Beneficial Aspect of Oral Estriol as Hormone Replacement Therapy: Consideration on Bone and Lipid Metabolism

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To improve the quality of life of elderly people in Japanese society where women have the longest life expectancy in the world, osteoporosis, and hyperlipidemia are among the major targets of medical treatment. To differentiate two types of regimens for hormone replacement therapy (HRT), we tried to evaluate the efficacy on lipid and bone metabolism. With informed consent, 34 postmenopausal women of more than 2 years were assigned to receive 1 of 2 types of HRT (the HRT group) for 12 months observation: one with a combination of conjugated equine estrogen (CEE) 0.625 mg/day and medroxyprogesterone acetate (MPA) 2.5 mg/day (the CEE group), and the other with oral estriol (E3) 2 mg/day (the E3 group). Parameters of serum lipid were measured, as well as those of bone metabolism with bone mineral density (BMD) by dual-energy X-ray absorptiometry (DEXA) using QDR-2000. In HRT groups, lipid and bone metabolism were confirmed to be improved. Whereas, an increase of triglycerides (TG) observed in the CEE group was not observed in the E3 group. Thus, in the clinical management of postmenopausal women, oral E3 preparation as an alternative regimen for HRT for CEE might be efficacious.

Key words: menopause, lipids, osteoporosis, HRT, sex hormones

INTRODUCTION

While Japanese women are now enjoying the longest life expectancy among women in the world, to elevate their quality of life still remains a major target in our society. In this context, the beneficial effects of hormone replacement therapy (HRT) on postmenopausal osteoporosis and hyperlipidemia were reported and discussed in our previous paper [1]. In the report, we analyzed the simultaneous natural course of lipid and bone metabolism in elderly women and evaluated effects of HRT on postmenopausal disturbance in both aspects simultaneously, which has mostly been reported separately [2–5]. When investigating the effects of HRT, conjugated equine estrogen (CEE) is the worldwide standard and thus the most widely used therapy. Whereas, oral estriol (E3) preparation is most preferably prescribed in Japan, since it has been approved for osteoporosis under the Japanese national medical insurance coverage. There have been relatively few studies investigating the effects of E3 on lipid and bone metabolism because of the unavailability of E3 in western countries [6]. In the present study, we attempted to elucidate the simultaneous effects of HRT on lipid and bone metabolism after menopause and to differentiate the regimens of HRT comparing E3 and CEE.

PATIENTS AND METHODS

To assess the effects of HRT, with their informed consent, postmenopausal women of more than 2 years were assigned into 1 of 2 types of HRT (the HRT group): one received a combination of CEE 0.625 mg/day and medroxyprogesterone acetate (MPA) 2.5 mg/day (the CEE group) and the other received E3 2 mg/day (the E3 group). These 2 types of prescriptions have regularly been prescribed for standard HRT regimens in our outpatient clinic. We have reported the usefulness of the CEE HRT regimen on bone and lipid metabolism in our previous paper [1]. For the present study, we retrospectively collected the medical records from our outpatients' database from 2003 to the end of 2006 (N = 166: the CEE group, n = 91; the E3 group, n = 75). These medical records, which had the required data points described below, were pooled, their matching characteristics analyzed and extracted, and finally 17 patients were selected to make up each group. For comparison, women who did not want HRT and who instead received an oral calcium drug, calcium aspartate 800 mg/day, were assigned to the control group. Under the same criteria, 15 patients were finally extracted to make up the control group from other medical records (n = 85) of the climacterium patients in the outpatient clinic during the same period.

The basic data of these 3 groups are summarized in

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Table 1 Profile of enrolled subjects

	Control	HRT	
		CEE + MPA	E3
	n = 15	n = 17	n = 17
Age	50.9 ± 0.52	51.1 ± 0.49	51.4 ± 0.51
BMI	21.8 ± 0.47	21.7 ± 0.51	22.1 ± 0.46
Postmenopausal years	2.47 ± 0.093	2.46 ± 0.087	2.49 ± 0.081

Postmenopausal women of the three groups were investigated for the HRT effects on lipid and bone metabolism. The patients of the groups were recruited from the pooled medical records for 4 years, as described in the text. The basic data of 3 groups were summarized in the Table: the data were designated as mean ± SEM. As indicated in the Table, there was no difference between three groups in age, body mass index (BMI), and the postmenopausal years.

