# TRANSDERMAL TESTOSTERONE TREATMENT IN WOMEN WITH IMPAIRED SEXUAL FUNCTION AFTER OOPHORECTOMY

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## ABSTRACT

***Background*** The ovaries provide approximately half the circulating testosterone in premenopausal women. After bilateral oophorectomy, many women report impaired sexual functioning despite estrogen replacement. We evaluated the effects of transdermal testosterone in women who had impaired sexual function after surgically induced menopause.

***Methods*** Seventy-five women, 31 to 56 years old, who had undergone oophorectomy and hysterectomy received conjugated equine estrogens (at least 0.625 mg per day orally) and, in random order, placebo, 150 $\mu$g of testosterone, and 300 $\mu$g of testosterone per day transdermally for 12 weeks each. Outcome measures included scores on the Brief Index of Sexual Functioning for Women, the Psychological General Well-Being Index, and a sexual-function diary completed over the telephone.

***Results*** The mean (±SD) serum free testosterone concentration increased from 1.2±0.8 pg per milliliter (4.2±2.8 pmol per liter) during placebo treatment to 3.9±2.4 pg per milliliter (13.5±8.3 pmol per liter) and 5.9±4.8 pg per milliliter (20.5±16.6 pmol per liter) during treatment with 150 and 300 $\mu$g of testosterone per day, respectively (normal range, 1.3 to 6.8 pg per milliliter [4.5 to 23.6 pmol per liter]). Despite an appreciable placebo response, the higher testosterone dose resulted in further increases in scores for frequency of sexual activity and pleasure–orgasm in the Brief Index of Sexual Functioning for Women ($P=0.03$ for both comparisons with placebo). At the higher dose, the percentages of women who had sexual fantasies, masturbated, or engaged in sexual intercourse at least once a week increased two to three times from base line. The positive-well-being, depressed-mood, and composite scores of the Psychological General Well-Being Index also improved at the higher dose ($P=0.04$, $P=0.03$, and $P=0.04$, respectively, for the comparison with placebo), but the scores on the telephone-based diary did not increase significantly.

***Conclusions*** In women who have undergone oophorectomy and hysterectomy, transdermal testosterone improves sexual function and psychological well-being. (N Engl J Med 2000;343:682-8.)



IN premenopausal women, the rate of production of testosterone is about 300 $\mu$g (1040 nmol) per day,[1] of which about half is derived from the ovaries and half from the adrenal glands.[2] In women who undergo bilateral oophorectomy before natural menopause, serum testosterone and estradiol concentrations decrease by approximately 50 and 80 percent, respectively.[3,4] These women are commonly treated with estrogen to prevent or ameliorate hot flashes, vaginal atrophy, osteoporosis, and heart disease.[5] Despite estrogen therapy, many surgically postmenopausal women have decreased sexual desire (libido), activity, and pleasure[6-8] and a decreased general sense of well-being.[9] These symptoms are believed to result from the lack of ovarian androgen production.

In a study of women in whom menopause had been induced by surgery, high doses of testosterone enanthate, given by intramuscular injection alone or in combination with estrogen, increased sexual desire, fantasies, and arousal more than placebo or estrogen alone.[6] In another study, therapy with testosterone and estradiol implants increased sexual activity, satisfaction, and pleasure and the frequency of orgasm more than estradiol alone.[10] However, the doses of testosterone enanthate were supraphysiologic, and in both studies the investigators knew which treatments the women received.[6,10,11] We undertook this study to determine the efficacy and safety of physiologic doses of testosterone, administered transdermally, in women who had impaired sexual function after surgically induced menopause.

## METHODS

### Study Subjects

We studied 75 healthy women, 31 to 56 years old, at nine clinical sites in the United States. All had undergone bilateral salpingo-oophorectomy and hysterectomy before natural menopause, at least 1 year but not more than 10 years earlier. All had serum testosterone concentrations of less than 30 ng per deciliter (1.0 nmol per liter) or serum free testosterone concentrations of less than 3.5 pg per milliliter (12.1 pmol per liter), which are below the median values for normal premenopausal women (Endocrine Sciences, Calabasas Hills, Calif.). All of the women had received conjugated equine estrogens at a daily dose of at least 0.625 mg

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orally for at least two months, had been in a stable, monogamous, heterosexual relationship for at least one year, and had a body-mass index (the weight in kilograms divided by the square of the height in meters) between 19.5 and 33.5. All were considered to have impaired sexual function on the basis of their affirmative answers to the following three questions: "At any time before surgery would you have characterized your sex life as active and satisfying?" "Since your surgery has your sex life become less active or less satisfying?" and "Would you prefer your sex life to be more active or more satisfying than it is now?"

