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Effects of Oral vs Transdermal Estrogen Therapy on Sexual Function in Early Postmenopause

Ancillary Study of the Kronos Early Estrogen Prevention Study (KEEPS)

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IMPORTANCE Sexual dysfunction, an important determinant of women's health and quality of life, is commonly associated with declining estrogen levels around the menopausal transition.

OBJECTIVE To determine the effects of oral or transdermal estrogen therapy vs placebo on sexual function in postmenopausal women.

DESIGN, SETTING, AND PARTICIPANTS Ancillary study of the Kronos Early Estrogen Prevention Study (KEEPS), a 4-year prospective, randomized, double-blinded, placebo-controlled trial of menopausal hormone therapy in healthy, recently menopausal women. Of 727 KEEPS enrollees, 670 agreed to participate in this multicenter ancillary study. Women were 42 to 58 years old, within 36 months from last menstrual period. Data were collected from July 2005 through June 2008 and analyzed from July 2010 through June 2017.

INTERVENTIONS Women were randomized to either 0.45 mg/d oral conjugated equine estrogens (o-CEE), 50 µg/d transdermal 17β-estradiol (t-E_2), or placebo. Participants also received 200 mg oral micronized progesterone (if randomized to o-CEE or t-E_2) or placebo (if randomized to placebo estrogens) for 12 days each month.

MAIN OUTCOMES AND MEASURES Aspects of sexual function and experience (desire, arousal, lubrication, orgasm, satisfaction, and pain) were assessed using the Female Sexual Function Inventory (FSFI; range, 0-36 points; higher scores indicate better sexual function). Low sexual function (LSF) was defined as an FSFI overall score of less than 26.55. Distress related to low FSFI score (required for the diagnosis of sexual dysfunction) was not evaluated.

RESULTS The 670 participants had a mean (SD) age of 52.7 (2.6) years. The t-E_2 treatment was associated with a significant yet moderate improvement in the FSFI overall score across all time points compared with placebo (average efficacy, 2.6; 95% CI, 1.11-4.10; adjusted $P = .002$). With o-CEE treatment, there was no significant difference in FSFI overall score compared with placebo (mean efficacy, 1.4; 95% CI, −0.1 to 2.8; adjusted $P = .13$). There was no difference in FSFI overall score between the t-E_2 and o-CEE groups on average across 48 months (adjusted $P = .22$). In the individual domains of sexual function, t-E_2 treatment was associated with a significant increase in mean lubrication (0.61; 95% CI, 0.25-0.97; $P = .001$) and decreased pain (0.67; 95% CI, 0.25-1.09; $P = .002$) compared with placebo. Overall, the proportion of women with LSF was significantly lower after t-E_2 treatment compared with placebo (67%; 95% CI, 55%-77% vs 76%; 95% CI, 67%-83%; $P = .04$). For o-CEE there was no significant reduction in the odds of LSF.

CONCLUSIONS AND RELEVANCE Treatment with t-E_2 modestly improved sexual function in early postmenopausal women, but whether it relieved symptoms of distress is not known.

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Supplemental content

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Hypoestrogenemia is the endocrine hallmark of menopause and is characterized by 5- to 10-fold reduction in circulating levels of estradiol (E_2).[1] Over time, low E_2 levels result in vaginal dryness and dyspareunia, often accompanied by symptoms of vulvovaginal atrophy.[2] These symptoms significantly contribute to the increased incidence of sexual disorders in menopausal women.[3-5] Estradiol is also a modulator of serotonergic function, affecting regions of the brain known to regulate mood and desire, which may have direct or indirect effects on sexual function.[1,6] At least 23% of naturally menopausal women are distressed by their low sexual desire,[7] whereas midlife women with higher levels of enjoyment from sexual activity experience a higher sense of purpose in life.[8] The US Food and Drug Administration has recently identified female sexual dysfunction (FSD) as a serious condition with unmet needs as part of its program on patient-oriented drug development.[9]

A recent meta-analysis revealed that treatment with estrogens alone or in combination with progestogens was associated with a small to moderate improvement in sexual function relative to placebo (particularly in pain), when used in women with menopausal symptoms or in early postmenopause (ie, within 5 years of amenorrhea).[10] However, the analysis did not stratify by the route or composition of estrogens used. We hypothesized that transdermal estradiol (t-E_2) might be more effective for treatment of se xual dysfunction in menopausal women than oral estrogens due to pharmacokinetics that result in an E_2 to estrone ratio that approximates that seen prior to menopause.[11] Indeed, plasma concentration of free E_2 with t-E_2 use is twice that seen with oral formulations.[12]

