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Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women

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Abstract

Objective: Circulating testosterone in women declines during the late reproductive years such that otherwise healthy women in their 40s have approximately half the testosterone level as women in their 20s. Despite this, research showing the benefits of androgen replacement has been limited to the postmenopausal years. In view of the known premenopausal physiological decline in testosterone, we have evaluated the efficacy of transdermal testosterone therapy on mood, well-being, and sexual function in eugonadal, premenopausal women presenting with low libido.

Design: Premenopausal women with low libido participated in a randomized, placebo-controlled, crossover, efficacy study of testosterone cream (10 mg/day) with two double-blind, 12-week, treatment periods separated by a single-blind, 4-week, washout period.

Results: Thirty-four women completed the study per protocol, with 31 women (mean age 39.7 ± 4.2 years; serum testosterone 1.07 + 0.50 nmol/L) providing complete data. Testosterone therapy resulted in statistically significant improvements in the composite scores of the Psychological General Well-Being Index [+12.9 (95% CI, +4.6 to +21.2), $P = 0.003$] and the Sabbatsberg Sexual Self-Rating Scale [+15.7 (95% CI, +6.5 to +25.0), $P = 0.001$] compared with placebo. A mean decrease in the Beck Depression Inventory score approached significance [−2.8 (95% CI, −5.7 to +0.1), $P = 0.06$]. Mean total testosterone levels during treatment were at the high end of the normal range, and estradiol was unchanged. No adverse effects were reported.

Conclusions: Testosterone therapy improves well-being, mood, and sexual function in premenopausal women with low libido and low testosterone. As a substantial number of women experience diminished sexual interest and well-being during their late reproductive years, further research is warranted to evaluate the benefits and safety of longer-term intervention.

Key Words: Female androgen insufficiency – Testosterone – Depression.

Total and free testosterone levels decline with age in premenopausal women such that women in their 40s have half the circulating levels of women in their 20s.[1] The levels remain stable across the menopausal transition[2] and then either remain stable or continue to decline with diminishing adrenal androgen production with increasing age.[4] In the decade preceding menopause, there is loss of the midcycle surge of free testosterone and androstenedione.[5] Thus, the proposed clinical manifestations of female androgen insufficiency–namely loss of libido, lowered mood, and fatigue[6]—may precede menopause but are not a consequence of natural menopause.[3] Published studies demonstrating beneficial effects of testosterone on sexual function[7-9,10-12] and mood and well-being[8,9,13,14] are limited to postmenopausal women, with no data regarding the effects of exogenous testosterone on sexual function and mood in premenopausal women. We undertook this study to investigate the efficacy of a physiological dose of testos-

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terone, administered as a transdermal cream, on well-being, mood, and sexual function in otherwise healthy premenopausal women who considered themselves to have low libido. As there is no defined level of testosterone below which women can be said to be deficient,[6] we did not recruit women on the basis of their having "low" testosterone but rather excluded women for whom we believed testosterone therapy would be contraindicated. For this we arbitrarily excluded women with a testosterone level in the upper quartile of the normal range and above.

METHODS

Study participants

The study involved premenopausal women (based on regular menstrual cycles and follicle-stimulating hormone less than 20 mIU/mL) with the following characteristics: 30 to 45 years of age, a body mass index between 18 and 35 kg/m^2, diminished sexuality (Sabbatsberg Sexual Self-Rating Scale[15] score less than 42[16]), no evidence of severe clinical depression on the Beck Depression Inventory (score less than 28),[17] and early morning serum total testosterone of less than 2.2 nmol/L. All participants were in general good health based on history and physical examination and had a normal cervical smear within the past year. The protocol permitted the inclusion of women using an oral contraceptive (OC). Women planning a pregnancy were excluded. Women who had relationship problems, poor feelings for their partner, or dyspareunia were excluded, as were women receiving pharmacotherapy for depression, taking medication known to interfere with normal sexual function (such as beta-blockers and alpha-blockers), or those who had received oral androgen therapy in the previous 3 months or androgen injections or implants in the previous 12 months. Women with a history of acne or hirsutism, estrogen related cancer, confirmed thromboembolic disease, a previous cerebrovascular accident, uncontrolled hypertension (blood pressure > 160/95 mm Hg), unstable cardiovascular disease (a myocardial infarction or coronary or peripheral angioplasty within preceding 3 months), genital bleeding of unknown cause, alcohol intake of more than 30 g/day, insulin-dependent diabetes mellitus or unstable noninsulin-dependent diabetes mellitus, homozygous familial hypercholesterolemia, abnormal liver function tests, or taking medications known to interfere with sex steroid metabolism were also excluded. The use of thyroid hormone was acceptable if the dose was expected to remain stable throughout the study.

