia with secondary avoidance of sexual activity. However, as previously noted, ERT reduces androgen levels, increasing SHBG, but it is important to supply these women with adequate estrogen transdermal replacement therapy.

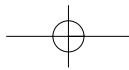
### The Biochemical Diagnosis of Androgen Deficiency

Therefore, the diagnosis of androgen deficiency requires measurement of free T or total T, together with SHBG, allowing the calculation of a free T index (T/SHBG x 100). The free T index has been shown to correlate well with free T measured using centrifugal ultrafiltration.<sup>28</sup> The major difficulty in this field has been the lack of suitably sensitive and widely available assays for total T. It is likely that the normal female range for total T concentration is approximately 0.6–2.8 nmol/l, although assays using extraction and chromatography give somewhat lower concentrations.<sup>29</sup> The previously referred to Consensus Conference emphasized the need for accurate and reliable androgen measurements. This conference recommended that clinical assessment of androgen status should include total T and SHBG, free T and SHBG, or free T and total T. This is because SHBG can be independently influenced, particularly by ERT (or thyroxine), so women on ERT may have apparently normal T levels but these are caused by markedly elevated SHBG levels. The place of DHEAS assay is less certain in clinical diagnosis. While assays for this steroid are reliable and not subject to diurnal variation, the relationship to clinical AIS is less clear. However, in adrenal insufficiency this measure is a useful one.

### Effects of Androgen Replacement Therapy Testosterone Trials

Many studies have demonstrated that exogenous androgen administration improves various sexual function parameters (coital frequency, desire and libido, arousal, pleasure, orgasm, thoughts or sexual fantasies) and mood or the sense of wellbeing, as well as health, body composition, and muscle mass in women with symptomatic AIS. There are myriad variables that make direct comparison between studies difficult. These include differences in study design, duration of exposure to the androgen, whether the androgen level attained was physiological or supraphysiological, type of menopause (natural or surgical), selection criteria for inclusion of patients (e.g. sexual dysfunction, low libido, mixture of menopausal symptoms), type of instruments for assessing sexual function, and whether it has been psychometrically validated, type of sexual activity measured, and number of study subjects. These considerations are especially important as there may be a substantial placebo effect in these types of studies.<sup>30</sup>

As shown in *Table 3*, the randomized, double-blind, placebo- or estrogen-controlled trials in women with low libido after menopause that



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**Table 2: Symptoms and Signs that Characterized Androgen Insufficiency Syndrome**

| Symptoms |  |
|----------|--|
|          | Low libido with global decrease in sexual desire, fantasy, or arousability |
|          | Persistent, unexplained fatigue  |
|          | Decreased sense of wellbeing   |
|          | Blunted motivation   |
|          | Flattened mood   |
| Signs    |  |
|          | Thinning or loss of public hair  |
|          | Decreased lean body mass   |
|          | Osteopenia or osteoporosis   |

used well-validated tools to measure sexual function have generally shown increased libido, satisfaction, and sexual activity with T therapy compared with the response seen with placebo or estrogen alone. Shifren et al.<sup>30</sup> studied the effect of a transdermal T patch in 65 oophorectomized women who were on a stable dose of estrogen therapy of at least 0.625mg of conjugated equine estrogen (CEE) daily for at least two months before study entry. In this double-blind, cross-over study, the women were randomized to three treatment groups for 12 weeks each of CEE plus 150µg per day of T, CEE plus 300µg of T, and CEE plus placebo. Serum total T levels were above the normal range, but the free and bioavailable T concentrations were within the normal range for young women, reflecting the fact that the majority of women receiving oral CEE had markedly elevated levels of SHBG. Shifren and colleagues measured sexual function at baseline and at the end of each 12-week treatment period, which included testing in the domains of sexual thoughts and desire, arousal, frequency of sexual activity, receptivity, pleasure and orgasm, relationship satisfaction, and other problems that can affect sexual function.

