

Comparative effects of oral esterified estrogens with and without methyltestosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire

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Objective: In some women, a decline in sexual interest accompanies a relative androgen insufficiency after menopause. We sought to characterize the hormonal effects of the combination of oral esterified estrogens and methyltestosterone and to investigate whether this regimen improves hypoactive sexual desire.

Design: Double-blind randomized trial.

Setting: Healthy volunteers in a multicenter research environment.

Patient(s): Postmenopausal women taking estrogen therapy who were experiencing hypoactive sexual desire.

Intervention(s): 4 months of treatment with 0.625 mg of esterified estrogens (n = 111) or the combination of 0.625 mg of esterified estrogens and 1.25 mg of methyltestosterone (n = 107).

Main Outcome Measure(s): Baseline and end-of-study measurements of total and bioavailable testosterone and sex hormone-binding globulin (SHBG), and mean change in level of sexual interest or desire as rated on the Sexual Interest Questionnaire.

Result(s): Treatment with the combination of esterified estrogens and methyltestosterone significantly increased the concentration of bioavailable testosterone and suppressed SHBG. Scores measuring sexual interest or desire and frequency of desire increased from baseline with combination treatment and were significantly greater than those achieved with esterified estrogens alone. Treatment with the combination was well tolerated.

Conclusion(s): Increased circulating levels of unbound testosterone and suppression of SHBG provide a plausible hormonal explanation for the significantly improved sexual functioning in women receiving the combination of esterified estrogen and methyltestosterone. (Fertil Steril® 2003;79:1341–52. ©2003 by American Society for Reproductive Medicine.)

Key Words: Estratest, methyltestosterone, hypoactive sexual interest, sex hormone-binding globulin

Although a definitive role of testosterone at physiologic doses has not been established in postmenopausal women, testosterone replacement continues to be evaluated as an adjunct to estrogen replacement therapy for surgically menopausal women and those with premature ovarian failure. Many studies (1–8) have evaluated testosterone replacement, but interpretation of the findings has been difficult. In addition,

the most effective formulation required for achieving therapeutic effects remains to be defined, resulting in the assessment of various formulations and dosages. Sensitive instruments designed specifically for assessing sexual function in postmenopausal women are lacking, and the aspects of sexual function mediated by the interventions have been unspecified.

Received August 19, 2002;
revised and accepted
December 13, 2002.

Supported by a grant from
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Inc.

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0015-0282/03/\$30.00
doi:10.1016/S0015-0282(03)
00358-3

A further limitation of some studies has been lack of parallel measurement of circulating levels of bioavailable testosterone and SHBG to provide a physiologic framework for understanding how endocrine status influences sexual functioning. In trials in which such information has been reported, measurements have been inconsistent because various different assays have been used.

With regard to the aspects of female sexual function predominantly affected by testosterone, several investigators (1, 2, 5) have proposed that androgen influences sexual motivation (central arousal or interest, loosely referred to as "libido") but not activity or response variables, such as vaginal lubrication and orgasm. This notion is consistent with the hypothesis that androgen in women primarily affects behavior, which is directly related to sexual motivation but not to the frequency of sexual activity or to the orgasmic response (9, 10).

The Sexual Interest Questionnaire (SIQ) is an unidimensional self-report scale that has been designed specifically to measure two domains of sexual function in postmenopausal females: desire (level of desire before menopause, current level of desire, degree of distress with current level, importance of desire, satisfaction with current level, frequency of sexual thoughts or fantasies) and sexual responsiveness (satisfaction with frequency of sexual activity, frequency of desire to engage in sexual activity).

We sought to characterize the effects of the combination of esterified estrogens and methyltestosterone on circulating levels of SHBG and total and bioavailable testosterone and to investigate the effects of oral methyltestosterone on improving hypoactive sexual desire in adequately estrogenized postmenopausal women. Another goal was to determine whether correlations exist between changes in SIQ scores and concentrations of bioavailable testosterone.

MATERIALS AND METHODS

Design

We performed a double-blind, randomized, controlled study of the combination of esterified estrogen and methyltestosterone versus esterified estrogen alone to treat postmenopausal women with loss of sexual interest or desire. The study, which was approved by the respective institutional review boards, was conducted in parallel at 20 centers in the United States. Before enrollment, all patients gave written informed consent.

Participants

The target population was healthy postmenopausal women (natural or surgical for ≥ 6 months) 40 to 65 years of age receiving estrogen who experienced hypoactive sexual interest or desire associated with the onset of menopause and who did not have overt mood disorders. To qualify for enrollment, women had to have a history of adequate sexual interest before the onset of menopause; to have been receiv-

ing the equivalent of 0.625 mg of conjugated equine estrogens for 3 or more months (women treated with the equivalent of 0.9 mg could qualify if the dose were decreased for the last cycle immediately before study screening); and to be in a stable, monogamous, heterosexual relationship.

Before enrollment, the women completed the Brief Index of Sexual Functioning for Women (BISF-W) and the SIQ. The BISF-W is a 22-item, validated, self-report instrument for the assessment of current levels of female sexual functioning and satisfaction (11). The SIQ was validated in a parallel study of 111 non-symptomatic postmenopausal women 40 to 65 years of age (i.e., healthy women receiving estrogen replacement and not experiencing diminished sexual desire associated with the onset of menopause). They were selected from postmenopausal women attending the clinical sites at which the study was conducted. Women qualified for the validation study on the basis of scoring higher than 3.0 on the Thoughts/Desire Dimension of the BISF-W and having the same or higher level of sexual interest as before menopause or no more than a one-level decrease since menopause.

After a screening interview, qualified non-clinical subjects completed the SIQ and BISF-W at the initial clinic visit and once at home, approximately 1 month later. Their ratings were compared with responses from the first 100 clinical patients who participated in this study. Analysis of variance, the Cronbach α coefficient, and the intraclass and Pearson correlation coefficients. The data validating the SIQ will be the subject of a separate article.