Table 2 Initial data in analyzed groups

	Control	HRT
N	15	34
Age	50.9 ± 0.52	51.2 ± 0.35
BMI	21.8 ± 0.47	21.9 ± 0.34
Postmenopausal years	2.47 ± 0.093	2.48 ± 0.088
E1 (pg/ml)	20.5 ± 4.3	18.4 ± 2.8
E2 (pg/ml)	21.1 ± 4.1	20.1 ± 2.9
LH (mlU/ml)	35.4 ± 3.9	37.5 ± 3.6
FSH (mlU/ml)	98.5 ± 9.2	88.7 ± 5.8
TC (mg/dl)	211.2 ± 10.2	216.3 ± 8.2
TG (mg/dl)	96.5 ± 11.2	106.3 ± 8.1
HDL-C (mg/dl)	65.5 ± 3.5	64.5 ± 2.4
LDL-C (mg/dl)	123.6 ± 10.8	122.3 ± 9.3
PTH (pg/ml)	410.9 ± 28.1	392.2 ± 23.4
1.25(OH)2D3 (pg/ml)	33.9 ± 4.2	34.9 ± 2.9
l-BGP (ng/ml)	4.5 ± 0.7	4.3 ± 0.5
b-ALP (IU/l)	64.3 ± 10.1	69.1 ± 7.2
TRAP (U/l)	3.1 ± 0.3	3.2 ± 0.2
BMD (g/cm^2)	0.905 ± 0.051	0.899 ± 0.039

At the beginning of HRT, analyzed data are compared in the table: the data are designated as mean ± SEM. There was no difference between the treated and control groups.

Table 1. For the present study, we analyzed the parameters before, in the 3rd, 6th, and 12th months after the treatment, similar to that in our previous report [1], for total cholesterol (TC), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), triglycerides (TG) in serum lipid profile, as well as the parameters for bone metabolism, i.e., calcium ion (Ca), inorganic phosphorus (IP), parathyroid hormone (PTH), 1,25(OH)2D3, bone-type alkaline phosphatase (b-ALP), intact bone gla protein (I-BGP), tartrate-resistant acid phosphatase (TRAP) in serum. For the analysis of bone mineral density (BMD) of lumbar spine, we utilized a dual-energy X-ray absorptiometry (DEXA) using QDR-2000 (Hologic, Waltham, MA, USA), the medical records, which include all the previous data, at the 6th, and 12th months after the treatment, were pooled, or otherwise omitted from the groups; hence, the data were finally for fewer than 20 patients in each group (Table 2).

Statistical analysis

One-way ANOVA was used with Bonferoni/Dunn's test as post hoc comparison when necessary. Unpaired *t*-test or Mann-Whitney U test was used for comparison between groups. A p value of less than 0.05 was considered as statistically significant.

RESULTS

HRT efficacy

The patients of the groups were extracted from the pooled medical records as previously described. The basic data among the three analyzed groups, summa-