Before enrollment the women completed the Brief Index of Sexual Functioning for Women,[12] a 22-item, multiple-choice questionnaire that provides scores pertaining to aspects of female sexuality (thoughts–desire, arousal, frequency of sexual activity, receptivity–initiation, pleasure–orgasm, relationship satisfaction, and problems affecting sexual function) and a composite score, ranging from −16 (poor function) to +75 (maximal function).[13] To qualify for the study, the women were required to have a composite score of less than 33.6, which is the mean value for normal women.[13] Women were excluded if they had received oral, topical, or vaginal androgen therapy in the previous three months or injectable or implantable androgen therapy in the previous six months; if they had more than 20 moderate or severe hot flashes per week, severe acne (grade 3 on the scale of Palatsi et al.[14]), moderate or severe hirsutism (score of 6 or more on the scale of Lorenzo[15]), hyperlipidemia, psychiatric illness, dyspareunia, or physical limitations that interfered with normal sexual functioning; or if they were taking glucocorticoids, selective serotonin-reuptake inhibitors, tricyclic antidepressants, antiandrogen agents, ginseng, yohimbine, phytoestrogens, dehydroepiandrosterone, or melatonin. The protocol was approved by the institutional review boards or ethics committees at all sites, and all the women gave written informed consent.

### Study Design

After screening and a 4-week base-line period, the women began three consecutive 12-week treatment periods during which they received, in random order, the following regimens of transdermal patches applied twice weekly: two placebo patches (no active drug), one active and one placebo patch (nominal dose of testosterone, 150 μg per day), and two active patches (nominal dose of testosterone, 300 μg per day) (where the nominal dose is the amount of drug that will be absorbed by a person with average skin permeability during the application time). Neither the women nor the investigators knew the contents of the patches. Throughout the study, including the base-line period, the women received concomitant oral conjugated equine estrogens at their prestudy doses. The identical-appearing experimental patches (Watson Laboratories, Salt Lake City) were applied on the abdomen and were changed every three to four days.[16,17]

### Serum Hormone Measurements

Serum free testosterone, bioavailable testosterone, total testosterone, dihydrotestosterone, and sex hormone–binding globulin were measured at base line and at weeks 4, 8, and 12 of each treatment period. Serum dehydroepiandrosterone sulfate, estradiol, estrone, luteinizing hormone, and follicle-stimulating hormone were measured at base line and at week 12 of each treatment period. Hormone assays were performed by Endocrine Sciences, Calabasas Hills, California.[17]

### Evaluation of Sexual Function and Mood

Evaluation by means of the Brief Index of Sexual Functioning for Women was repeated at the end of the base-line period and at week 12 of each treatment period. The scores are expressed here as a percentage of the mean values derived from a previous study of 187 normal women between the ages of 20 and 55 years who had regular sexual partners.[13]

A telephone-based diary was also used to assess the frequencies of sexual thoughts, desires, and activities on a daily basis for 28 days during the base-line period and for the last 28 days of each treatment period. The women called a toll-free telephone number and responded to a series of recorded questions by using the telephone keypad. An overall frequency index was calculated as the sum of the frequencies of sexual thoughts, desires, and activities during the 28-day period.

Mood was assessed with the Psychological General Well-Being Index, a validated 22-item, multiple-choice questionnaire[18] that has been used in previous studies of postmenopausal women.[9,19] The Psychological General Well-Being Index provides scores for vitality, self-control, well-being, general health, depressed mood, and anxiety and a composite score that ranges from 0 (most negative affective experience) to 110 (most positive affective experience).[18]

### Evaluation of Safety

Scores for hirsutism on the scale of Lorenzo (possible range, 0 to 20, with higher scores indicating greater hirsutism),[15] scores for acne on the scale of Palatsi et al. (possible range, 0 to 3, with higher scores indicating more acne),[14] facial-depilation rate (the number of times in the previous month that hair was removed from the chin or upper lip), serum lipid concentrations, fasting serum glucose concentrations, serum insulin concentrations, blood counts, indicators of liver function, and frequency of hot flashes were determined at base line and at the end of each treatment period. Tolerance of the skin to the transdermal systems and the occurrence of adverse events were recorded throughout the study.