The Kronos Early Estrogen Prevention Study (KEEPS) is a randomized, double-blinded, placebo-controlled trial originally designed to test whether estrogen treatment reduces progression of atherosclerosis when initiated within 36 months of the last menstrual period.[13] In KEEPS, transdermal 17β-estradiol (t-E_2) was directly compared with oral conjugated equine estrogen (o-CEE) to determine whether both have equivalent effects on menopause-associated symptoms.[14] The ancillary KEEPS-sexual study examined changes in sexual function over time in recently postmenopausal women randomized to either o-CEE or t-E_2 for 4 years.

Key Points

Question What are the effects of transdermal or oral estrogen therapy on sexual function in recently postmenopausal women over time?

Findings In this ancillary study of a randomized clinical trial that included 670 healthy menopausal women within 3 years of their last menstrual period, transdermal estradiol improved overall sexual function score compared with placebo.

Meaning Transdermal estradiol therapy may improve sexual function in postmenopausal women with low sexual function.

Methods

Menopausal women from 9 recruitment sites across the United States participated in KEEPS. They were within 3 years of their final menstrual period, and all provided written informed consent. Institutional review boards at participating sites approved the study procedures. A detailed description of recruitment, participating clinical centers, inclusion and exclusion criteria, safety monitoring, and randomization and blinding protocols for KEEPS has been published.[15-17] (See Supplement 1 for the Trial Protocol.) In brief, eligible women were between 42 and 58 years of age and at least 6 months and no more than 36 months from last menstrual period, with plasma follicle-stimulating hormone level at least 35 mIU/mL (to convert to IU per liter, multiply by 1.0) and/or E_2 levels less than 40 pg/mL (to convert to picomoles per liter, multiply by 3.671). Women excluded from the study were those who had undergone hysterectomy or surgically induced menopause; abnormal mammogram result; severe psychiatric illness including untreated major depression; a history of clinical cardiovascular disease including myocardial infarction, angina, congestive heart failure, or thromboembolic disease; those with coronary artery calcification with Agatston score at least 50 U (indicating significant subclinical coronary artery disease); as well as current moderate or heavy smoking (>10 cigarettes/d by self-report), severe obesity (body mass index [BMI, calculated as weight in kilograms divided by height in meters squared] >35), dyslipidemia (low-density lipoprotein cholesterol >190 mg/dL [to convert to millimoles per liter, multiply by 0.0259]), hypertriglyceridemia (triglycerides >400 mg/dL [to convert to millimoles per liter, multiply by 0.0113]), uncontrolled hypertension (systolic blood pressure >150 mm Hg and/or diastolic blood pressure >95 mm Hg), or fasting glucose level greater than 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555).

Eligible KEEPS participants were randomized in a ratio of 4:4:5 to either oral o-CEE, 0.45 mg/d and placebo patches with micronized progesterone, 200 mg, for 12 days each month; t-E_2, 50 µg/d and placebo pills with micronized progesterone, 200 mg, for 12 days each month; or placebo pills and patches. The administered dose of 50 µg/d t-E_2 was found to be equivalent to 0.3 to 0.625 mg/d o-CEE with regard to changes in urinary calcium excretion, vaginal epithelial maturation, and symptom relief; 0.45 mg/d o-CEE was chosen to approximate the equivalent dose and allow adequate symptom relief.[17,18]

Sexual function data were collected at 4 of the parent study visits: baseline and months 18, 36, and 48. Sex hormone–binding globulin (SHBG) levels were assayed at baseline and 36 and 48 months.[19] Participants completed the Female Sexual Function Inventory (FSFI) questionnaire, a validated tool assessing the key dimensions of sexual function along 6 domains of sexual function, including desire, arousal, lubrication, orgasm, satisfaction, and pain.[20,21] In brief, each domain has a score range that, when multiplied by a domain-specific factor, gives the individual domain score. The overall FSFI scale score equals the sum of the 6 domain scores, with higher scores reflecting better sexual function (range of total FSFI score, 0-36). Although an FSFI overall score of less than 26.55 has been found to be the optimal cutoff score for identifying women (age range, 18-74 years) with sexual dysfunction,[22] the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) requires sexual symptoms

to be associated with clinically significant distress as a diagnostic criterion.[9,23] Because we did not evaluate distress, we defined overall FSFI score of less than 26.55 as low sexual function (LSF) rather than sexual dysfunction.