Statistically significant differences ($P < .001$) between the clinical and nonclinical groups were observed for the SIQ desire domain, SIQ total score, the BISF-W Thoughts/Desire Dimension, and the BISF-W Composite Score. Test-retest reliability was high ($r = 0.79$) for the nonclinical control group. Convergent validity was established, with high correlation coefficients, for the SIQ desire items compared to the BISF-W Thoughts/Desire Dimension, used as the gold standard. It was concluded that the SIQ was psychometrically robust, with demonstrated ability to discriminate between symptomatic and nonsymptomatic postmenopausal women in terms of low sexual desire.

The Screening SIQ consists of four items to be rated only at screening, whereas the Monthly SIQ contains ten items to be rated at baseline and at monthly intervals during drug administration. The items are rated over the past week on a seven-point scale evaluating desire, frequency of desire, and responsiveness (orgasm and pleasure). To qualify for the study, component scores measuring desire had to indicate hypoactive desire (≤ 3.0 on the Thoughts/Desire Dimension [items 3 and 4] of the BISF-W [1 standard deviation below the mean] and a deficit of two or more points from the premenopausal level of desire as measured on items 1 and 2 of the Screening SIQ).

Women were excluded if they had dyspareunia, unresolved or recent sexual abuse; depressive or anxiety symptoms or physical limitations that interfered with normal sexual functioning; an abnormal mammogram; relevant clinical laboratory test abnormalities; or recent previous high-dose estrogen replacement therapy, other sex hormones, lipid-lowering agents, antidepressants (including selective serotonin-reuptake inhibitors), anxiolytics, thyroid replacement medication (unless a stable dose), or antihypertensive drugs.

The study was conducted according to the provisions of the Declaration of Helsinki as revised in 1996, and in adherence to International Conference on Harmonization guidelines for good clinical practice. The local ethics review committees approved the protocol, and written informed consent was obtained from all participants.

Treatment and Study Procedures

After a 2-week screening/run-in period during which patients received esterified estrogen (0.625 mg/d), qualified patients were randomized in a 1:1 ratio to daily treatment with esterified estrogens (0.625 mg) and methyltestosterone (1.25 mg) (Estratest-HS; Solvay Pharmaceuticals, Inc., Marietta, GA) or esterified estrogens (0.625 mg) alone (Estratab; Solvay Pharmaceuticals, Inc.) for 16 weeks. The randomization schedule prepared by the Biometrics Department of Solvay Pharmaceuticals, Inc., was provided to each center. To achieve blinding, patients received either an active esterified estrogens and methyltestosterone tablet plus an esterified estrogen placebo tablet or a placebo esterified estrogens and methyltestosterone tablet plus an active esterified estrogen tablet.

Patients were evaluated with the SIQ and BISF-W after 4, 8, 12, and 16 weeks of treatment.

Serum total testosterone was measured by recombinant immunoassay after extraction and celite chromatography. Intra- and inter-assay coefficients of variation were 6% and 13.5%, respectively. The assay does not cross-react with methyltestosterone. Free testosterone was calculated as the product of total and percent dialyzable free testosterone, according to the method of Vermeulen et al. (12). The intra- and inter-assay coefficients of variation were 5% and 6.6%. Bioavailable testosterone was calculated as the product of total testosterone and the percent unbound to SHBG after ammonium sulfate precipitation. The intra- and inter-assay coefficients of variation were 6% and 11%. Sex hormone-binding globulin was measured by immunoradiometric assay (radioimmunoassay). Serum estrone E_1 and E_2 were measured by recombinant immunoassay after extraction and LH 20 column chromatography. For E_1 , the intra- and inter-assay coefficients of variation were 12% and 7.0%, and for E_2 , they were 3.2% and 9.2%.

All hormone assays were performed by Esoterix, Inc., Calabasas Hills, California. Only endocrine data from 41

randomized patients were excluded from analysis because of concerns about the specificity of the radioimmunoassays used at a different laboratory.

In women with an intact uterus, endometrial biopsy was performed on the last study visit. All women were prescribed a progestogen after the endometrial biopsy.

Safety and tolerability were assessed by physical examination, biochemical and hematologic evaluations (including lipids), blood pressure, body weight, spontaneously reported adverse events, determinations of scores for hirsutism on the scale of Lorenzo (13), and acne on the scale of Palatsi et al. (14).

Statistical Analysis

The intention-to-treat approach was used for data analysis. The primary efficacy end point was the mean change from baseline at week 16 in the level of sexual interest or desire, as rated on item 1 of the monthly SIQ. Secondary and exploratory end points included SIQ dimensions of frequency of desire, responsiveness, and total SIQ score, and frequency and pleasure/orgasm dimensions on the BISF-W. Mean changes in SIQ scores and serum hormone levels for each treatment were compared by analysis of variance. Statistical tests were carried out using both "visit-wise" (observed cases) and last-observation-carried-forward data. All statistical tests were two-sided, with an α level of .05.

Criteria for defining markedly abnormal hepatic enzymes were set at two times the upper limit of normal for γ -glutamyltransferase and at three times the upper limit of normal for alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase.

Post hoc analysis of the data was performed to assess the possibility of an association between the treatment effect on scores of the various sexual dimensions as assessed on the SIQ and BISF-W and serum levels of bioavailable testosterone. Linear trends were evaluated by regression analysis and were considered significant if the respective P values were less than .05.

RESULTS

Of the 421 women screened, 200 failed to qualify for randomization. The most frequent reasons for failure to qualify were symptoms of depression or anxiety, too high a score on the BISF-W Thoughts/Desire dimension (i.e., normal libido), use of medications, no previous receipt of estrogen replacement therapy, and abnormal laboratory values. Of the 221 women enrolled in the study, post-randomization data were available for 218 women, of whom 107 received esterified estrogen and methyltestosterone and 111 received esterified estrogen alone.