### Statistical Analysis

The primary efficacy end points were the composite score on the Brief Index of Sexual Functioning for Women and the overall frequency index from the telephone-based diary. Secondary end points included the scores for the various dimensions of the Brief Index of Sexual Functioning for Women and the composite and subscale scores from the Psychological General Well-Being Index. An intention-to-treat analysis was performed on data from all the women who completed the Brief Index of Sexual Functioning for Women at least once during treatment. Least-squares means corresponding to each treatment were estimated by a repeated-measures analysis of variance, with terms for period, sequence, and carryover effects (persistent effects from the preceding treatment period) included in the model.[20] Pairwise comparisons of values for each active dose with those for placebo (with base-line values subtracted) were performed with t-tests based on analysis of variance. On the basis of the categorical responses to question 7 of the Brief Index of Sexual Functioning for Women,[12,13] the percentages of women who reported having sexual fantasies, masturbating, or engaging in sexual intercourse at least once a week were estimated for descriptive purposes. In a post hoc analysis, composite and dimension scores on the Brief Index of Sexual Functioning for Women were analyzed for the subgroups of women who were less than 48 years old (the median age of the enrolled population) and those who were 48 or older. Serum hormone values during each treatment period were averaged and compared by analysis of variance.

## RESULTS

Seventy-five women were enrolled in the study and received at least one dose of transdermal study medication. The base-line characteristics of these 75 women are shown in Table 1. Eighteen women withdrew or were withdrawn from the study because of adverse events (three while receiving placebo, one while receiving 150 μg of testosterone per day, and two while receiving 300 μg of testosterone per day), poor compliance with the telephone diary (six women), or personal reasons (six women). Sixty-five women who had at least one evaluation for efficacy during treatment were included in the intention-to-treat analyses of scores on the Brief Index of Sexual Function-

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE 75 WOMEN.

| CHARACTERISTIC | VALUE |
|---|---|
| Age — yr | |
| Mean | 47 |
| Range | 31–56 |
| Body-mass index | |
| Mean | 25.8 |
| Range | 19.5–33.5 |
| Race or ethnic group — no. (%) | |
| White | 62 (83) |
| Black | 8 (11) |
| Hispanic | 4 (5) |
| Asian | 1 (1) |
| Years since oophorectomy and hysterectomy | |
| Mean | 4.7 |
| Range | 1–10 |
| Marital status — no. (%) | |
| Married | 66 (88) |
| Cohabiting | 7 (9) |
| Single, not cohabiting | 2 (3) |
| Dose of conjugated equine estrogens — no. (%) | |
| 0.625 mg/day | 41 (55) |
| 0.9 mg/day | 12 (16) |
| 1.25 mg/day | 20 (27) |
| 1.8 mg/day | 1 (1) |
| 2.5 mg/day | 1 (1) |
| Previous androgen therapy — no. (%) | |
| Yes | 23 (31) |
| No | 52 (69) |

ing for Women, the telephone-based diary, and the Psychological General Well-Being Index.

#### Serum Hormone Concentrations

The mean serum concentrations of free and bioavailable testosterone remained at low or low-normal values during placebo treatment, increased to mid-normal values during treatment with 150 μg of testosterone per day, and increased to high-normal values during treatment with 300 μg of testosterone per day (Table 2). The mean serum concentrations of total testosterone and dihydrotestosterone also increased and exceeded the respective normal ranges during treatment with 300 μg of testosterone per day. The mean serum concentration of sex hormone–binding globulin was high at base line because the women were taking oral conjugated equine estrogens and decreased slightly during testosterone treatment. The serum concentrations of dehydroepiandrosterone sulfate, estrone, estradiol, luteinizing hormone, and follicle-stimulating hormone did not change significantly during treatment.