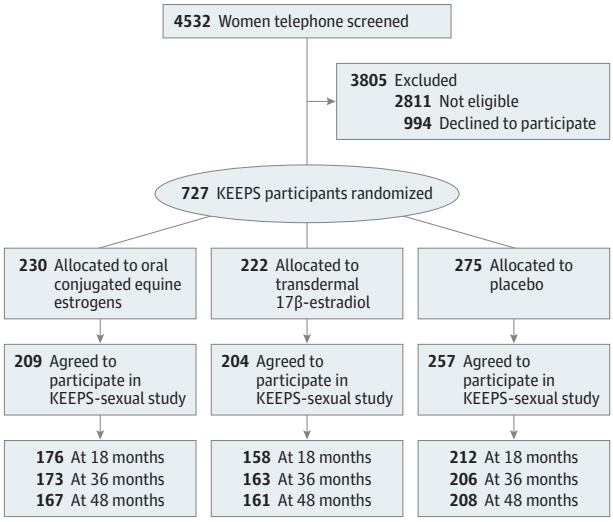
Statistical Analysis

Descriptive analyses using χ^2 tests and analysis of covariance were conducted to compare the participants' demographic and clinical characteristics at baseline. Mixed model repeated-measures analysis was used primarily to evaluate the efficacy of treatments. The approach proposed by Fitzmaurice et al[24(pp126-132)] was used. Unstructured covariance matrix was used to account for the correlation between repeated assessments within the same individual. Time and group interaction was included as the main effect. Linear contrasts were performed to compare the change from baseline at each time point across groups. The advantage of this approach included the use of maximum likelihood method for statistical efficiency and the capacity to use all available data to handle missing values under missing at random assumption.[25] Duration of menopause prior to enrollment, age at enrollment, history of menopausal hormone treatment, education, ethnicity, and income were included in covariate adjustment because those variables are either conceptual confounders or associated with missing data. The FSFI overall score was the primary end point, whereas the 6 subscales of FSFI and SHBG level served as secondary outcomes. The primary analyses evaluated the overall efficacy of o-CEE and t-E_2 in improving FSFI overall score compared with placebo and the efficacy of o-CEE compared with t-E_2. Bonferroni correction was used to control for these comparisons. Therefore, the original *P* values were multiplied by 3 to control for type I error rate for primary efficacy test and denoted as adjusted *P* values. The supportive analyses were conducted using the same approach for 6 domains of the FSFI. In addition, participants were classified as either having or not having LSF dichotomized at an FSFI score of 26.55.[20,21] The change in likelihood of FSD was analyzed using mixed-effect logistic regression analysis adjusting for individual baseline FSD status. The overall proportion of LSF and 95% confidence interval were estimated as supportive evidence secondary to the efficacy test on the primary outcome. Moderation of the treatment effect by baseline characteristics was also evaluated to identify subgroups that may benefit most from the treatment. All the supportive and exploratory analyses used 2-sided $P < .05$ as significance level. SAS, version 9.4 (SAS Institute), was used to perform the statistical analysis.

Results

The trial began in July 2005, with complete enrollment of 727 participants in the parent trial by June 2008. Data collection concluded by March of 2012. Six hundred seventy of the 727 KEEPS enrollees agreed to participate in the sexual function ancillary study (n = 209 in the o-CEE group, n = 204 in the t-E_2 group, and n = 257 in the placebo group). **Figure 1** displays the ancillary study's CONSORT flow diagram. Participant demographic characteristics for the KEEPS-sexual study population are presented in **Table 1**. No significant differences were observed in baseline characteristics among the groups. There were also no significant differences between the treatment groups in the scores for each individual sexual function domain nor in the overall sexual function score or in SHBG levels at baseline. Last, FSFI overall and subdomain scores, as well as SHBG levels, were comparable at baseline across the 3 treatment groups when participants were stratified by LSF (**Table 2**).

Figure 1. CONSORT Flow Diagram of the Ancillary Kronos Early Estrogen Prevention Study (KEEPS)–Sexual Study



Numbers indicate the number of enrolled KEEPS participants completing the Female Sexual Function Inventory questionnaire at that time point.

Significant improvements were observed in FSFI overall scores for participants who received o-CEE and t-E_2 treatment compared with those who received placebo. We also observed significant improvement in all subdomain scores at 18 months in the t-E_2 treatment group (**Figure 2** and eTable in Supplement 2).