The baseline characteristics of each treatment group were well matched (Table 1). Thirty-six women were prematurely withdrawn from the study because of adverse events, lack of

TABLE 1

Baseline characteristics of the sample.

Characteristic	EE/MT group (n = 107)	EE group (n = 111)
Mean age (range) (y)	52.9 ± 5.7 (40–65)	53.8 ± 5.7 (40–65)
Mean body mass index (range) (kg/m ²)	25.5 ± 4.6 (18.4–44.4)	26.7 ± 5.4 (17.3–47.1)
Race (%)		
White	90.7	92.8
Black	5.6	3.6
Hispanic	2.8	1.8
Other	0.9	1.8
Mean time since menopause (y)		
Mean (±SD)	6.9 ± 6.0 (1–31)	7.3 ± 6.0 (1–27)
Range		
Type of menopause (%)		
Natural	69.2	68.5
Surgical	30.8	31.5
Marital status (%)		
Married	84.1	81.1
Single, separated, divorced, or widowed, not cohabitating	15.9	18.9
Highest educational level (%)		
Graduate school or college	72.0	78.3
High school	28.0	21.7
Brief Index of Sexual Functioning for Women Score (items 3 and 4)	1.8 ± 1.0	1.7 ± 1.2
Sexual Interest Questionnaire score ^a		
Desire before menopause	5.29 ± 1.00	5.19 ± 0.97
Desire after menopause	1.81 ± 0.74	1.85 ± 0.77
Distress due to low desire	4.63 ± 1.71	4.79 ± 1.75

Note: EE = esterified estrogens; EE/MT = esterified estrogen and methyltestosterone.

^a 7-point scale.

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efficacy, or administrative reasons (20 in the esterified estrogens and methyltestosterone group and 16 in the esterified estrogen group) (Fig. 1).

Serum Hormone Concentrations

Baseline levels of total and bioavailable testosterone were similar in both treatment groups and consistent with levels seen in postmenopausal women and those who have undergone oophorectomy (12, 15) (Table 2). During therapy with esterified estrogen, the mean serum concentrations of total and bioavailable testosterone remained essentially unchanged from baseline. In contrast, the mean serum concentration of bioavailable testosterone significantly increased, approximately doubling between baseline and the end of the study in patients receiving esterified estrogen and methyltestosterone ($P < .010$) for between-treatment difference.

Total testosterone levels decreased modestly, reaching significance ($P < .010$) in patients receiving combination therapy; compared with recipients of esterified estrogen alone, the treatment difference was significant ($P = .020$). Serum concentrations of SHBG were high at baseline in both groups because the women were taking esterified estrogens. No important change from baseline in SHBG levels was observed in patients treated with esterified estrogen, but a significant ($P < .010$) decrease occurred in patients receiving combination therapy ($P < .010$ for treatment difference).

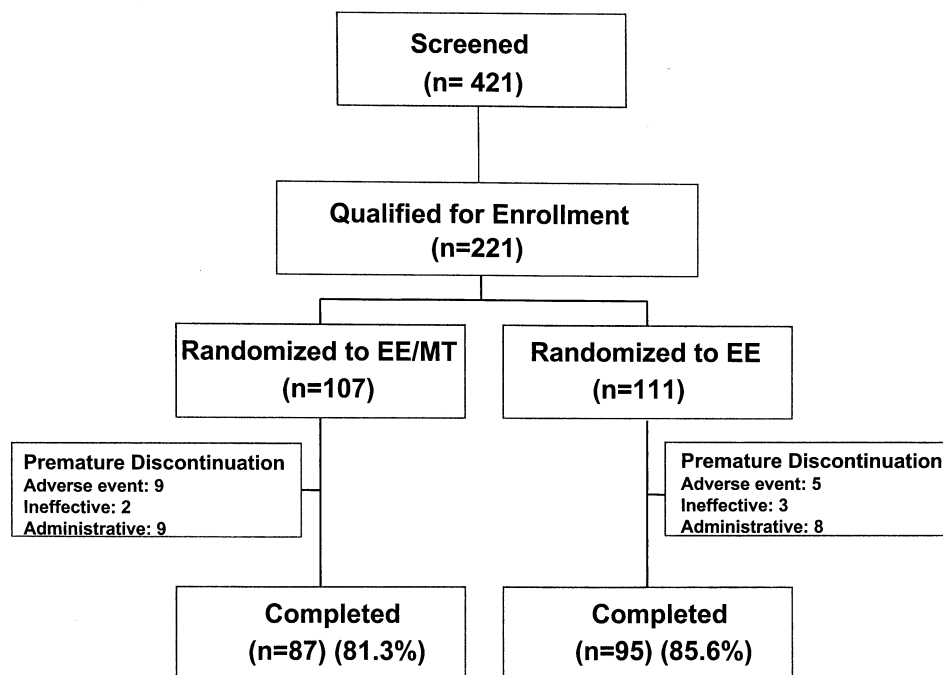
At baseline, estrogen levels were in the expected range for women receiving replacement therapy. Unexpectedly, a significant between-treatment difference was found for E₁ concentrations, with lower levels in the combination therapy group. The patterns of the changes from baseline in sex hormones and SHBG for each treatment group in the subgroups defined by type of menopause (natural vs. surgical) were similar to those observed in the overall sample.

Effects on Sexual Function

The primary efficacy variable was the change from baseline in the level of sexual interest or desire as rated on the SIQ. The mean (±SD) sexual interest/desire score of the SIQ at the end of the study was significantly greater in women treated with combination therapy than those receiving esterified estrogen alone ($2.8 ± 1.6$ vs. $2.4 ± 1.4$, respectively; $P = .047$) (Table 3). Both treatments produced increases in the SIQ sexual interest/desire score beginning as early as week 4, but the magnitude of the improvement was consistently greater with esterified estrogens and methyltestosterone, with the treatment difference reaching significance at week 16 (Fig. 2A). The major impact of esterified estrogens and methyltestosterone treatment on the score for this dimension was achieved by week 8, with modest further improvement by week 16.