The investigators reported that the CEE plus 300µg of T demonstrated increased frequency of sexual activity ( $p=0.03$ ) and pleasure/orgasm ( $p=0.03$ ). A dose-dependent effect was demonstrated as there was an increased percentage of women with increased frequency of sexual fantasies, masturbation, and sexual intercourse in the CEE plus 300µg of T group compared with the 150 µg of T group. The sense of wellbeing ( $p=0.04$ ) and mood ( $p=0.03$ ) improved significantly in the 300µg of T group compared with the placebo group. Another trial conducted by Goldstat, which investigated the use of T cream in pre-menopausal women with a mean age of 40 years and low libido, demonstrated an improvement not only in sexual function, but also in mood and wellbeing. Thirty-one women provided complete data using 10mg of 1% T cream applied daily to the thigh. The study participants were randomized in a double-blind fashion to treatment or placebo for 12 weeks then crossed over (after a four-week wash-out time period) for another 12 weeks of treatment or placebo. The mean baseline serum T level was near the lowest quartile of the normal range for reproductive-age women. Serum total T levels increased with T treatment to the upper limit of the normal range, whereas the free androgen index (total T/SHBG x 100) increased to above the upper limit of normal. Of note, there was no change in serum estradiol levels.<sup>31</sup>

Braunstein et al. reported the results of a six-month double-blind, placebo-controlled trial using varying doses of transdermal T delivered by a

matrix delivery system patch in parallel groups of randomized surgically menopausal women ( $n=447$ ) receiving ERT with complaints of lowered libido after their oophorectomy. A 300µg daily transdermal dose was found to be optimal in this trial, which tested daily doses of 150, 300, and 450µg. Again, transdermal T demonstrated significant improvement in sexual desire with minimal side effects. There was a 30% increase ( $p<0.05$ ) in total satisfying sexual activity after six months of treatment with 300µg of transdermal T compared with placebo and an 81% increase ( $p<0.05$ ) from baseline using a weekly sexual activity log. The sexual desire score was also significantly increased by 18% ( $p<0.05$ ) with T as measured by the Profile of Female Sexual Function (PFSF). There was no difference in reports of adverse effects between the placebo and T groups.<sup>32</sup>

There are several controlled trials evaluating estrogen alone versus estrogen plus T that support the benefits of androgen replacement. Lobo et al. performed a randomized, double-blind study with 218 post-menopausal women using a combined oral estrogen-androgen preparation (0.625mg EO plus 1.25mg methyltestosterone [MT]) and estrogen alone (0.625mg EO) over four months. Sexual function measurement was performed at one, two, three, and four months of treatment, and both groups demonstrated increases in sexual interest after one month of treatment, with the increase in sexual interest or desire being greater for the combined therapy group.<sup>33</sup>

### Dehydroepiandrosterone Trials

As DHEA is converted to A and then to T, several studies have examined the effects of DHEA administration on sexual function in women. Morales et al. conducted a six-month randomized, placebo-controlled, cross-over study using 50mg of DHEA in 17 women aged 40–70 years.<sup>34</sup> Within two weeks of treatment, serum DHEA and DHEAS levels were within the normal range for reproductive-age women and there was a two-fold increase in A, T, and DHT. Although 84% of the women reported an improvement in wellbeing, there was no improvement in libido.

Baulieu et al. conducted a trial with 50mg oral DHEA daily over a period of one year in 140 women aged between 60 and 79 years in a double-blind, randomized, placebo-controlled study.<sup>35</sup> Serum androgens reached supraphysiological levels after six months of therapy but decreased to physiological levels after 12 months of therapy. Estradiol levels increased significantly ( $p<0.001$ ), but did not exceed early follicular-phase levels after six months of therapy and were maintained after 12 months of therapy. Sexual attitudes, libido, activities, and satisfaction were measured with a questionnaire at baseline and at six and 12 months of treatment. The authors found a significant improvement in sexual parameters in women older than 70 years. In the former, there was an increase in libidinal interest after six months of therapy that reached significance after 12 months of therapy. Of note, libido increased from baseline before the significant increases demonstrated in sexual activities ( $p<0.03$ ) and sexual satisfaction ( $p<0.01$ ) after 12 months of therapy.