The risk of virilization of a female fetus with testosterone excess was included in the participant information and consent form and was reinforced at screening. Necessity of contraception was stressed, and all participants received contraceptive counseling. Any woman who declined contraception was excluded.

Participants were recruited from the Jean Hailes Center, Melbourne, Australia, and from the general population via television and radio announcements over a 6-month period commencing April 2000. The study was completed in April 2001. The protocol was approved by the Human Research and Ethics Committee, Monash Medical Center, Melbourne, Australia, and all participants gave written informed consent.

Study design

The protocol was a placebo-controlled, crossover design with two double-blind, 12-week treatment periods separated by a single-blind, 4-week, washout period. Participants were randomly assigned to the order in which they received testosterone or placebo treatment. During each treatment period, participants self-administered either 10 mg of testosterone 1% cream to the thigh on a daily basis or an equal amount of identical-appearing placebo cream with the dose being based on an earlier pharmacokinetic study.[18] During the washout period, all women self-administered placebo cream in a single-blind manner. Measurements were taken at screening and then on four visits. Visit 1 was the baseline measurement at the start of period 1; visit 2 was at 12 weeks, the end of period 1; visit 3 was the baseline measurement at the start of period 2; and visit 4 was at 28 weeks, the end of period 2. All participants were required to have a pregnancy test at each visit. The active and placebo creams were supplied, packaged and randomized by Lawley Pharmaceuticals (Perth, Australia).

Serum hormone measurements

Serum total testosterone, sex hormone-binding globulin (SHBG), and estradiol (E_2) were measured at baseline and at each visit, in morning blood samples taken after day 7 and before day 28 of the menstrual cycle. This was done because testosterone is typically low in the early follicular phase but rises and remains at a relatively constant higher level throughout the mid to late follicular phase and the luteal phase.[19] Thyroid stimulating hormone, prolactin and follicle-stimulating hormone were measured at screening. Hormone analyses were performed by the Department of Clinical

Pathology, Southern Health, Melbourne, Australia.[11] Total testosterone was measured using the Bayer ACS 180 Automated Chemiluminescence System with a coefficient of variation at 1.7 nmol/L (50 ng/dL) of 13.8%. Free androgen index (FAI) was calculated as total testosterone nmol/L divided by SHBG nmol/L $\times$ 100.[20]

Evaluation of well-being, mood, and sexual function

Overall general well-being was assessed with the Psychological General Well-Being Index, a validated 22-item, multiple-choice questionnaire.[21] It includes subscales for anxiety, depressed mood, positive well-being, self-confidence, general health, and vitality. The composite score ranges from 0 (most negative affective experience) to 110 (most positive affective experience). Depressed mood was assessed by the Beck Depression Inventory, a widely used, validated questionnaire that contains 13 variables to assess mood and depression.[17] Possible scores ranged from 0 (minimal depression) to 63 (severe depression). The Sabbatsberg Sexual Self-Rating Scale[15] is a multiple-choice questionnaire containing seven aspects of sexuality (sexual interest, sexual activity, satisfaction of sexual life, experience of sexual pleasure, sexual fantasy, orgasm capacity, and sexual relevancy), which has been validated in premenopausal women.[16] Possible composite scores range from 0 (low sexuality) to 84 (high sexuality). Each of the three questionnaires was self-administered at screening, at baseline, and at each study visit.