FSFI Overall Score

The mean FSFI overall score moderately yet significantly increased by 2.6 points (95% CI, 1.1 to 4.1; adjusted $P = .002$) from baseline in the t-E_2 treatment group compared with that in placebo on average across 48 months, which corresponds to a 7.2% improvement over placebo on the FSFI range of 36 points. The mean FSFI overall score increased with t-E_2 treatment relative to placebo, with consistent effect size of 2.9, 2.1, and 2.8 points at 18, 36, and 48 months, respectively ($P = .001$, .02, and .005, respectively; $P = .63$ for difference among visits), although in both the t-E_2 and placebo groups the mean absolute FSFI score trended downward over time (Figure 2A and eTable in Supplement 2). With o-CEE treatment, the mean overall FSFI score increased by 1.4 points compared with placebo (95% CI, −0.1 to 2.8; adjusted $P = .13$), a 3.9% improvement. However, the increase peaked at 36 months (mean, 2.3 points; 95% CI, 0.6 to 4.1; $P = .008$), returning to baseline levels at 48 months (mean change from baseline, −0.3; 95% CI, −1.7 to 1.1; $P = .70$).

Table 1. Participant Demographic Characteristics at Randomization

Characteristic	Treatment (N = 670)			*P* Value
	o-CEE (n = 209)	t-E_2 (n = 204)	Placebo (n = 257)	
Age, mean (SD), y	52.8 (2.6)	52.7 (2.6)	52.5 (2.5)	.37
Time from last menstrual period to randomization, mean (SD), d	654.7 (306.3)	668.7 (263.2)	639.3 (284.6)	.54
Baseline sexual domain scores, mean (SD)				
Desire	2.7 (1.1)	2.6 (1.2)	2.6 (1.2)	.46
Arousal	2.8 (2.0)	2.7 (2.0)	2.8 (2.0)	.70
Lubrication	2.9 (2.2)	2.8 (2.3)	3.0 (2.2)	.54
Pain reduction	3.1 (2.6)	2.9 (2.6)	3.1 (2.6)	.68
Orgasm	3.0 (2.2)	2.8 (2.4)	3.0 (2.2)	.68
Satisfaction	3.4 (1.7)	3.4 (1.7)	3.5 (1.7)	.62
Female Sexual Function Inventory	19.1 (9.5)	18.4 (10.2)	19.1 (9.6)	.70
Sex hormone-binding globulin level	62.3 (28.8)	62.7 (29.8)	58.9 (28.0)	.28
Hormone use, No. (%)				
Never	155 (74.2)	168 (82.4)	207 (80.5)	.10
Past/current	54 (25.8)	36 (17.6)	50 (19.5)	
Smoking, No. (%)				
Yes	46 (22.0)	42 (20.6)	58 (22.6)	.87
No	163 (78.0)	162 (79.4)	199 (77.4)	
Education, No. (%)				
College and above	151 (72.2)	154 (75.5)	185 (72.0)	.58
Others	58 (27.8)	50 (24.5)	72 (28.0)	
Ethnicity, No. (%)				
White	164 (78.5)	155 (76.0)	198 (77.0)	.83
African American	14 (6.7)	14 (6.9)	21 (8.2)	
Hispanic	15 (7.2)	14 (6.9)	19 (7.4)	
Others	16 (7.7)	21 (10.3)	19 (7.4)	
Household income, No. (%), $				
<20 000	3 (1.4)	3 (1.5)	8 (3.1)	.85
20 000-40 000	15 (7.2)	15 (7.4)	11 (4.3)	
40 000-60 000	21 (10.0)	21 (10.3)	26 (10.1)	
60 000-100 000	31 (14.8)	27 (13.2)	36 (14.0)	
>100 000	35 (16.7)	32 (15.7)	49 (19.1)	
Not answered	104 (49.8)	106 (52.0)	127 (49.4)	
Marital status, No. (%)				
Married or partner	147 (70.3)	127 (62.3)	179 (69.6)	.14
Others	62 (29.7)	77 (37.7)	78 (30.4)	
Menopausal Symptoms				
Depressive symptoms				
None	127 (60.8)	127 (62.3)	164 (63.8)	.90
Mild	60 (28.7)	60 (29.4)	72 (28.0)	
Moderate to severe	22 (10.5)	17 (8.3)	21 (8.2)	
Insomnia				
None	68 (32.5)	73 (35.8)	83 (32.3)	.40
Mild	80 (38.3)	60 (29.4)	87 (33.9)	
Moderate to severe	61 (29.2)	71 (34.8)	87 (33.9)	
Irritability				
None	85 (40.7)	88 (43.1)	105 (40.9)	.74
Mild	87 (41.6)	78 (38.2)	113 (44.0)	
Moderate to severe	37 (17.7)	38 (18.6)	39 (15.2)	