Genazzani et al. treated some post-menopausal women aged between 50 and 55 years with 25 or 50mg/day of DHEA orally (based on basal DHEA-S serum levels). All patients underwent hormonal evaluation before therapy and at three and six months of therapy and their sexual function was evaluated by the Female Sexual Function Index questionnaire (FSFI). The authors observed that levels of DHEA, DHEAS, androstenedione,

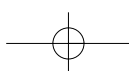


Table 3: Testosterone Trials

| Randomized, double-blind, placebo-controlled trials       |   |                  |   |                  |
|---|---|------------------|---|------------------|
| Study   | Therapy   | Mean Age (years) | Sexual Function Parameter   | Study design     |
| Sherwin et al.  | IM<br>E, T, or E+T [150mg TE+E, or 200mg TE q mo] | 46               | ↑ Desire <sup>a</sup><br>↑ Fantasy <sup>a</sup><br>↑ Arousal <sup>a</sup>   | Cross-over       |
| Myers et al.  | Oral<br>E, E+MPA, or E+MT [5mg MT q d]            | 58               | ↑ Pleasure from masturbation <sup>a</sup>   | Parallel         |
| Shifren et al.  | E + transdermal T [150µg qd; 300µg qd]            | 47               | Effect of 300µg dose<br>↑ Frequency <sup>a</sup><br>↑ Pleasure, orgasm <sup>a</sup>   | Cross-over       |
| Braunstein et al.   | E + transdermal T [150µg qd; 300µg qd; 450µg d]   | 49–50            | ↑ Desire <sup>a</sup><br>↑ Satisfying activity <sup>a</sup>   | Parallel         |
| Goldstat et al.   | T 1% cream [10mg qd]                              | 40               | ↑ Interest <sup>a</sup><br>↑ Activity <sup>a</sup><br>↑ Satisfaction <sup>a</sup><br>↑ Pleasure <sup>a</sup><br>↑ Fantasy <sup>a</sup><br>↑ Orgasm <sup>a</sup> | Cross-over       |
| Randomized, double-blind, estrogen-only comparison trials |   |                  |   |                  |
| Sarrel et al.   | Oral<br>E or E+T [2.5mg MT qd mo]                 | 52               | ↑ Frequency (at 4 wks) <sup>b</sup><br>↑ Sensations <sup>b</sup><br>↑ Desire <sup>b</sup><br>↑ Responsiveness <sup>a</sup><br>↑ Interest or desire <sup>a</sup> | Placebo lead-in  |
| Lobo et al.   | Oral<br>E or E+T [1.25mg MT qd]                   | 53               | ↑ Interest or desire <sup>a</sup><br>↑ Responsiveness <sup>a</sup>  | Parallel         |
| Randomized, single-blind, estrogen-only comparison trials |   |                  |   |                  |
| Dow and Hart  | SC<br>E or E+T [100mg]                            | 47               | ↑ Orgasm at 2 months <sup>b</sup><br>(low dyspareunia patients only)  | Parallel         |
| Burger et al.   | SC<br>E or E+T [50mg]                             | 43<br>(E+T)      | ↑ Libido <sup>b</sup><br>↑ Enjoyment <sup>b</sup>   | Parallel         |
| Davis et al.  | SC<br>E or E+T [50mg q 3 mo]                      | 57<br>(E+T)      | ↑ Activity <sup>a</sup><br>↑ Satisfaction <sup>a</sup><br>↑ Orgasm <sup>a</sup><br>↑ Pleasure <sup>a</sup><br>↑ Relevancy <sup>a</sup>                          | Parallel         |
| Other trials  |   |                  |   |                  |
| Burger et al.   | SC<br>E or E+T [100mg]                            | 42 yr            | ↑ Libido <sup>b</sup><br>↑ Enjoyment <sup>b</sup><br>↑ Climax <sup>b</sup><br>↑ Initiation <sup>b</sup><br>↑ Desire <sup>a</sup>                                | Pilot study      |
| Sherwin et al.  | IM<br>E or E+TE [15mg q mo]                       | 47 yr<br>(E+T)   | ↑ Desire <sup>a</sup><br>↑ Arousal <sup>a</sup><br>↑ Fantasy <sup>a</sup><br>↑ Frequency <sup>a,e</sup><br>↑ Orgasm <sup>a,e</sup>                              | 2-year follow-up |