Evaluation of safety

At each visit, hirsutism was evaluated using the Ferriman and Gallwey score.[22] Acne and voice changes were also assessed clinically by the same physician, who was blinded to treatment allocation. Any adverse events or changes in medication were recorded.

Statistical analysis

Primary endpoints were the composite score on the Psychological General Well-Being Index and Sabbatsberg Sexual Self-Rating Scale. Secondary endpoints included the Beck Depression Inventory, subscale scores for the Psychological General Well-Being Index and Sabbatsberg Sexual Self-Rating Scale, and hormone profiles including total testosterone, SHBG, FAI, and E_2. Analysis included all women who completed the study and for whom there was complete data from the questionnaires and hormone assays. Data obtained at baseline in the first period (visit 1) and at the end of the washout period (visit 3, which is baseline of the second period) were tested for differences with a repeated-measures analysis of variance in both treatment groups to determine the strength of any carry-over effect. The primary analysis consisted of a repeated-measures analysis of variance to compare, between treatment groups, within-subject changes over the course of a treatment period, assuming no carry-over effect of testosterone on aspects of sexuality. A secondary analysis was necessary for the composite and subscale scores of the Sabbatsberg Sexual Self-Rating Scale because of the presence of a carry-over effect. This analysis consisted of fitting a maximum likelihood linear model to the outcome measurements, with a random subject effect and with fixed effects for time period (first or second 12 weeks), time in period (baseline or end of 12-week period), treatment period (testosterone or placebo), sequence (testosterone period first or placebo period first), an interaction between treatment period and time in period (which was the treatment effect of interest) and a carry-over effect of previous treatment period that was assumed to exist only for the baseline measurement in the subsequent treatment period.[23]

An intention-to-treat analysis was undertaken using two imputation strategies to handle missing data. The first was an endpoint analysis where the participant's last observation was carried forward, such that the participant's last known state is included in the analysis. The second was a worst-case analysis such that imputed values resulted in an overall treatment effect favoring placebo. For participants dropping out in the first period of the crossover study, baseline data was imputed for remaining entries. If dropout occurred in the second period of the crossover study, imputed values were dependent on treatment being received at the time of dropout, given the crossover nature of this study design. For participants on placebo at the time of dropout, the higher of the baseline or week-16 values were imputed so that overall treatment effect was in favor of placebo; whereas, for participants on active treatment, the lower of the baseline or visit-16 values were imputed so that overall treatment effect was against active treatment.

Statistical analyses were undertaken with Stata (Version 6.0, Texas, 1999). Baseline data were summarized as means, standard deviations, and range to describe the study participants. Treatment outcomes are summarized as means and standard deviations, or means and 95% CIs. A P value of 0.05 is considered significant, and all P values are two-tailed.

RESULTS

A total of 61 women were screened, of which 49 were enrolled in the study and underwent randomization. Reasons for exclusion included testosterone above 2.2 nmol/L, elevated Beck Depression Inventory score, or irregular menstrual bleeding. Thirty-four women completed the study according to protocol; complete data was available for 31 women, with questionnaire data for week 28 missing in 3 women. One woman withdrew so that she could conceive after completing the baseline visit only. Three women withdrew because of inability to attend follow-up visits—two after completing the baseline visit only, one on placebo and one on active treatment; one after completing 22 weeks of the study while on placebo. Two women were lost to follow-up—one after completing the baseline visit only, and the other after completing 12 weeks of the study; both were using placebo at the time. Nine women withdrew for perceived lack of treatment effect—two after completing the baseline visit only, one after completing 6 weeks of the study, five after completing 16 weeks of the study, and the other after completing 22 weeks of the study. At withdrawal, seven of these women were using placebo. The two women who withdrew while on active treatment had received testosterone for less than 6 weeks. Six of the nine women who withdrew for perceived lack of treatment effect commenced antidepressant therapy. No significant difference was found among women who did and did not complete the study in relation to age, body mass index, baseline hormone levels, or baseline composite score on the Psychological General Well-Being Index, Beck Depression Inventory, or Sabbatsberg Sexual Self-Rating Scale. Six women used a combined OC throughout the study period, and exclusion of these women from statistical analysis did not change the outcome for any parameter.