(continued)

Table 1. Participant Demographic Characteristics at Randomization (continued)

Characteristic	Treatment (N = 670) o-CEE (n = 209)	t-E_2 (n = 204)	Placebo (n = 257)	*P* Value
Hot flashes				
None	37 (17.7)	28 (13.7)	31 (12.1)	.41
Mild	80 (38.3)	90 (44.1)	107 (41.6)	
Moderate to severe	92 (44.0)	86 (42.2)	119 (46.3)	
Mood swings				
None	87 (41.6)	90 (44.1)	108 (42.0)	.92
Mild	90 (43.1)	79 (38.7)	108 (42.0)	
Moderate to severe	32 (15.3)	35 (17.2)	41 (16.0)	
Night sweats				
None	74 (35.4)	65 (31.9)	79 (30.7)	.48
Mild	61 (29.2)	74 (36.3)	85 (33.1)	
Moderate	58 (27.8)	47 (23.0)	77 (30.0)	
Severe	16 (7.7)	18 (8.8)	16 (6.2)	
Heart palpitations				
None	143 (68.4)	151 (74.0)	183 (71.2)	.36
Mild	52 (24.9)	46 (22.5)	55 (21.4)	
Moderate to severe	14 (6.7)	7 (3.4)	19 (7.4)	
Vaginal dryness				
None	85 (40.7)	83 (40.7)	95 (37.0)	.70
Mild	68 (32.5)	70 (34.3)	88 (34.2)	
Moderate	39 (18.7)	35 (17.2)	59 (23.0)	
Severe	17 (8.1)	16 (7.8)	15 (5.8)	

Abbreviations: o-CEE, oral conjugated equine estrogens; t-E_2, transdermal 17β-estradiol.

Table 2. Sexual Function Domain and Female Sexual Function Inventory (FSFI) Scores at Baseline in Participants With and Without Low Sexual Function (LSF)[a]

LSF	No.[b]	Mean (SD) Desire	Arousal	Lubrication	Pain Reduction	Orgasm	Satisfaction	FSFI
No								
o-CEE	50	3.8 (0.8)	5.0 (0.8)	5.1 (1.1)	5.7 (0.7)	5.2 (0.8)	5.2 (0.8)	30.1 (2.5)
t-E_2	53	3.7 (1.2)	5.1 (0.6)	5.4 (0.7)	5.4 (1.0)	5.3 (1.0)	5.2 (0.9)	30.1 (2.5)
Placebo	61	3.9 (1.0)	5.0 (0.8)	5.1 (1.0)	5.7 (0.5)	5.2 (0.9)	5.4 (0.7)	30.3 (2.4)
P value		.64	.63	.22	.08	.75	.62	.93
Yes								
o-CEE	140	2.4 (0.9)	2.4 (1.7)	2.5 (2.0)	2.5 (2.4)	2.5 (2.0)	2.7 (1.4)	15.1 (7.8)
t-E_2	129	2.2 (1.0)	2.0 (1.6)	2.1 (1.9)	2.3 (2.4)	2.2 (2.0)	2.7 (1.4)	13.5 (7.9)
Placebo	173	2.3 (0.9)	2.3 (1.7)	2.6 (2.0)	2.6 (2.4)	2.5 (2.0)	2.9 (1.4)	15.1 (8.0)
P value		.10	.12	.08	.69	.30	.32	.14

Abbreviations: o-CEE, oral conjugated equine estrogens; t-E_2, transdermal 17β-estradiol.

[a] Low sexual function was defined as FSFI score less than 26.55.