FIGURE 1

Recruitment of the sample. EE = esterified estrogen; EE/MT = esterified estrogen and methyltestosterone.



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The score measuring the dimension of frequency of interest/desire at the end of study was higher in the esterified estrogens and methyltestosterone group than in the esterified estrogen group, but the trend failed to reach significance (3.2 ± 1.5 vs. 2.9 ± 1.6 ; $P = .133$). The change in the frequency of interest/desire score over differed significantly from baseline in the combination therapy group beginning at week 8 and persisted with little additional increase through the end of the study (Fig. 2B).

The SIQ responsiveness score showed a greater than twofold improvement in patients treated with esterified estrogens and methyltestosterone compared to patients treated with esterified estrogen alone (3.3 ± 5.6 vs 1.3 ± 4.7 ; $P = .002$). The mean total SIQ score and change from baseline in mean total SIQ score were similar to those for the frequency of desire.

The changes from baseline in BISF-W dimensions were exploratory efficacy variables, and the dimension scores corresponding to sexual interest/desire as rated on the SIQ are Sexual Thoughts/Desires and Composite Sexual Function. Each showed an improvement with combination therapy compared with esterified estrogen alone, although the difference between groups was of borderline significance ($P = .057$).

Post hoc analysis of the influence of age, race, and type of menopause (natural vs. surgical) on the change from baseline in the SIQ scores was performed. No difference in response was seen between naturally menopausal women and those who had undergone oophorectomy, and changes in scores were similar regardless of age or race.

For the overall sample, no correlation was found between change from baseline on individual items of the SIQ and change in mean hormone levels. However, for the subgroup of women with baseline SHBG levels in the normal range (80 to 250 nmol/L), highly significant correlations were observed between change of bioavailable testosterone and changes in interest ($r = .329$; $P = .015$), responsiveness ($r = .464$; $P < .001$), and total score on the SIQ ($r = .431$, $P = .001$) (Fig. 3).

Safety

Treatment with esterified estrogens and methyltestosterone was well tolerated. Most adverse effects in both treatment groups were trivial and not thought to be related to the study drug. The total number of women with one or more adverse events was slightly higher in the combination therapy group than in the esterified estrogen group (64.5% vs. 57.7%, respectively) (Table 4). Among common adverse events, the ones for which the incidence was relevantly higher in patients receiving combination therapy were head-

TABLE 2

Change in endocrine variables^a.

Variable	EE/MT group	EE group	P value for treatment difference ^b
Total testosterone (ng/dL) ^c			
Baseline	18.9 ± 8.4	20.8 ± 1.1	
Change from baseline	-3.7 ± 6.8	-0.1 ± 7.4	.020
P for change ^b	<.010	.905	
Bioavailable testosterone (pg/mL) ^d			
Baseline	2.7 ± 1.5	3.1 ± 2.7	
Change from baseline	2.0 ± 2.0	-0.3 ± 2.4	<.010
P for change ^b	<.010	.264	
SHBG (nmol/L) ^e			
Baseline	160.6 ± 91.4	164.7 ± 99.8	
Change from baseline	-104.2 ± 80.3	-18.2 ± 76.7	<.010
P for change ^b	<.010	.053	
DHEA-S (μg/dL) ^f			
Baseline	60.3 ± 32.1	63.7 ± 35.6	
Change from baseline	2.3 ± 17.6	-0.6 ± 20.7	.357
P for change ^b	.312	.806	
Androstenedione (ng/dL) ^g			
Baseline	63.3 ± 25.2	67.3 ± 24.6	
Change from baseline	-1.8 ± 25.7	-2.0 ± 27.5	.907
P for change ^b	.600	.553	
Total E ₂ (pg/mL) ^h			
Baseline	36.2 ± 35.3	33.6 ± 25.8	
Change from baseline	-9.6 ± 47.0	3.1 ± 32.6	.112
P for change ^b	.133	.459	
E ₁ (pg/mL) ⁱ			
Baseline	94 ± 73	94 ± 96	
Change from baseline	-11 ± 81	35 ± 104	<.010
P for change ^b	.306	.010	

Note: Values are mean ± SD. DHEA = dehydroepiandrosterone; EE = esterified estrogens; EE/MT = esterified estrogen/methyltestosterone; SHBG = sex hormone-binding globulin.

^a Endocrine data from a total of 41 randomized patients were excluded from analysis because of concern regarding the specificity of the immunoradioassay used at one laboratory.

^b By analysis of variance.

^c Normal menopausal range, 7–40 ng/dL.

^d Normal range in women, 1.1–4.3 pg/mL.

^e Normal range, 28–112 nmol/L.

^f Normal range, 20–157 μg/dL.

^g Normal range, 30–120 ng/dL.

^h Normal value in menopause <20 pg/mL.

ⁱ Normal value in menopause <40 pg/mL.

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ache (9.3% vs. 7.2%), infection (9.3% vs. 6.3%), and acne (5.6% vs. 2.7%). Adverse events led to the premature withdrawal of 9 (8.4%) patients receiving combination therapy and methyltestosterone and 5 (4.5%) patients randomized to esterified estrogen. Among patients treated with esterified estrogens and methyltestosterone, only two specific events leading to withdrawal occurred in 2 or more patients (hot flashes in 3 patients and acne in 2 patients). Neither of the latter adverse events led to premature withdrawal in patients randomized to esterified estrogen.

Serious adverse events were reported in one patient randomized to combination therapy (cellulitis/stomatitis) and in

two patients receiving esterified estrogen (one case of duodenitis and one case of cholecystitis). Only the episode of cholecystitis was considered related to the study drug. Hirsutism and acne scores at the end of treatment showed no significant between-treatment differences (Table 5).