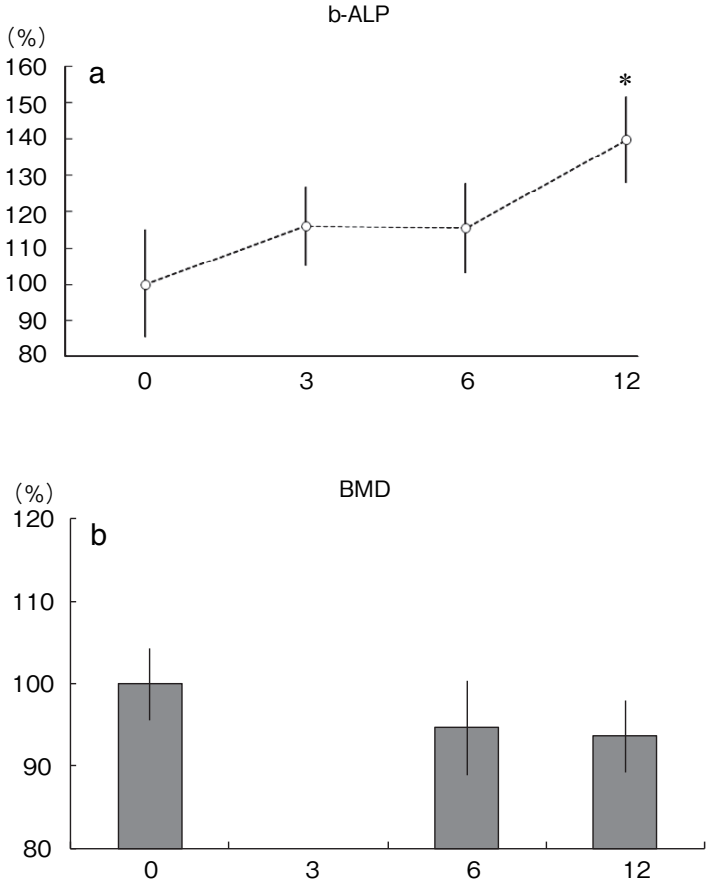

Fig. 1 Change of parameters in the control group during the 12-month observation period
Compared with the HRT groups, parameters in the control group were expected to remain constant or unchanged for 12 months. Against our expectations, b-ALP (a) showed an increasing tendency of statistical significance at the 12th month. Whereas, BMD (b) showed no statistical significance. Other parameters in the control group were constant or unchanged during the 12-month study period.
*$p < 0.05$ among the data points in the control group.

rized in Table 1, shows no statistical difference in age, body mass index (BMI), or the postmenopausal years.

At the beginning of treatment, there was no statistical difference on parameters compared between control and HRT group as in Table 2. Also there was no difference between the CEE and E3 groups (data not shown).

For comparison and analysis of the parameters of lipid or bone metabolism, the data are expressed percentages of those of the control group at the same period during treatment for each value, as shown in Fig. 3–5. Though we expected constancy during the observation period in the control group for this analysis, only one parameter, b-ALP, showed a statistical increase at the 12th month (Fig. 1a). On the other hand, BMD showed a tendency to decrease over 12 months, but without statistical significance (Fig. 1b). Since 9 of 10 analyzed parameters were constant during the 12 months of observation, all data are expressed percentages of those of the control group during the same period as analyzed below.

Concerning the lipid profile during the 12 months of treatment, serum TG decreased after the 6th month ($p < 0.05$, Fig. 2a), but TC decreased only transiently in the 3rd month ($p < 0.05$, Fig. 2b). While HDLC increased ($p < 0.05$ in the 12th month, Fig. 2c), LDLC decreased ($p < 0.05$ in the 3rd month, Fig. 2d).

Concerning bone metabolism, HRT increased PTH levels during middle period ($p < 0.01$ at the 3rd and 6th months, Fig. 3a) with no statistical change of 1,25(OH)D3 (Fig. 3b). Both bone formation markers, I-BGP and b-ALP, were decreased (Fig. 4a, b) significantly at the 12th month ($p < 0.05$). The bone resorption marker, TRAP, was also decreased in HRT with statistical significance (Fig. 3c). HRT significantly increased BMD (Fig. 3d) after the 6th month ($p < 0.05$).

E3 versus CEE therapy

In the HRT groups, there was no statistical difference on analyzed parameters comparing the CEE and E3 groups except in TG and BMD. Concerning lipid profiles, TG in the CEE group (Fig. 5a) showed a transient increase, whereas those in the E3 group (Fig. 5a) showed almost no change ($p < 0.05$) at the 3rd month (Fig. 5a).