#### Effects on Sexual Function and Mood

The mean (±SD) composite score on the Brief Index of Sexual Functioning for Women, expressed as a percentage of the mean value for normal women,[13] increased from 52±27 percent at base line to 72±38 percent during placebo treatment, 74±37 percent during treatment with 150 μg of testosterone per day, and 81±37 percent during treatment with 300 μg of testosterone per day ($P=0.05$ for the comparison with placebo) (Table 3). The scores for thoughts–desire, frequency of sexual activity, and pleasure–orgasm were lowest at base line and increased in a dose-dependent fashion. With the testosterone dose of 300 μg per day, the increases in scores for frequency of sexual activity and pleasure–orgasm were significantly greater than those with placebo ($P=0.03$ for both comparisons). The score for problems affecting sexual function was 116±48 percent of the normative mean at base line and decreased to 98±49 percent during treatment with 300 μg of testosterone per day ($P=0.07$ for the comparison with placebo).

To illustrate how the prevalence of particular types of sexual behavior varied during treatment, the following descriptive statistics were derived from the Brief Index of Sexual Functioning for Women. The percentage of women who reported having sexual fantasies at least once a week was 12 percent at base line, 10 percent during placebo treatment, 18 percent during treatment with 150 μg of testosterone per day, and 24 percent during treatment with 300 μg of testosterone per day. The percentage of women who reported masturbating at least once a week was 3 percent at base line, 5 percent during placebo treatment, and 10 percent during treatment with either 150 or 300 μg of testosterone per day. Finally, the percentage of women who engaged in sexual intercourse at least once a week was 23 percent at base line, 35 percent during treatment with either placebo or 150 μg of testosterone per day, and 41 percent during treatment with 300 μg of testosterone per day.

Compliance with the 28-day telephone-based diary was problematic and led to the withdrawal of six women. Missing calls averaged about four per month (14 percent of the data). The mean overall frequency index of sexual thoughts, desires, and activities was 13±12 events per month at base line and increased similarly by 5±12 events per month during treatment with placebo, 7±13 events per month during treatment with 150 μg of testosterone per day, and 6±13 events per month during treatment with 300 μg of testosterone per day. Although this index is less sensitive to treatment effects than the Brief Index of Sexual Functioning for Women, the changes in the overall frequency index of the telephone-based diary correlated significantly with the changes in the composite score on the Brief Index of Sexual Functioning for Women ($r=0.54$ for placebo; $r=0.66$ for 150 μg of testosterone per day; $r=0.58$ for 300 μg of testosterone per day; $P<0.001$ for all regimens). On the basis of the analysis-of-variance models used to analyze these primary outcome measures, there were no statistically significant effects of the treatment period, sequence, or carryover.

**TABLE 2.** MEAN (±SD) SERUM HORMONE CONCENTRATIONS IN THE WOMEN AT BASE LINE AND DURING EACH TREATMENT PERIOD.*

| HORMONE† | BASE LINE | PLACEBO | 150 μg OF TESTOSTERONE PER DAY | 300 μg OF TESTOSTERONE PER DAY | NORMAL RANGE‡ |
|---|---|---|---|---|---|
| Free testosterone (pg/ml) | 1.1±0.7 | 1.2±0.8 | 3.9±2.4§ | 5.9±4.8§ | 1.3–6.8 |
| Bioavailable testosterone (ng/dl) | 2.0±1.4 | 2.2±1.3 | 7.1±4.1§ | 11.4±9.5§ | 1.6–12.7 |
| Total testosterone (ng/dl) | 21±10 | 22±12 | 64±25§ | 102±39§ | 14–54 |
| Dihydrotestosterone (ng/dl) | 7.6±4.0 | 8.4±4.8 | 17.8±7.0§ | 27.7±10.6§ | 4.4–20.4 |
| Sex hormone–binding globulin (nmol/liter) | 210±112 | 218±111 | 205±107¶ | 204±100§ | 36–185 |
| Dehydroepiandrosterone sulfate (μg/dl) | 61±34 | 60±34 | 58±33 | 57±34 | 60–255 |
| Estrone (pg/ml) | 148±114 | 130±133 | 143±110 | 146±88 | 32–159 |
| Estradiol (pg/ml) | 36±22 | 40±57 | 42±27 | 45±43 | 34–225 |
| Luteinizing hormone (mIU/ml) | 33.8±16.8 | 31.8±16.2 | 30.5±14.8 | 29.9±16.0 | 0.4–7.4 |
| Follicle-stimulating hormone (mIU/ml) | 42.7±22.8 | 41.4±21.1 | 39.0±20.4 | 38.2±20.9 | 1.7–7.2 |

*Seventy women with at least one hormone assessment during treatment were included in this analysis. All the women received conjugated equine estrogens throughout the study.