At the final assessment, two patients (one in each treatment group) had abnormal findings on biopsy indicating hyperplasia of the endometrium; both lacked cytologic atypia. It was not possible to determine whether these results represented an abnormal shift from baseline because endometrial biopsy was not performed at screening for either participant: The protocol stated that no biopsy was required

TABLE 3

Sexual Dimension Scores on the Sexual Interest Questionnaire.

Dimension	EE/MT group (n = 107)	EE group (n = 109)	P value for between-group difference ^a
Item 1: sexual interest/desire (range, 1–7)			
Baseline	2.1 ± 1.3	2.1 ± 1.1	
Change at week 16	0.8 ± 1.6	0.3 ± 1.4	.024
P for change	<.010	.018	
Level of frequency of interest/desire (range, 1–7)			
Baseline	2.6 ± 1.3	2.8 ± 1.4	
Change at week 16	0.6 ± 1.4	0.0 ± 1.4	<.010
P for change	<.010	.738	
(Items 7–10: responsiveness): (range, 4–28) ^b			
Baseline	9.07 ± 4.44	10 ± 4.92	
Change at week 16	3.29 ± 5.55	1.28 ± 4.65	.002
P for change	<.001	.005	
Total (range, 10–70)			
Baseline	22.3 ± 9.1	23.7 ± 9.4	
Change at week 16	7.3 ± 11.9	2.9 ± 10.5	<.010
P for change	<.010	<.010	

Note: EE = esterified estrogens; EE/MT = esterified estrogen and methyltestosterone.

^a Using least-square mean.

^b Data available for 106 EE/MT recipients and 110 EE recipients.

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if participants were asymptomatic and were taking a progestin for endometrial protection before the study.

No combination therapy recipient had markedly abnormal hepatic enzymes at the final visit, whereas one esterified estrogen recipient had an elevated γ -glutamyltransferase level at the end of the study. All other liver enzymes for this participant were within normal limits. The γ -glutamyltransferase level was deemed not clinically significant by the investigator, and no repeated laboratory tests were performed.

Combination therapy recipients had a significant ($P < .010$) decrease from baseline in total cholesterol level (-16.8 ± 26.1 mg/dL) compared with monotherapy recipients (2.4 ± 26.1 mg/dL). The between-treatment difference was significant ($P < .010$) (Table 6). At baseline, both treatment groups were in the desirable range for high-density lipoprotein (HDL) cholesterol (67.4 ± 15.6 mg/dL in the combination therapy group and 64.2 ± 15.4 mg/dL in the monotherapy group). At week 16, the combination therapy group had a significant decrease (-12.4 ± 11.4 mg/dL [$-17.5\% \pm 14.9\%$]; $P < .010$) and the esterified estrogen recipients had a significant increase (3.2 ± 11.0 mg/dL [$7.8\% \pm 29.3\%$]; $P < .010$) in HDL cholesterol level ($P < .010$ for between-treatment difference).

The ratio of total cholesterol to HDL cholesterol significantly increased from baseline in the combination therapy group (3.4 ± 0.9 to 3.9 ± 1.0 ; $P < .010$) and significantly decreased in the esterified estrogen recipients (3.5 ± 1.2 to 3.4 ± 0.9 ; $P = .046$). However, individual data showed that only 6 women (5.7%) receiving combination therapy had

HDL cholesterol levels less than 35 mg/dL at the end of study (the median baseline HDL level for these women was 46.5 mg/dL).

Low-density lipoprotein cholesterol levels remained unchanged from baseline in both groups. Combination therapy recipients showed a significant decrease (-31.1 ± 51.8 mg/dL [$-20.5\% \pm 34.3\%$]; $P < .010$) in triglyceride levels, whereas esterified estrogen recipients showed no change (-7.5 ± 50.0 mg/dL [$-0.7\% \pm 34.6\%$]; $P = .147$).

DISCUSSION

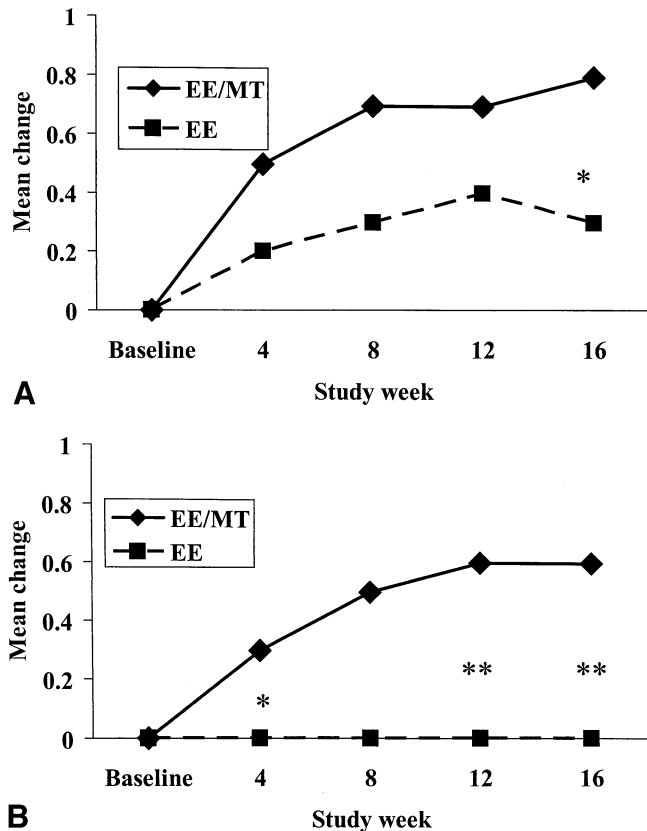
In this double-blind, randomized study, treatment with the combination of 0.625 mg of esterified estrogens and 1.25 mg of methyltestosterone increased the mean concentration of bioavailable testosterone and suppressed SHBG. These observations imply that oral estrogen-androgen therapy increases the bioavailable fraction of testosterone by decreasing circulating SHBG levels.