Effect on serum hormone levels

At baseline, the mean total testosterone was within the lower third of the normal female reproductive range for the 31 women who completed the study per protocol (Table 1). The mean serum total testosterone increased by 0.22 nmol/L (95% CI, +0.01 to +0.42) with placebo and 1.54 nmol/L (95% CI, +1.01 to +2.07) with testosterone. The FAI increased by 0.4 (95% CI, +0.1 to +0.8) with placebo and 3.6 (95% CI, +2.0 to +5.1) with testosterone. The mean values for total testosterone remained within the normal female reproductive range, whereas the mean FAI rose to above the upper limit of normal with testosterone treatment. No change was seen in serum E_2 (Table 2).

TABLE 1. *Clinical and serum hormone characteristics of the 31 women at baseline*

Characteristic	Value
Age (y)	
Mean ± SD	39.7 ± 4.2
Range	32-45
Body mass index (kg/m2)	
Mean ± SD	25.1 ± 3.6
Range	17.9-33.7
Psychological General Well-Being Index	
Mean ± SD	74.1 ± 16.6
Range	39-98
Beck Depression Inventory	
Mean ± SD	7.6 ± 6.3
Range	0-21
Sabbatsberg Sexual Self-Rating Scale	
Mean ± SD	26.7 ± 10.7
Range	5-51
Total testosterone (nmol/L)	
Mean ± SD	1.07 ± 0.50
Range	0.3-2.1
Normal range	*0.5-2.7*
Sex hormone binding globulin (nmol/L)	
Mean ± SD	62.5 ± 25.1
Range	27-129
Normal range	*18-114*
Free androgen index	
Mean ± SD	2.0 ± 1.1
Range	0.4-4.8
Normal range	*0-4.5*
Estradiol (pmol/L)	
Mean ± SD	448 ± 360
Range	60-1667
Normal follicular phase range	*143-694*

To convert values for total testosterone to ng/dL, divide by 0.035.
To convert values for estradiol to pg/mL, divide by 3.671.
The free androgen index is total testosterone/sex hormone-binding globulin × 100.

Effect on general well-being, mood, and sexual function

Statistically significant improvements of 12.9 and 15.7 units were seen on the composite scores for Psychological General Well-Being Index and Sabbatsberg Sexual Self-Rating Scale, respectively, with testosterone in the per protocol analysis (Table 3). A mean decrease in the Beck Depression Inventory score did not achieve statistical significance. Of note was the statistical lack of placebo effect for all the parameters measured (CIs crossing 1.0). The composite score for the Psychological General Well-Being Index increased by 9.2 (95% CI, +2.5 to +15.9) with testosterone, compared with a decrease of −3.7 (95% CI, −8.8 to +1.4) with placebo. The beneficial effect of testosterone was seen for all subscale scores of the Psychological Gen-

TABLE 2. *Mean serum hormone concentrations at baseline and after 12 weeks of treatment*