†To convert values for free testosterone to picomoles per liter, multiply by 3.467; to convert values for total and bioavailable testosterone to nanomoles per liter, multiply by 0.03467; to convert values for dihydrotestosterone to nanomoles per liter, multiply by 0.03444; to convert values for dehydroepiandrosterone sulfate to micromoles per liter, multiply by 0.02714; to convert values for estrone to picomoles per liter, multiply by 3.698; and to convert values for estradiol to picomoles per liter, multiply by 3.671.

‡The normal ranges in premenopausal women are from Endocrine Sciences, Calabasas Hills, California.

§$P<0.001$ for the comparison with placebo.

¶$P=0.002$ for the comparison with placebo.

**TABLE 3.** MEAN (±SD) SCORES ON THE BRIEF INDEX OF SEXUAL FUNCTIONING FOR WOMEN, EXPRESSED AS PERCENTAGES OF THE MEAN VALUES IN NORMAL WOMEN.*

| DIMENSION | BASE LINE | PLACEBO | 150 μg OF TESTOSTERONE PER DAY | 300 μg OF TESTOSTERONE PER DAY |
|---|---|---|---|---|
| Composite score | 52±27 | 72±38 | 74±37 | 81±37† |
| Thoughts–desire | 48±31 | 67±40 | 72±40 | 77±40 |
| Arousal | 58±31 | 80±40 | 73±40 | 84±40 |
| Frequency of sexual activity | 41±31 | 53±41 | 58±40 | 64±40‡ |
| Receptivity–initiation | 68±33 | 89±39 | 86±39 | 92±39 |
| Pleasure–orgasm | 48±42 | 65±53 | 70±52 | 80±52‡ |
| Relationship satisfaction | 73±33 | 82±32 | 86±32 | 87±32 |
| Problems affecting sexual function | 116±48 | 108±49 | 97±49 | 98±49 |

*Sixty-five women from the intention-to-treat analysis were included in this analysis. Values are expressed as percentages of the mean values in normal women with partners, which were as follows: composite score, 33.6; thoughts–desire, 5.3; arousal, 6.2; frequency, 3.9; receptivity–initiation, 8.9; pleasure–orgasm, 4.9; relationship satisfaction, 8.9; and problems, 4.5.[13] All women received conjugated equine estrogens throughout the study. Least-squares mean values were estimated by analysis of variance, with terms for period, sequence, and carryover effects included in the model. P values are for the comparisons between the values during testosterone treatment (with base-line values subtracted) and the values during placebo treatment (with base-line values subtracted).

†$P=0.05$.

‡$P=0.03$.

The mean composite score on the Psychological General Well-Being Index was 78±15 at base line and increased by 1±14 during treatment with placebo, 2±14 during treatment with 150 μg of testosterone per day, and 5±14 during treatment with 300 μg of testosterone per day (P=0.04 for the comparison with placebo) (Table 4). There also were increases with testosterone treatment (indicative of improved mood) on the vitality, positive-well-being, depressed-mood, and anxiety subscales, which were significant at a dose of testosterone of 300 μg per day for positive well-being and depressed mood (P=0.04 and P=0.03 for the respective comparisons with placebo).

A post hoc analysis of the influence of age on the scores on the Brief Index of Sexual Functioning for Women was performed by comparing the subgroups of women under the median age of 48 years (31 women) with those 48 years of age or older (34 women). At base line, the mean composite score was 50±28 percent in the younger women and 53±27 percent in the older women. During placebo treatment, the composite score increased to 80±42 percent in the younger women, and there was no further improvement during testosterone treatment. In the older women, the composite score increased to 63±36 percent during placebo treatment, 76±37 percent during treatment with 150 μg of testosterone per day (P=0.03 for the comparison with placebo), and 81±38 percent during treatment with 300 μg of testosterone per day (P=0.003 for the comparison with placebo). The serum free testosterone concentrations were similar at base line and during treatment in both subgroups.