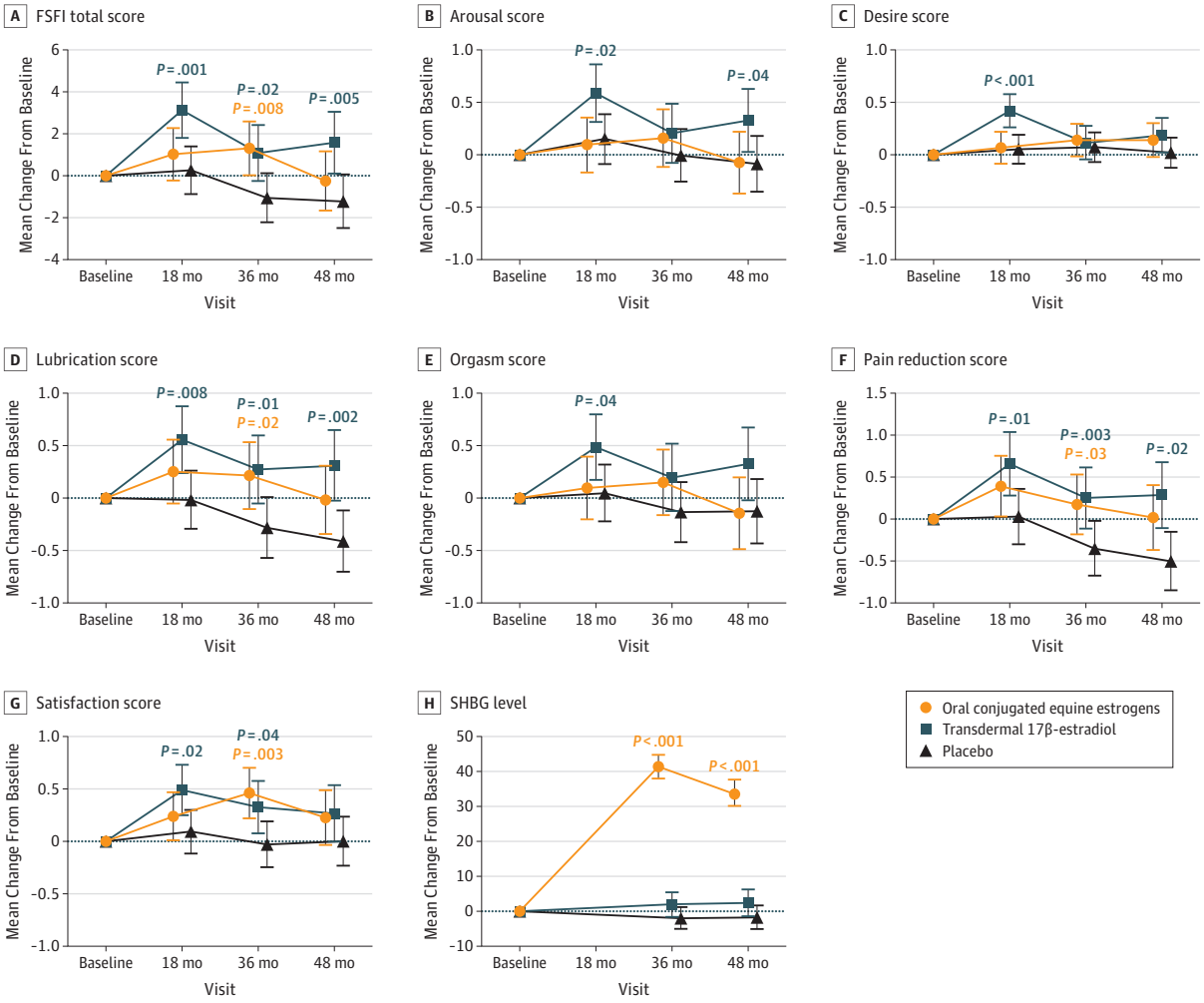
[b] Because 64 participants were missing scores for 1 or 2 domains, their baseline LSF status was not determined.

There was no difference in effect on FSFI with t-E_2 compared with o-CEE (adjusted $P = .22$). However, at 18 months the t-E_2 group improved by a mean of 2.1 points more than the o-CEE group (95% CI, 0.3-4.0; $P = .02$). Finally, there was little change in treatment efficacy and in the differences between the estrogen groups after controlling for changes in hot flashes at the time points examined (36 and 48 months; data not shown).