Hormone	Baseline mean ± SD	Treatment mean ± SD	Treatment effect[a] mean (95% CI)	*P* value	Normal range[b]
Total testosterone (nmol/L)					
Placebo	0.87 ± 0.52	1.09 ± 0.44		0.000	0.5-2.7
Testosterone	1.04 ± 0.59	2.58 ± 1.22	+1.33 (+0.77, +1.88)		
Sex hormone-binding globulin (nmol/L)					
Placebo	62.9 ± 24.8	64.9 ± 29.0		0.115	18-114
Testosterone	62.0 ± 26.7	56.7 ± 26.6	−7.4 (−16.5, +1.8)		
Free androgen index					
Placebo	1.6 ± 1.1	2.0 ± 1.3		0.000	0.0-4.5
Testosterone	1.9 ± 1.3	5.5 ± 4.1	+3.1 (+1.6, +4.7)		
Estradiol (pmol/L)					
Placebo	409 ± 346	623 ± 1762	−225 (−901, +451)	0.508	143-694[c]
Testosterone	422 ± 340	410 ± 438			

Baseline values were measured at the beginning of week 1 or week 16, and treatment values were measured at the end of week 12 or week 28. *P* values are for the difference between treatment groups, by repeated analysis of variance. To convert values for total testosterone to ng/dL, divide by 0.035. To convert values for estradiol to pg/mL, divide by 3.671. The free androgen index is total testosterone/sex hormone-binding globulin × 100.

[a]Mean effect of testosterone–mean effect of placebo.

[b]The normal ranges in premenopausal women are from the Department of Clinical Pathology, Southern Health, Melbourne, Australia.

[c]Follicular phase range.

TABLE 3. *Mean composite scores on the Psychological General Well-Being index, Sabbatsberg Sexual Self-Rating Scale and Beck Depression Inventory*

	Visits 1, 2			Visits 3, 4			Mean effect		
Assessment method	Visit 1 (wk 0) mean	Visit 2 (wk 12) mean	Visit 2 - Visit 1 mean (95% CI)	Visit 3 (wk 16) mean	Visit 4 (wk 28) mean	Visit 4 - Visit 3 mean (95% CI)	Mean (95% CI) testosterone effect	Mean (95% CI) placebo effect	Mean (95% CI) treatment effect
Psychological General Well-Being[a] (range 0–110)									
T//P *n* = 18	73.1	82.6	+9.5 (+1.7, +17.3)	78.6	72.4	−6.2 (−12.8, +0.4)	+8.9 (+2.2, +15.7)	−3.7 (−8.8, +1.4)	+12.6 (+4.3, +20.9) *P* = 0.004
P//T *n* = 13	75.3	74.9	−0.4 (−9.3, +8.5)	74.2	82.4	+8.3 (−5.0, +21.5)			
Sabbatsberg Sexual Self-Rating Scale[a] (range 0–84)									
T//P *n* = 18	24.0	36.2	+12.2 (+2.5, +21.8)	33.0	30.1	−2.9 (−11.1, +5.3)	+14.9 (+7.0, +22.8)	−0.9 (−6.1, +4.3)	+15.7 (+6.5, +25.0) *P* = 0.001
P//T *n* = 13	30.5	32.4	+1.9 (−4.2, +8.1)	26.9	45.5	+18.6 (+3.8, +33.4)			
Beck Depression Inventory[b] (range 0–63)									
T//P *n* = 18	7.9	5.4	−2.5 (−6.1, +1.1)	6.6	7.9	+1.3 (−2.5, 5.1)	−2.7 (−4.9, −0.5)	+0.1 (−1.9, 2.0)	−2.8 (−5.7, +0.1) *P* = 0.062
P//T *n* = 13	7.1	5.4	−1.7 (−8.1, +4.8)	6.7	3.7	−3.0 (−9.0, +3.0)			

Baseline values were measured at the beginning of week 1 (visit 1) or week 16 (visit 4), and treatment values were measured at the end of week 12 (visit 3) or week 28 (visit 6). *P* values are for the difference among treatment groups, by repeated analysis of variance. T, testosterone; P, placebo.

[a]Higher scores indicate a more positive effect on well-being/better sexual function.

[b]Higher scores indicate a higher severity of depressive symptoms.