Regarding bone metabolism, the observed param-

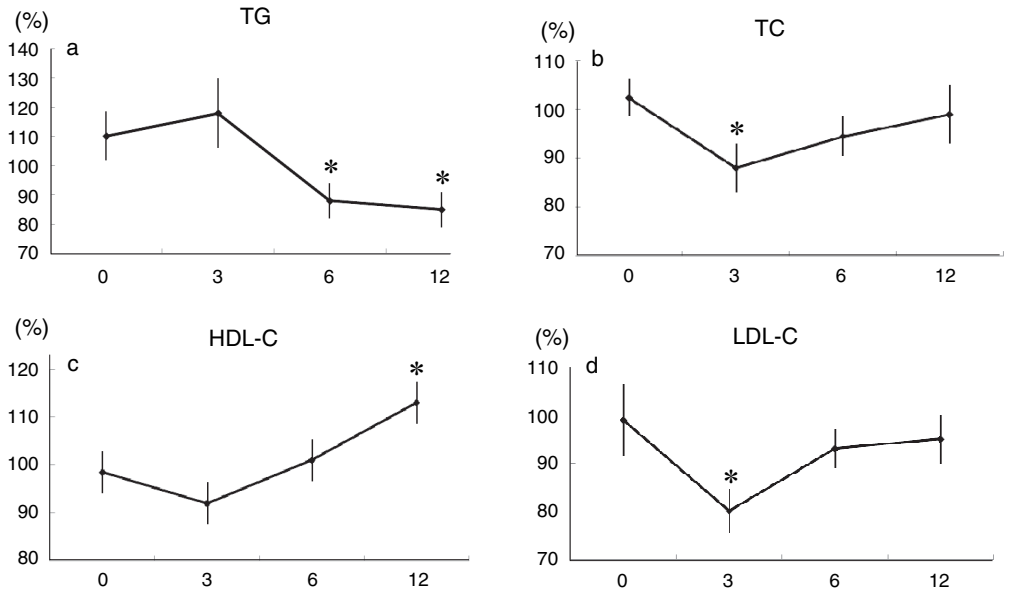

Fig. 2 Change of parameters of lipid metabolism during HRT
Changes of TG during HRT (a), TC (b), HDLC (c), LDLC (d) are expressed percentages of those of the control group over the same period of treatment for each value.
*$p < 0.05$ versus the control group.

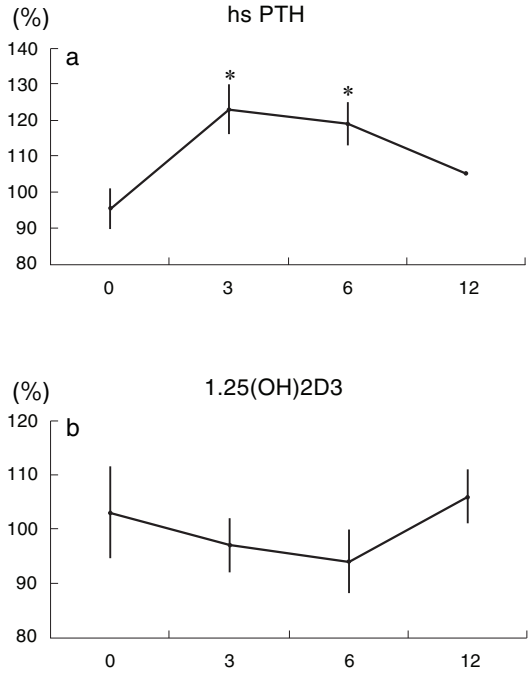

Fig. 3 Change of parameters of bone metabolism during HRT (1)
Changes during HRT of PTH (a), 1,25(OH)D3 (b) are expressed % of those of control group at the same period during treatment for each value.
*$p < 0.05$ versus the control group.

eters were almost parallel with no statistical differences between the E3 and CEE groups (data not shown) except in BMD; and where the E3 group showed a significant increase compared with the control group, there were no significant differences between the CEE and E3 groups (Fig. 5b).

DISCUSSION

One of the aims in the present study was to investigate the simultaneous effects of E3 on lipids and bone metabolism. For that purpose, we evaluated the overall effect of HRT for postmenopausal women as the first step, and subsequently attempted to differentiate the E3 treatment from the CEE treatment by comparing the two regimens. In our data, suppression of bone biochemical markers was clearly demonstrated with significant increase in BMD as an overall benefit of HRT as previously reported [1]. While TC did not show any change after the 6th month, we detected significant changes in its sub-fractions, HDLC and LDLC, where a beneficial fraction of TC, *i.e.,* HDLC did increase significantly later, with earlier decrease of a detrimental fraction of TC, *i.e.,* LDLC [7]. This beneficial effect of HRT on the lipid profile is also