In parallel with the increase in bioavailable testosterone, SIQ scores measuring the level of sexual interest/desire and frequency of sexual interest/desire increased from baseline with combination therapy and were significantly greater than those observed in patients receiving esterified estrogen alone. By week 8 of randomized treatment, the majority of the effect on scores of the sexual dimensions had been achieved.

Reduction in circulating levels of SHBG by exogenous testosterone is well documented (16), and the associated increase in bioavailable testosterone that we observed was

FIGURE 2

(A), Mean scores of sexual desire as measured by item 1 of the Sexual Interest Questionnaire. * $P < .02$ vs. baseline; ** $P < .01$ vs. baseline. (B), Mean scores for frequency of desire as measured by items of the Sexual Interest Questionnaire. * $P < .05$ vs. baseline. EE = esterified estrogen; EE/MT = esterified estrogen and methyltestosterone.



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also reported by others investigating androgen replacement therapy in women (8). However, as far as we are aware, our study is the first to find a significant association between changes in female sexual interest or desire and responsiveness and concentrations of bioavailable testosterone. This finding suggests that the improvement in sexual interest or desire in postmenopausal women associated with esterified estrogens and methyltestosterone treatment may be explained, at least in part, by the effect of methyltestosterone in decreasing levels of SHBG, yielding increased concentrations of bioavailable testosterone. In addition, some of the improvement in sexual interest or desire may be directly attributable to circulating levels of methyltestosterone, in that methyltestosterone is biologically as potent as testosterone (15).

The significant positive effect of esterified estrogens and methyltestosterone on measures of sexual interest and desire

observed in our trial are consistent with the findings of other studies demonstrating improvement in several aspects of sexuality in postmenopausal women treated with different combinations of testosterone and estrogen replacement (3, 5, 7). Sherwin et al. (1, 2) found that 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 in oophorectomized women. Shifren et al. (8) found that transdermal testosterone, 300 $\mu\text{g}/\text{d}$, compared with placebo had significant effects on frequency of sexual activity and pleasure and orgasm, but not on thoughts and desire. Using a different design, Myers et al. (6) reported that conjugated equine estrogens and methyltestosterone treatment did not significantly alter mood ratings, sexual behavior, or psychophysiologically measured sexual arousal.

The administration of much higher doses of methyltestosterone as hormonal therapy for cancer has been associated with an increase in liver function disorders (17). Recent data do not support any detrimental effects of low-dose methyltestosterone on hepatic enzymes or blood pressure over 24 months (18, 19). Thus, the safety profile of esterified estrogens and methyltestosterone appears to be acceptable when dosing avoids supraphysiologic testosterone levels.

Legitimate concerns exist about the masculinizing effects, such as hirsutism, acne, and lowering of voice, of androgen replacement therapy. On the basis of symptom scale scores, treatment with esterified estrogens and methyltestosterone was not associated with clinically important changes in acne or hirsutism.

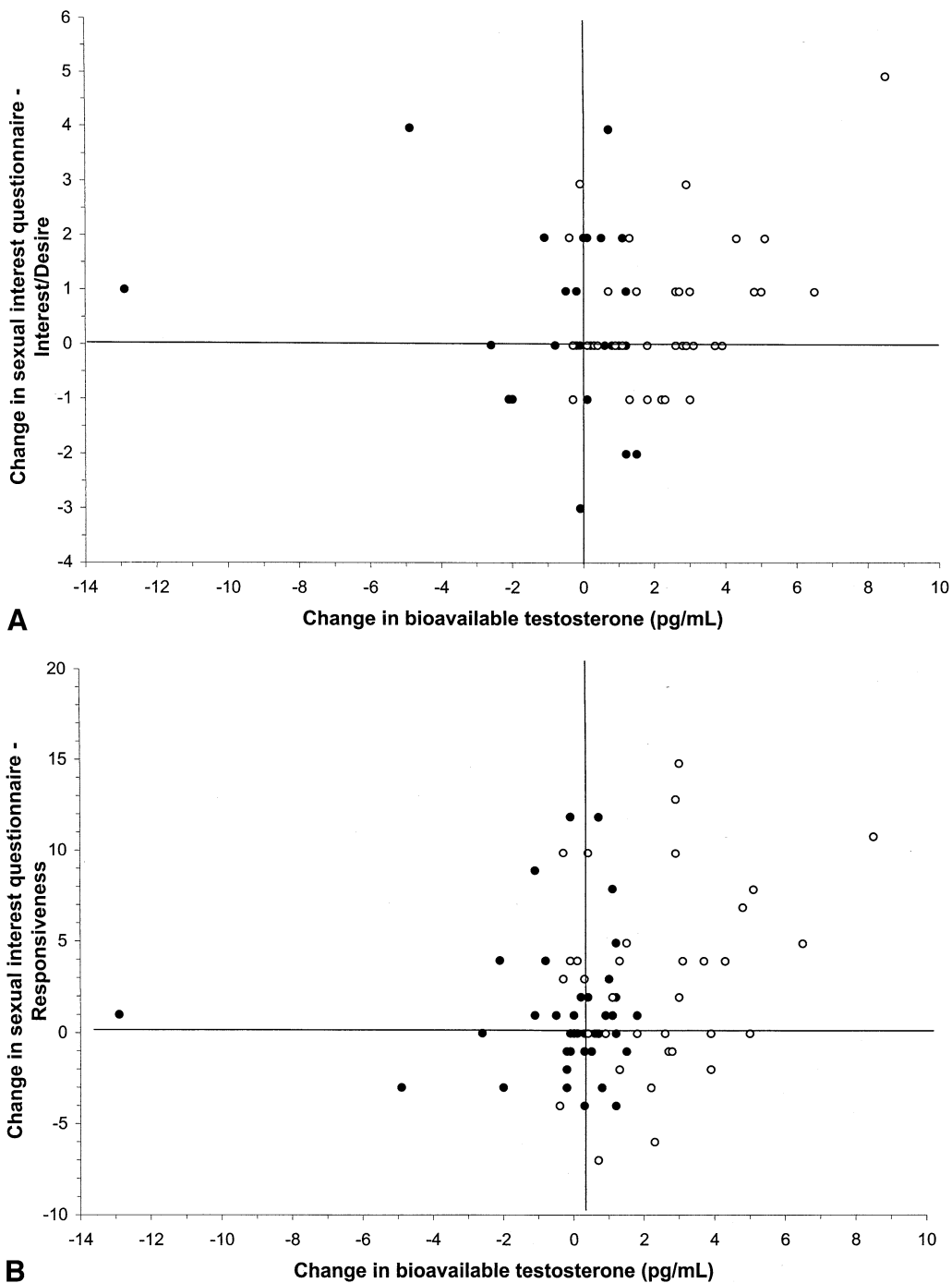
The changes in serum lipids observed in the present trial are consistent with the known effects of androgens on lipids (20) and match the results of other trials evaluating esterified estrogens and methyltestosterone (18, 21, 22).