FSFI Subscales for 6 Domains

Changes in scores for the 6 domains of the FSFI are shown in Figure 2B-G. The least-square means and 95% confidence intervals are presented in the eTable in Supplement 2. Compared with placebo, the t-E_2 group showed significant improvements in desire, arousal, orgasm, and satisfaction scores at 18 months ($P < .001$, $P = .02$, $P = .04$, and $P = .02$, respectively), and significant improvements in scores for lubrication and pain at

Figure 2. Mean Change From Baseline Over Time in the Different Sexual Function Domains, Overall Female Sexual Function Inventory (FSFI) Score, and Sex Hormone–Binding Globulin (SHBG) Levels



P values are presented comparing with placebo. Error bars indicate 95% confidence intervals.

all 3 time points. The t-E_2 group also showed improved scores relative to the o-CEE group in the domains of desire and arousal, but only at 18 months (*P* = .01 and .002, respectively). Treatment with o-CEE demonstrated fewer significant improvements relative to placebo.

SHBG Levels

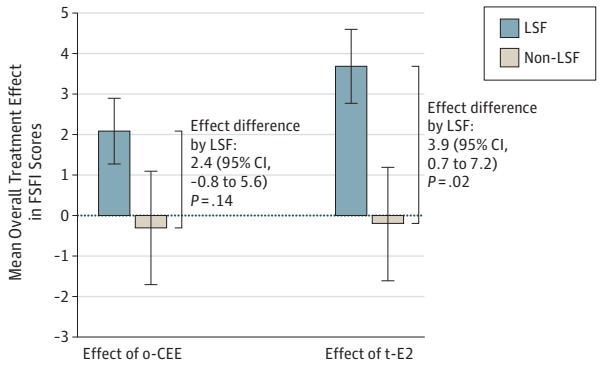
Because SHBG levels were available only at baseline and 36 and 48 months, analysis was limited to these time points. As expected, SHBG levels were stable over time in the placebo and t-E_2–treated groups with no significant differences in the levels between these 2 groups (Figure 2H and eTable in Supplement 2). Conversely, SHBG levels significantly increased with o-CEE treatment relative to both baseline and the other treatment groups at 36 and 48 months (*P* < .001), although it declined significantly from 36 to 48 months (mean, 7.5; 95% CI, 4.3-10.6 nmol/L).

Low Sexual Function

At baseline, the prevalence of LSF was 74% (140 of 190), 71% (129 of 182), and 74% (173 of 234) among the o-CEE, t-E_2, and placebo groups, respectively (*P* = .76) (Table 2). Only t-E_2 treatment significantly reduced the overall rate of LSF compared with placebo (adjusted rate, 67%; 95% CI, 55%-77% vs 76%; 95% CI, 67%-83%; *P* = .04).

Low sexual function was the only baseline characteristic that affected overall t-E_2 treatment efficacy. The overall mean effect of t-E_2 treatment on FSFI scores compared with placebo was 3.7 points (95% CI, 2.0-5.4) for women with LSF at baseline (*P* < .001). In contrast, the effect was −0.2 points (95% CI, −3.0 to 2.6; *P* = .88) for women without LSF at baseline. The *P* value for interaction was .02 (**Figure 3**), indicating the significant effect modification by baseline LSF status. Similarly, the overall o-CEE effect on FSFI score was significant only in the LSF subgroup (2.1 points; 95% CI, 0.5 to 3.7; *P* = .01 vs −0.3 points; 95% CI, −3.1 to

Figure 3. Treatment Effect Stratified by Baseline Low Sexual Function (LSF) Status



The efficacy of transdermal 17β-estradiol (t-E_2) treatment was moderated by baseline LSF. FSFI indicates Female Sexual Function Inventory; o-CEE, oral conjugated equine estrogens. Error bars correspond to standard errors.

2.4; P = .81 for women without LSF). However, the difference was not statistically significant (P = .14 for interaction).

Discussion

The importance of the sexual function ancillary study of KEEPS is due to its ability to discern the effects of treatment with t-E_2 vs o-CEE on multiple domains of female sexual function, as well as on LSF in recently postmenopausal women. Symptoms related directly to tissue effects of estrogens on the reproductive tract, such as lubrication and pain on penetration, demonstrated a progressive exacerbation with time in the untreated group and were alleviated with the use of t-E_2 across all time points. The more subjective domains of desire, arousal, orgasm, and sexual satisfaction demonstrated a relatively steady state over time in the untreated group and were improved only at 18 months of treatment with t-E_2. This may suggest that the effect of t-E_2 on psychological aspects of the sexual response is independent from its effect on physiological aspects. Similarly, the overall improvement in FSFI in the o-CEE–treated group at 36 months appears to be predominantly due to significant improvements in the physical aspects of sexual function (lubrication and pain), although not in libido-related aspects.