E = estrogen; T = testosterone; MT = methyltestosterone; ↑ = increased/improved; unk = unknown; T E = T enanthate; MPA = medroxyprogesterone acetate.

<sup>a</sup> Significant change between groups.

<sup>b</sup> Significant change from baseline within group, or, self-report (11) of increase or improvement.

<sup>c</sup> Only 22 patients crossed over to all four treatment groups; seven were surgically menopausal.

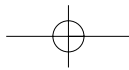
<sup>d</sup> Data not provided in statistical terms; 67% preferred E+T compared with E alone in terms of increased sense of wellbeing and libido; 23.5% of E+T users reported an increase in libido; 42% of T-alone users reported increased libido.

<sup>e</sup> Between-group significance during first two weeks after injection only.

testosterone, and dihydrotestosterone increased progressively from the third month of treatment. It is important to note that, with the improved female androgenic profile, there was an underlying improvement in sexual thoughts and fantasies as well as an enhancement in mood and wellbeing (data on file).

### Tibolone Trials

Tibolone is a steroid hormone that possesses estrogenic, progestogenic, and androgenic properties. There are several studies that evaluate oral daily administration of tibolone and its impact on sexual activity.<sup>36–38</sup> It is difficult to interpret the results because of the estrogenic and



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progestational activities of tibolone and the differences between the potency of tibolone and the comparators used in the studies. Also, as tibolone lowers SHBG, whereas estrogens increase it, the differences in results may actually reflect alterations in the free endogenous androgen levels rather than a direct androgenic activity of tibolone.

### Safety of Androgen Replacement Therapy in Women

The various studies that have investigated the administration of androgens in women have found that androgen replacement therapy is well tolerated and devoid of serious side effects. All may result in unwanted mild androgenic effects such as acne and hirsutism if supraphysiological T concentrations are reached, but are rarely associated with more serious virilization. Due to the first-pass effect on the liver after absorption from the gastrointestinal tract, oral androgen preparations generally exhibit a greater degree of lowering SHBG and greater increase in the free androgen levels than parenteral or transdermal androgen preparations. This also leads to a reduction of high-density lipoprotein (HDL) cholesterol levels not usually found with androgens given in replacement doses by a non-oral route.

Fortunately, many of the adverse reactions listed in the product labels of various androgen preparations and in the literature concerning androgen therapy for male hypogonadism, such as liver dysfunction, sleep apnea, and breast

stimulation, have not been found in women receiving androgen replacement therapy. A larger retrospective observational study on breast cancer incidence in post-menopausal women using androgen replacement therapy (n=508) suggested that the addition of testosterone to conventional hormone therapy for post-menopausal women does not increase (and may indeed reduce) the hormone-therapy-associated breast cancer risk, thereby returning the incidence to the normal rate observed in the general untreated population.<sup>39</sup>

### Conclusion

The physiological mechanism of female AIS and subsequent symptoms are not entirely clear. The decline of androgen production is well documented and probably a consequence of the effects of advancing age on the adrenals and the ovaries rather than menopause. It is clear that women with hypopituitarism, adrenal insufficiency, or oophorectomy are often androgen-insufficient. Why some women become symptomatic and others do not has yet to be determined. An important underlying factor is that women now live approximately one-third of their lives after menopause. Therefore, the consideration of androgen therapy for symptomatic naturally menopausal women has gained increasing support and attention in the lay and medical communities. In addition, men now have longer life expectancies and can have therapy to address their sexual function. The quality of life of women now increasingly includes the ability to enjoy an intimate sexual relationship. ■

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