TABLE 4. *Mean composite and subscale scores on the Psychological General Well-Being Index at baseline and after 12 weeks of treatment*

	Baseline mean ± SD	Treatment mean ± SD	Treatment effect mean (95% CI)	*P* value	Range
Psychological General Well-Being[a]					
Placebo	77.2 ± 15.4	73.5 ± 16.9	+12.9 (+4.6 to +21.2)	0.003	0-110
Testosterone	73.6 ± 18.7	82.5 ± 16.3			
Anxiety					
Placebo	17.5 ± 3.9	16.1 ± 4.6	+3.2 (+0.8 to +5.6)	0.009	0-25
Testosterone	16.7 ± 4.7	18.5 ± 4.5			
Depressed mood					
Placebo	12.3 ± 2.6	12.0 ± 2.8	+1.3 (0.0 to +2.5)	0.053	0-15
Testosterone	12.1 ± 2.3	13.2 ± 2.4			
Positive well-being					
Placebo	12.3 ± 3.7	11.8 ± 4.0	+2.4 (+0.6 to +4.2)	0.009	0-20
Testosterone	11.6 ± 4.0	13.5 ± 3.2			
Self confidence					
Placebo	12.1 ± 2.6	11.5 ± 3.0	+1.5 (+0.2 to +2.7)	0.024	0-15
Testosterone	11.8 ± 3.3	12.6 ± 3.0			
General health					
Placebo	11.7 ± 2.0	11.3 ± 2.7	+1.3 (+0.3 to +2.3)	0.014	0-15
Testosterone	11.0 ± 2.5	11.9 ± 2.0			
Vitality					
Placebo	11.4 ± 4.1	10.9 ± 3.4	+3.1 (+0.8 to +5.4)	0.010	0-15
Testosterone	10.4 ± 5.1	12.7 ± 4.7			

Baseline values were measured at the beginning of week 1 or week 16, and treatment values were measured at the end of week 12 or week 28. *P* values are for the difference among treatment groups, by repeated analysis of variance.
[a]Higher scores indicate a more positive effect on well-being.

eral Well-Being Index, as shown in Table 4. The mean score with testosterone decreased by −2.7 (95% CI, −4.9 to −0.5) compared with an increase of 0.1 (95% CI, −1.9 to +2.0) with placebo. The difference in effect between testosterone and placebo approached statistical significance (P = 0.06). (See Table 3). The mean composite score on the Sabbatsberg Sexuality Scale increased by 14.9 (95% CI, +7.0 to +22.8) with testosterone but decreased by −0.9 (95% CI, −6.1 to +4.3) with placebo. The beneficial effect of testosterone on sexual function was seen for all subscale scores except for "importance of sex," as shown in Table 5. Preliminary analysis indicated the presence of a carry-over effect for the composite and subscale scores of the Sabbatsberg Sexual Self-Rating Scale in the group treated with testosterone in period 1. The composite score for the Sabbatsberg Sexual Self-Rating Scale remained elevated, at a mean of 33.0, in the testosterone-treated group after the 4-week washout period, compared with a visit 1 mean of 24.0 (P = 0.017 for the difference) (Table 3). From the maximum likelihood linear model, the average improvement in composite Sabbatsberg Sexual Self-Rating Scale score with testosterone compared with placebo treatment was 14.3 (95% CI, +1.2 to +27.3). In terms of relevance to clinical practice, 46% of women achieved a 50% or greater increase in their total sexual self-rating score with testosterone treatment, versus only 19% of women during placebo treatment (*P* = 0.030).

Intention to treat analysis

Using the endpoint imputation strategy for missing data, the composite score for the Psychological General Well-Being Index increased by 9.2, the composite Sabbatsberg Sexual Self-Rating Scale score increased by 6.0, and the Beck Depression Inventory score decreased by 2.1. These changes correspond to treatment effects of +13%, +24% and −26%, respectively. For the worst-case imputation strategy, the composite score for the Psychological General Well-Being Index increased by 7.5, the composite Sabbatsberg Sexual Self-Rating Scale score increased by 5.1, and the Beck Depression Inventory score decreased by 1.6, corresponding to treatment effects of +11%, +20% and −16%, respectively.