The degree of improvement in FSFI that was observed with t-E_2 use may be clinically meaningful. Temporally, t-E_2 appears to be effective earlier than o-CEE (a mean of 2.1 points at 18 months, which corresponds to 11.6% difference in improvement in FSFI score) and last longer (a mean of 1.8 points better at 48 months, a 10.3% difference). This efficacy may be due to consistently elevated E_2 levels detected in t-E_2–treated KEEPS participants relative to placebo and to o-CEE–treated women.[19] Still, at 36 months, there was no significant difference in improvement between the 2 treatment arms.

While the treatment efficacy of t-E_2 was limited to women with LSF, this population made up the majority of healthy menopausal women in the KEEPS cohort. Women with LSF may have been motivated to enroll in a trial of hormone therapy based on previously reported benefits of hormone therapy for treatment of LSF, thus increasing the proportion of women in the trial with LSF. In addition, our definition of LSF was based entirely on an FSFI score of less than 26.55. Because we did not collect information on distress related to sexual function, which is required for the diagnosis of LSF, the proportion of women in the general population with LSF may be much lower.[26] Women without preexisting LSF based on the FSFI in KEEPS showed a gradual decline in sexual function after menopause independent of treatment regimen. While women with LSF at baseline benefited from menopausal hormone therapy, those without dysfunction did not appear to experience improved sexual function, an FSFI threshold-dependent improvement that was not previously explored.

Estrogen therapy alleviates menopause-related symptoms, including hot flashes, night sweats, palpitations, insomnia, irritability, and vaginal atrophy.[27,28] The presence of hot flashes has previously been associated with poor sexual function.[29-32] We therefore sought to explore whether alleviation of these symptoms over time significantly improves sexual function. Controlling for changes in hot flashes, however, did not significantly affect changes in FSFI overall score nor group comparisons, suggesting that symptoms relief following treatment does not significantly contribute to the improvements observed in sexual function.

The lack of improvement with o-CEE treatment in libido-related domains of desire and arousal relative to placebo is in accord with the association of hepatic induction of SHBG (mediated by oral estrogens), resultant decline in free (bioavailable) androgens, and decreasing libido in postmenopausal women.[33-36] In contrast, physical symptoms of lubrication and pain seem unmitigated by the increase in SHBG levels. We therefore conclude that potential reduction in the bioavailability of testosterone may only explain the lower efficacy of o-CEE relative to t-E_2 in libido-associated domains but cannot account for variations in physical aspects of sexual function. In support, modest improvements in the physical aspects of sexual function in postmenopausal women treated with low-dose t-E_2 were unaffected by endogenous testosterone levels.[37]

Limitations

Advantages of the ancillary KEEPS–sexual study include the large sample size and randomized placebo-controlled design of the trial, as well as the unique nature of the studied population (menopausal women within 3 years of onset of menopause), the latter minimizing potential confounders related to aging that have previously been shown to be associated with sexual dysfunction.[38-41] Limitations include the restricted generalizability of the findings to other ethnic groups or to women with a lower educational level and socioeconomic status because the KEEPS population is composed predominantly of white women of a higher educational background than the general US population.

Furthermore, although relationship change is known to affect sexual function at the menopause transition,[42,43] follow-up measures of partner status were not available for our cohort, precluding analysis of the effect of change of partner status on the efficacy of hormone treatment. Moreover, this

study did not account for lack of sexual activity, as well as women who prefer forms of sexual activity other than penetrative intercourse, which in both cases may lead to underestimation of FSFI overall score.

Another potential limitation is the cutoff score used to define LSF that is validated for women aged 18 to 74 years.[22] Therefore, additional measures, such as distress associated with sexual function (ie, through the Female Sexual Distress Scale[44]) or a clinical interview by a trained expert in sexual function may have been informative, as they can potentially "correct" for the FSFI score defining sexual dysfunction in early postmenopausal women. Although the latter would have also allowed for a clinical diagnosis of sexual dysfunction, it is not practical in a large clinical trial in which sexual function is just one of many end point measures. Finally, assessing symptoms of vulvovaginal atrophy (ie, dryness and dyspareunia) could have confirmed the improvement observed in the physical aspects of sexual function and put them in a clinically relevant context.

Conclusions

In summary, in a randomized clinical trial of hormone therapy in early postmenopausal women, treatment with t-E_2 provided modest benefits for sexual function. The efficacy of o-CEE treatment seemed to be less than that of t-E_2, especially in the subgroup of women with LSF, although there was no statistically significant difference between the hormone groups on overall sexual function.

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