**TABLE 4.** MEAN (±SD) SCORES ON THE PSYCHOLOGICAL GENERAL WELL-BEING INDEX.*

| INDEX SCALE† | BASE LINE | CHANGE WITH PLACEBO | CHANGE WITH 150 μg OF TESTOSTERONE PER DAY | CHANGE WITH 300 μg OF TESTOSTERONE PER DAY |
|---|---|---|---|---|
| Composite score | 78±15 | 1±14 | 2±14 | 5±14‡ |
| Anxiety | 17±4 | 0±4 | 0±4 | 1±4 |
| Depressed mood | 12±2 | 0±2 | 0±2 | 1±2§ |
| General health | 12±2 | 0±2 | 0±2 | 0±2 |
| Positive well-being | 12±3 | 0±3 | 1±3 | 2±3‡ |
| Self-control | 12±3 | 0±2 | 1±2 | 0±2 |
| Vitality | 12±4 | 0±4 | 1±4 | 1±4 |

*Sixty-five women from the intention-to-treat analysis were included in this analysis. All the women received conjugated equine estrogens throughout the study. Least-squares mean changes from base line were estimated by analysis of variance, with terms for period, sequence, and carryover effects included in the model. P values are for the comparisons between changes from base line during testosterone treatment and changes from base line during placebo treatment.

†The range of possible scores is as follows: composite score, 0–110; anxiety, 0–25; depressed mood, 0–15; general health, 0–15; positive well-being, 0–20; self-control, 0–15; and vitality, 0–20.[18] For all scales, lower scores indicate a more negative affective experience and higher scores indicate a more positive affective experience.

‡P=0.04.

§P=0.03.

### Safety

The hirsutism and acne scores did not change significantly during treatment (Table 5). The mean facial-depilation rate increased slightly during treatment with 300 μg of testosterone per day. The frequency of moderate or severe hot flashes averaged less than two per week at base line and was unaffected by testosterone treatment. The transdermal systems were well tolerated, with only one woman withdrawing because of a skin reaction caused by the placebo patches. Five serious adverse events occurred during the study. Four of these events (acute abdominal pain, angioplasty, bowel surgery, and a vasovagal episode) were considered to be unrelated to treatment; one (depression in a woman during placebo treatment) was considered to be possibly related. Treatment-related adverse events led four women to withdraw from the study (two who became anxious or agitated while receiving testosterone, one who had recurrence of a pink nipple discharge while receiving testosterone, and one with an application-site reaction). Transdermal testosterone treatment had no significant effects on the serum concentrations of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, or fasting glucose or insulin; blood counts; or the results of liver-function tests (Table 5).

## DISCUSSION

The women in this study had no ovarian androgen production and therefore had low serum concentrations of free and bioavailable testosterone at base line. These concentrations increased to the mid-normal and high-normal ranges, respectively, during transdermal treatment with 150 and 300 μg of testosterone per day. The supraphysiologic elevations in serum total testosterone and dihydrotestosterone at the higher dose were a consequence of the concomitant oral estrogen therapy, which raises serum concentrations of sex hormone–binding globulin[21] and reduces the clearance of androgens.[22,23] Serum estrogen concentrations did not change significantly during transdermal testosterone administration, indicating that aromatization of testosterone to estradiol[24] was minimal at the doses given.

Although they were receiving standard estrogen-replacement therapy, the base-line sexual function of the women was markedly impaired in comparison with that of normal women of similar age, as reflected by scores on the Brief Index of Sexual Functioning for Women.[13] The dimensions of thoughts–desire,