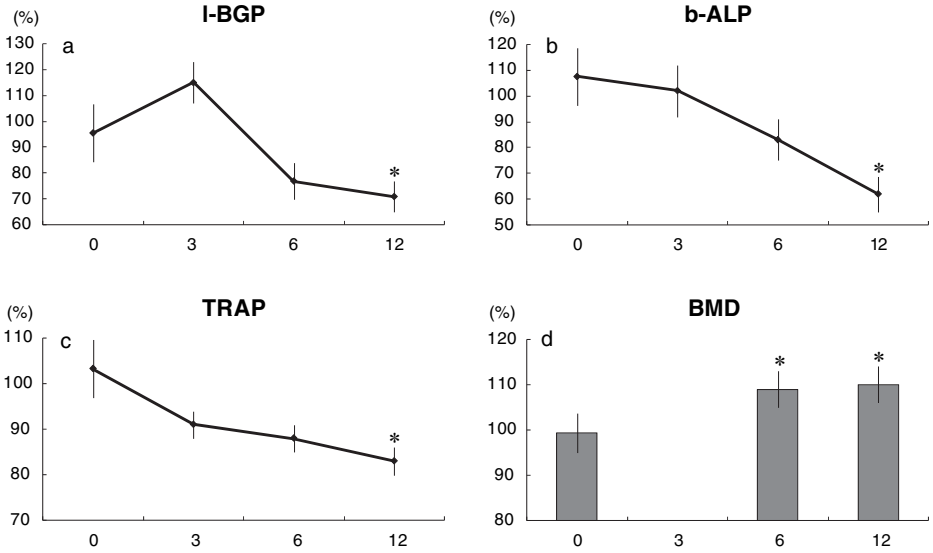

Fig. 4 Change of parameters of bone metabolism during HRT (2)
Changes during HRT of I-BGP (a), b-ALP (b), TRAP (c), and BMD (d) are expressed percentages of those of the control group at the same period during treatment for each value.
*$p < 0.05$ versus the control group.

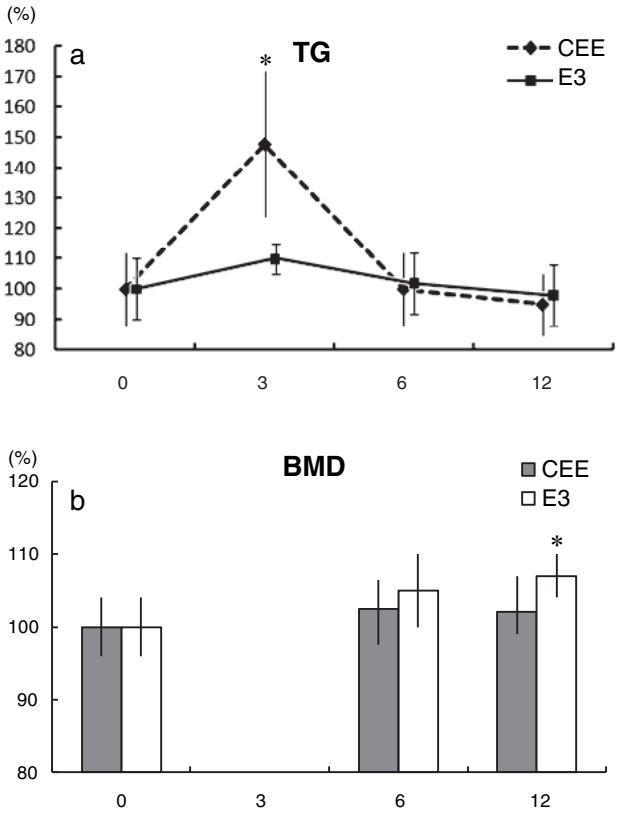

Fig. 5 Change of parameters between two regimens of HRT
In the HRT groups, there were no statistical differences in parameters comparing the CEE and E3 groups, except in TG (a) and BMD (b). Changes during HRT of parameters are expressed percentages of those of the control group at the same period during treatment for each value.
(a) Of the lipid profiles, TG in the CEE group (dashed line) showed a transient increase, whereas those in the E3 group (solid line) showed almost no changes. (b) E3 (open boxes) showed significant increase in BMD compared with the control, while CEE (closed boxes) did not show a significant increase.
*$p < 0.05$ versus the control group.

consistent with our previous report [1].

In bone metabolism, the bone turnover rate after menopause is reported to be high [8], then the suppression of bone biochemical markers is necessary for the treatment to stop reducing BMD or to recover BMD, regardless of whether or not the marker indicates the formation or resorption of bone. Our data clearly demonstrated the suppression of I-BGP, b-ALP, and TRAP with the increase in BMD as a beneficial result. In the course of suppression on those markers, TRAP (a bone resorption marker) responded earlier than the two bone formation markers (I-BGP and b-ALP), indicating that the slowdown occurred first in bone resorption followed by a decrease in bone formation. This consequence could be important to increase BMD and was consistent with our previous report [1].