Safety

The hirsutism score did not change significantly with either testosterone or placebo. It increased by 0.10 (95% CI, −0.14 to +0.34) with testosterone and decreased by −0.06 (95% CI, −0.35 to +0.22) with placebo. The difference in effect between testosterone and placebo was +0.16 (95% CI, −0.20 to +0.52). None of

TABLE 5. *Mean composite and subscale scores on the Sabbatsberg Sexuality Scale at baseline and after 12 weeks of treatment*

	Baseline mean ± SD	Treatment mean ± SD	Treatment effect mean (95 percent CI)	*P* value	Range
Sabbatsberg Sexuality Scale[a]					
Placebo	31.9 ± 14.2	31.1 ± 14.2	+15.7 (+6.5 to +25.0)	0.001	0-84
Testosterone	25.2 ± 10.7	40.1 ± 19.5			
Sexual interest					
Placebo	3.7 ± 2.1	3.5 ± 2.3	+3.0 (+1.3 to +4.6)	0.001	0-12
Testosterone	2.7 ± 1.7	5.5 ± 3.1			
Sexual activity					
Placebo	3.8 ± 2.1	3.8 ± 2.1	+2.3 (+0.7 to +3.8)	0.006	0-12
Testosterone	3.2 ± 1.6	5.5 ± 3.0			
Satisfaction of sexual life					
Placebo	4.7 ± 2.4	4.5 ± 2.4	+2.4 (+0.8 to +4.0)	0.004	0-12
Testosterone	3.3 ± 2.0	5.5 ± 3.3			
Sexual pleasure					
Placebo	5.1 ± 2.2	4.7 ± 2.4	+2.2 (+0.7 to +3.7)	0.004	0-12
Testosterone	4.0 ± 1.8	5.7 ± 2.9			
Sexual fantasy					
Placebo	3.9 ± 2.3	3.6 ± 2.4	+2.7 (+1.3 to +4.1)	0.000	0-12
Testosterone	3.1 ± 1.7	5.6 ± 3.0			
Orgasm					
Placebo	4.8 ± 2.4	4.4 ± 2.9	+2.1 (+0.7 to +3.5)	0.005	0-12
Testosterone	3.9 ± 2.0	5.6 ± 2.8			
Importance of sex					
Placebo	5.9 ± 2.9	6.5 ± 2.4	+1.1 (−0.3 to +2.5)	0.108	0-12
Testosterone	4.9 ± 2.7	6.6 ± 2.9			

Baseline values were measured at the beginning of week 1 or week 16, and treatment values were measured at the end of week 12 or week 28. *P* values are for the difference among treatment groups, by repeated analysis of variance.
[a]Higher scores indicate better sexual function.

the women developed acne or experienced voice change by self-report or clinical assessment. Application of the transdermal cream was well tolerated, with no women reporting any skin reactions. No serious adverse event occurred.

DISCUSSION

We have demonstrated substantial and clinically meaningful improvements in psychological and sexual well-being with transdermal testosterone therapy in healthy premenopausal women who were not clinically depressed and who did not have profound sexual dysfunction but did have the primary complaint of low libido. The only other distinguishing feature of the women in this study was a mean total serum testosterone level in the low normal female range when measured in the morning and outside the menstrual phase. We did not exclude OC users who met all other criteria. Although we would encourage OC users to use another contraceptive method if lowered testosterone induced side effects, rather than addition of testosterone therapy, we accept that, for many women, OC use is the optimal therapy.

The Psychological General Well-Being Index was developed to measure affective states to reflect subjective well-being or distress. It has been applied to the general population in the national Health and Nutrition Examination Survey sample,[24] in which the average composite score was 80.3. Baseline composite score and subscale scores in this study were similar to values reported for oophorectomized women treated with estrogen alone.[9] Treatment with testosterone in our study and that of Shifren et al restored general well-being to average levels seen in the general population.[9,24] The magnitude of improvement in mood with testosterone treatment, as assessed by the Beck Depression Inventory and the Psychological General Well-Being subscale relating to depressed mood, may be clinically relevant. However, the former was just outside the limit of statistical significance.