The unwanted 17.5% decrease in HDL cholesterol level associated with esterified estrogens and methyltestosterone treatment was opposed by a favorable 20.5% decrease in triglyceride level. The clinical significance of these collective changes in serum lipids in the present context is not known.

Libido is a complex and highly subjective end point that is affected by hormonal and nonhormonal factors. No standardized instrument was available at the time of our study to measure sexual interest or desire in postmenopausal women. In particular, the libido questions on the BISF-W might not be responsive to change; these were used to select the sample. The SIQ, a newer instrument intended for evaluating response to treatment in clinical trials, was developed specifically to assess sexual interest and desire in postmenopausal women. It was validated in women selected from the same community sample as the participants, and it successfully differentiates symptomatic from nonsymptomatic women (unpublished data).

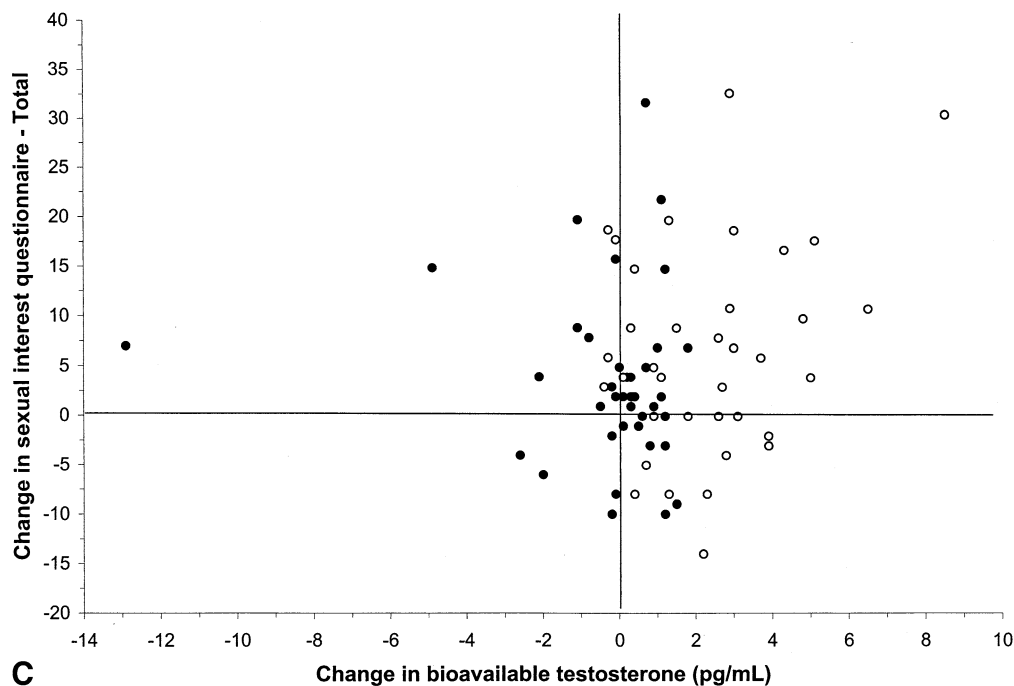
FIGURE 3

Association between change in Sexual Interest Questionnaire Interest score (A), Responsiveness score (B), and total score (C), and change in bioavailable testosterone concentrations from baseline to week 16. Each open circle and closed circle represents a single participant receiving esterified estrogen and methyltestosterone or esterified estrogens alone, respectively. The majority of open circles cluster in the right upper quadrant of the graph, indicating a significant correlation between an increase in bioavailable testosterone and improvement in Sexual Interest Questionnaire score in combination therapy recipients.



Lobo. Methyltestosterone endocrine profiles. *Fertil Steril* 2003.

FIGURE 3 CONTINUED



C Lobo. Methyltestosterone and endocrine profiles. *Fertil Steril* 2003.

The dimension of sexual desire was selected as the primary efficacy parameter because it is more responsive to the action of androgen than are the other dimensions of human sexual response. The other components of sexual response were defined as secondary or supportive measures. With respect to sexual interest, the two most important BISF-W scales (Sexual Thoughts/Desires and Composite Sexual Function) showed trends in a direction similar to the SIQ scores but did not reach statistical significance. Our study may have been underpowered to detect BISF-W differences.

The decision not to include a true placebo arm was based on the premise that measurement of sexual interest could be confounded by symptoms of estrogen deficiency. In addition, placebo recipients would be more likely to have hot flushes, which could potentially unblind the study. Accordingly, we used standard estrogen replacement in both groups and administered additional methyltestosterone (the test compound) to only one group.