Theoretically, the balance between bone resorption and should be weighted more heavily on bone formation for the recovery in BMD, while there is no clinically applicable ratio of the markers to evaluate such a balance. In this context, b-ALP was significantly suppressed by CEE with a relatively smaller increase of BMD compared with the E3 treatment (Fig. 5), which might suggest the better efficacy of the E3 treatment for osteoporosis compared with the CEE regimen.

Estrogen's role in calcium metabolism is thought to inhibit PTH-induced bone resorption as well as to produce D3 in the kidney [9]. However, in the present study, compared with the control group, PTH significantly increased whereas D3 did not increase in the HRT group (Fig. 3). These actual dynamic changes might reflect the total response of several factors concerning bone metabolism. Bone formation markers decreased after HRT compared with the control group: I-BGP reached the nadir after the 6th month, and b-ALP was still decreasing after the 12th month. This difference may reflect the intrinsic sensitivity and usefulness of HRT. TRAP, a bone resorption marker, showed decreased tendency at the 3rd month. HRT apparently reduces the bone turnover rate. Lumbar BMD had already increased by the 6th month of HRT. Assuming the measurement variance of DEXA, HRT is evaluated as useful for not only prevention but also treatment of osteoporosis, and this effect is more evident and clearer in the E3 group. Bone markers responded earlier than did BMD regarding medical responders, and their changed magnitude was greater than that of BMD. In spite of the importance of bone markers, comparing BMD for its quick response and clinical evaluation, some markers changed directions, which makes the evaluation difficult. Concerning lipid metabolism, only HDLC was significantly increased after the 12-month HRT out of all the lipid parameters. At the 3rd month of HRT, TC and LDLC decreased and TG increased as somewhat significant changes (Fig. 2b). However significant, the beneficial effect of decreased TC and LDLC is transient according to our data. Since the patients' lipid profile was within normal range at the beginning, this transient effect of estrogen on the lipid profile may be explained by the fact that the early pharmacological effect of estrogen was rearranged in physiological circumstances and reset into so far a normal range. Then, if hypercholesterolemia was detected at the beginning, a lowered or normal-ranged TC level after the 12-month treatment could be expected. Though transient in our study, the elevation of TG is a reported side effect of estrogen [10]. However, particular care should be given to patients exhibiting high-serum TG before starting CEE treatment.

In HRT, E3 is as common as CEE in Japan. Because the E3 therapy is less potent to allow proliferation into the endometrium, and hence produces fewer adverse events of uterine bleeding than does therapy with E1 or E2 [6], E3 is prescribed especially for elderly women, and believed to have good compliance for long-term treatment for osteoporosis. In the present study, E3 increased BMD without elevation of TG ($p < 0.05$ versus CEE, Fig. 5a). Moreover, our results suggest that E3 has less effect for TG increase and fewer side effects of metrorrhagia than does CEE therapy (data not shown). While these current patients had cervical and endometrial smear tests before and after the 12-month treatment, which were all within normal cytological parameters, concrete evidence for the contingency of MPA may be required for further prolonged E3 therapy. On the other hand, MPA was reported to reduce the beneficial effect of estrogen to lipid metabolism [11]. While we could not distinguish any reduced beneficial effect of MPA in our study, the possible additional effect of MPA should keep in mind when comparing the E3 regimen with that of CEE. In consideration of these results, especially from the preventive aspect for osteoporosis as well as for other benefits [12], we would recommend E3 over CEE therapy. In the clinical management of postmenopausal women, oral estriol preparation should be considered as an alternative regimen for conventional HRT of CEE in certain cases.

Besides our recommendation of E3 for HRT, the risk of breast cancer might be a pivotal concern for selection of the preparation. While sufficient evidence supports the fact that progesterone has a beneficial effect on the estrogen-induced risk of endometrial cancer, its effect on breast cancer is still controversial [13]. As an estrogenic potency for breast physiology, estriol has some unique effects that differentiate it from estradiol, estrone, and CEE, and estriol likely has less risk for breast cancer [14]. Even though we have herein suggested this possibility of E3, further randomized controlled trials are warranted to clarify its priority and efficacy.

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