The improvement in the composite score of the Sabbatsberg Sexual Self-Rating Scale was large and persisted after accounting for a carry-over effect of testosterone treatment even after 4 weeks of treatment washout. Not only did the mean sexual score increase from being in the lowest quartile for premenopausal women to the median for such women,[16] but nearly half of the women had a 50% improvement in their individual sexual function score. These effects on sexual function have not been previously demonstrated in premenopausal women. Lack of placebo effect for all end-

points is an interesting observation but not an unexpected one and may reflect a low level of susceptibility in the group of women enrolled.

Low testosterone has been closely correlated with reduced coital frequency and loss of sexual desire in women of different ages.[25-27] In young healthy women, free testosterone is correlated with libido and frequency of masturbation.[28] Furthermore, antiandrogens depress female sexual function.[29] The favorable effects of testosterone on mood and libido, as seen in our study, may be mediated either directly via the androgen receptor or more likely as a consequence of conversion of testosterone to E_2 in critical areas of the brain.[30] The improvements in mood and well-being may underpin the restoration of sexual desire, key components of which are drive and motivation;[31] conversely, improved sexual interest may have improved intimate relationships, thus enhancing well-being. Chronic testosterone therapy improves vasomotor function in estrogenized, postmenopausal women.[12] Acutely supraphysiological testosterone administration enhances vaginal pulse amplitude and self-reported sexual responsiveness to erotic videos in young eugonadal women.[32] Hence, testosterone may also improve sexual responsiveness by enhancing vaginal blood flow and lubrication.[33]

The transdermal application of the cream resulted in total testosterone levels in the high normal range, with values for the FAI crossing the upper limit of normal. None of the participants developed any virilizing features as a consequence of therapy, and the cream was well tolerated. However, as the potential for excessive use exists in clinical practice, we recommend routine measurement of serum testosterone levels before each patient review visit. Cognizant of the potential risk of virilization of a female fetus with exogenous testosterone, we were insistent on adequate contraception for all participants. However, virilization of a fetus does not appear to be tightly correlated with maternal testosterone levels, with the occurrence limited to women exhibiting masculinization,[34,35] a side effect that did not occur with the dose of testosterone we administered.

To best describe the efficacy of testosterone, the analysis included only women with complete data sets for biochemistry and questionnaires. Of the 15 women who did not fulfill these criteria, 12 were using placebo at the time of discontinuation. Seven of the nine who discontinued for lack of benefit were using placebo, and the two lost to follow-up never received active therapy. Given that discontinuations were more frequent during treatment with placebo and as a result of perceived lack of benefit from treatment, we can be reasonably confident that analysis of data of the participants who remained in the trial, and hence provided the data on which our treatment effect is estimated, will underestimate any true benefit from testosterone treatment in comparison with placebo.

An intention-to-treat analysis was also undertaken, given the number of dropouts. Various strategies for dealing with missing data in clinical trials have been described.[36] A guiding aim in these strategies is one of conservatism, such that imputation of missing data errs on the side of caution with respect to the size of treatment effect in comparison with placebo. Given that our complete-case analysis likely provides a conservative estimate of treatment effect, the results of our intention-to-treat analysis could be viewed as ultraconservative

CONCLUSIONS

In summary, we have demonstrated significant efficacy of transdermal testosterone therapy in women in their mid to late reproductive years on well-being and sexual function, such that women with values below average for a healthy population normalized. Because testosterone levels seem to decline from the mid reproductive years, our findings have considerable implications in terms of the psycho-sexual health of women in their latter premenopausal years and indicate that larger effectiveness studies addressing this issue are warranted.

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