**TABLE 5.** MEAN (±SD) CLINICAL AND BIOCHEMICAL MEASURES AT BASE LINE AND DURING TREATMENT WITH TRANSDERMAL TESTOSTERONE PATCHES.*

| MEASURE† | BASE LINE | PLACEBO | 150 μg OF TESTOSTERONE PER DAY | 300 μg OF TESTOSTERONE PER DAY | NORMAL RANGE‡ |
|---|---|---|---|---|---|
| Androgenic skin effects | | | | | |
| Hirsutism score§ | 1.6±1.7 | 1.4±1.6 | 1.3±1.5 | 1.4±1.4 | NA |
| Acne score¶ | 0.03±0.2 | 0.05±0.2 | 0.02±0.2 | 0.08±0.3 | NA |
| Facial depilation‖ | 0.5±1.2 | 0.8±1.6 | 0.7±1.8 | 1.4±4.0** | NA |
| Serum lipids (mg/dl) | | | | | |
| Total cholesterol | 214±31 | 221±36 | 220±39 | 221±34 | 134–253 |
| HDL cholesterol | 70±15 | 73±18 | 71±17 | 70±17 | 34–80 |
| LDL cholesterol | 117±26 | 121±36 | 122±39 | 123±33 | 72–164 |
| Hematocrit (%) | 39.5±2.6 | 39.4±2.4 | 39.4±2.5 | 39.7±2.4 | 34.9–44.5 |
| Liver function | | | | | |
| Serum aspartate aminotransferase (U/liter) | 20±5 | 19±6 | 19±5 | 19±5 | 12–31 |
| Serum γ-glutamyltransferase (U/liter) | 20±13 | 19±11 | 17±8 | 19±14 | 6–29 |
| Serum albumin (g/dl) | 4.3±0.3 | 4.2±0.3 | 4.2±0.3 | 4.2±0.4 | 3.5–5.0 |

*Sixty-seven women with at least one assessment during treatment were included in this analysis. All the women received conjugated equine estrogens throughout the study.

†HDL denotes high-density lipoprotein, and LDL low-density lipoprotein. To convert values for cholesterol to micromoles per liter, multiply by 0.026.

‡The normal ranges are from Mayo Medical Laboratories, Rochester, Minnesota. NA indicates that normal ranges were not available.

§Hirsutism was measured by the scale of Lorenzo (possible range, 0 to 20, with higher scores indicating greater hirsutism).[15]

¶Acne was measured by the scale of Palatsi et al. (possible range, 0 to 3, with higher scores indicating more acne).[14]

‖Facial depilation was measured on an index ranging from 0 to 28 times per month.

**P=0.04 for the comparison with base line.

arousal, frequency of sexual activity, and pleasure–orgasm were most affected. Although sexual function improved during placebo treatment, treatment with 300 μg of testosterone per day was associated with significantly greater improvement.

We can only speculate as to the origin of the strong placebo response in our study, why it was greater in the younger women, and why it tended to mask further effects of testosterone. As a condition of enrollment, all the women in our study wanted their sex lives to be more active or satisfying. Participating in the clinical trial may have facilitated communication within couples. In addition, the visible presence of the transdermal patches (active or placebo) might have been a stimulus to some women or their partners to increase sexual activity. Because the younger women had been in shorter relationships than the older women (13 vs. 18 years), they may have felt greater pressure to improve their sexual functioning. Finally, despite the use of statistical models that included terms for sequence and carryover effects, the crossover design (without washout periods) could have inflated the placebo response or caused "ceiling effects" in some couples who altered their patterns of sexual activity early in the study and then maintained the new patterns.

In contrast to the Brief Index of Sexual Functioning for Women, the 28-day telephone-based diary was less sensitive to treatment effects, and missed reporting days were a problem. These results are consistent with those of a recent methodologic study in which the required daily telephone reporting of sexual activity met with poor compliance.[25]

In regard to psychological status, testosterone replacement had a beneficial effect on well-being and depressed mood. The differences in the scores on the Psychological General Well-Being Index between the placebo and testosterone periods in our study are similar to the differences in scores between women who received estrogen alone after hysterectomy and bilateral oophorectomy and women who underwent hysterectomy without oophorectomy.[9] As expected, the serum free testosterone concentrations were higher in the women with intact ovaries.[9]

Finally, transdermal testosterone was not associated with clinically important changes in acne, hirsutism, or laboratory-test results, nor did it negate the beneficial effects of oral estrogen-replacement therapy on hot flashes and serum concentrations of high-density lipoprotein cholesterol.

In summary, treatment with transdermal testoster-

one combined with oral conjugated equine estrogens increased the serum concentrations of free and bioavailable testosterone to within the normal ranges and was well tolerated. Treatment with the higher dose of testosterone improved sexual function and psychological well-being substantially more than placebo treatment.

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