TABLE 4

Most frequent adverse events (incidence $\geq 5\%$).

Adverse event	EE/MT group (n = 107)	EE group (n = 111)
All adverse events	69 (64.5)	64 (57.7)
Headache	10 (9.3)	8 (7.2)
Infection	10 (9.3)	7 (6.3)
Hot flushes	7 (6.5)	7 (6.3)
Flu syndrome	6 (5.6)	6 (5.4)
Acne	6 (5.6)	3 (2.7)
Rhinitis	4 (3.7)	6 (5.4)
Breast pain	4 (3.7)	7 (6.3)

Note: Values are numbers (percentages) of patient. EE = esterified estrogens; EE/MT = esterified estrogen and methyltestosterone.

Lobo. Methyltestosterone endocrine profiles. *Fertil Steril* 2003.

TABLE 5

Changes in scores of androgen skin effects.

Effect	EE/MT group (n = 107)	EE group (n = 109)	P value for between-group difference ^a
Hirsutism score			
Baseline	2.3 \pm 2.5	2.9 \pm 3.3	
Change at week 16	0.0 \pm 1.9	-0.4 \pm 2.2	.160
P for change ^a	.915	.063	
Acne score			
Baseline	0.1 \pm 0.4	0.2 \pm 0.5	
Change at week 16	0.2 \pm 0.5	0.1 \pm 0.5	.169
P for change ^a	<.010	.033	

Note: Data are means (\pm SD). EE = esterified estrogens; EE/MT = esterified estrogen and methyltestosterone.

^a By analysis of variance.

Lobo. Methyltestosterone and endocrine profiles. *Fertil Steril* 2003.

TABLE 6

Baseline values and mean changes for serum lipids.

Lipid	EE/MT group (n = 106)	EE group (n = 110)	P value for between-group difference ^a
Total cholesterol (mg/dL)			
Baseline	216.0 ± 32.4	213.1 ± 32.6	
Change at Wk 16	-16.8 ± 26.1	2.4 ± 26.1	<.010
P for change ^a	<.010	.369	
HDL cholesterol (mg/dL)			
Baseline	67.4 ± 15.6	64.2 ± 15.4	
Change at week 16	-12.4 ± 11.4	3.2 ± 11.0	<.010
P for change ^a	<.010	<.010	
LDL cholesterol (mg/dL)			
Baseline	124.0 ± 31.9	120.6 ± 31.7	
Change at 16	1.7 ± 23.1	1.0 ± 24.0	.829
P for change ^a	.489	.675	
Triglycerides (mg/dL)			
Baseline	121.4 ± 55.3	138.0 ± 60.7	
Change at week 16	-31.1 ± 51.8	-7.5 ± 50.0	<.010
P for change	<.010	.147	

Note: Data are means (±SD). EE = esterified estrogens; EE/MT = esterified estrogen and methyltestosterone.

^a By analysis of variance.

Lobo. Methyltestosterone and endocrine profiles. *Fertil Steril* 2003.

We did not assess the use of estrogen combined with a progestin for women with a uterus. Progestins can have varying effects on SHBG levels (23, 24), may exert androgenic effects by displacing testosterone from SHBG (25), and may have direct central nervous system effects reflected in sexual functioning (26). Further study is needed to investigate the effects of combined estrogen-progestin coadministered with methyltestosterone on hypoactive sexual desire.

Increased circulating levels of unbound testosterone and suppression of SHBG provide a plausible hormonal explanation for the improved sexual functioning in women receiving the combination of esterified estrogen and methyltestosterone. Although the significant increase in the SIQ score measuring sexual interest/desire cannot be extrapolated to clinical relevance, the correlation between serum bioavailable testosterone and improvement in SIQ score supports the important influence of circulating testosterone on sexual interest/desire in postmenopausal women.

Acknowledgments: The authors thank the following: David F. Archer, M.D., Eastern Virginia Medical School, Norfolk, Virginia; Gloria A. Bachmann, M.D., University of Medicine and Dentistry of New Jersey, New Brunswick, New Jersey; Brian Bear, M.D., Definitive Health Services, Inc., Milwaukee, Wisconsin; Richard Beyerlein, M.D., Advanced Clinical Trials, Inc., Eugene, Oregon; Ray Borel, Pharm.D., RPh., and John Brennan, Ph.D., Solvay Pharmaceuticals, Inc., Marietta, Georgia; James Crane, M.D., Health Advance Institute, Peoria, Illinois; Charles L. Goldsmith, M.D., Gynecology of South Florida, North Miami Beach, Florida; Richard E. Hedrick, M.D., Salem Research Group, Inc., Winston-Salem, North Caro-

lina; G. Robert Klomp, M.D., Advanced Clinical Research, Boise, Idaho; James Maly, M.D., Women's Clinic of Lincoln, Lincoln, Nebraska; Jack Rothman, M.D., Clearwater, Florida; Mark Saunders, M.D., Advanced Clinical Research, Salt Lake City, Utah; Larry Seidman, D.O., Philadelphia, Pennsylvania; Robert Semo, M.D., San Diego, California; Donna M. Shoupe, M.D., University of Southern California Women's Health Center, Los Angeles, California; James A. Simon, M.D., Women's Health Research Center, Laurel, Maryland; Randall R. Stoltz, M.D., GFI Pharmaceutical Services, Inc., Evansville, Indiana; Elizabeth Street, M.D., Health Advance Institute, Marietta, Georgia; Gailyn Thomas, M.D., Women's Health Source, Upland, Pennsylvania; Michelle Warren, M.D., Columbia Presbyterian Eastside, New York, New York; Brenda Williams, M.D., Pacific Coast Clinical Coordinators, Boise, Idaho.

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