Effects of estrogen replacement therapy on symptoms and clinical parameters in post menopausal women

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ABSTRACT

Objective: To evaluate the effect of oral estrogen replacement therapy (ERT) in healthy postmenopausal women on lipid profile, body mass index (BMI), blood pressure, and blood glucose; and on postmenopausal symptoms.

Subjects and Methods: This prospective cohort research was carried out over a period of eight months, from Jun 2007 to February of 2008**.** Fifty six postmenopausal women (mean SD age of 53.3±3 years; mean menopausal period, 5 years); previously diagnosed by gynecologist were involved in this study. Thirty six postmenopausal women were treated with oral conjugated equine estrogen (CEE) (premarin®) 0.625 mg daily for two months. Twenty postmenopausal women were served as control and received daily dose of placebo.

Results: In postmenopausal women treated with conjugated equine estrogen, serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were decreased significantly as compared with placebo, while there was no significant change in the serum level of high-density lipoprotein cholesterol(HDL-c). In both groups, estrogen induced changes in plasma triglyceride and reduced the size of LDL particles. These observations suggest that the plasma TG increase may reduce the size of LDL particle. CEE lowered blood pressure, decreased fasting blood sugar and increased BMI of postmenopausal women . Significant positive correlation was found between the BMI and total blood cholesterol whereas significantly negative correlation was found between the BMI and LDL of treated postmenopausal women. CEE effectively alleviated bothersome symptoms of postmenopausal women such as hot flushes, night sweat and vaginal dryness. Whereas, it has no detectable effects in attenuating bone pain.

Conclusion: CEE causes change in lipid profile, BMI, blood pressure and attenuates bothersome symptoms in postmenopausal women.

Keywords: Post menopausal women, estrogen replacement therapy.

الخلاصة

الهدف: لتقييم تأثير العلاج التعويضي لعقار الاستروجين عن طريق الفم في النساء في سن الأمل على واجهة الدهون ومؤشر كتلة الجسم وفرط الدم الشرياني ومستوى السكر قي الدم وعلى أعراض سن الأمل.

الأشخاص وطرق العمل: أجريت هذه الدراسة المستقبلية نوع كوهرت خلال فترة ثمانية أشهر من حزيران ٢٠٠٧ ولغاية شباط ٢٠٠٨. وشملت الدراسة ٥٦ من النساء في سن الأمل (معدل العمر ± الانحراف المعياري: ٥٣± ٣ سنة ومعدل فترة سن الأمل ٥ سنوات). وكانت الدراسة تحت إشراف أخصائية في الأمراض النسائية. وأعطي عقار الاستروجين المتحد والمشتق من الخيل وبجرعة ٠,٦٢٥ ملغم في اليوم ولمدة شهرين ل ٣٦ امرأة. أما العينة الضابطة فقد شملت ٢٠ امرأة في سن الأمل وأعطيت جرعة كاذبة يوميا ولمدة شهرين.

النتائج: أدى علاج النساء في سن الأمل لعقار الاستروجين المتحد والمشتق من الخيل إلى خفض مستوى الكولسترول الكلي ومستوى البروتين ألشحمي خفيض الكثافة مقارنة بالمجموعة الضابطة. بينما لم يكن هناك تغيير معنوي في

مستوى البروتين ألشحمي عالي الكثافة. كما ان الاستروجين المتحد قلل من فرط الدم الشرياني ومستوى السكر في الدم ورفع مؤشر كتلة الجسم. كما قلل الاستروجين المتحد من الأعراض المزعجة المرافقة لسن الأمل مثل الاحمرار الحار وألتعرق الليلي والجفاف المهبلي بينما لم يؤثر العقار على الم العظام.
الاستنتاج: سبب الاستروجين المتحد والمشتق من الخيل تغييرا في واجهة الدهون ورفع مؤشر كتلة الجسم وبينما قلل من فرط الدم الشرياني ومستوى السكر في الدم و من أعراض سن الأمل عند النساء.

In postmenopausal women, the principle source of circulating estrogen is adipose tissue stroma, where estron is synthesized from dehydroepiandrosterone secreted by the adrenals[1]. Peak estradiol (200-400 pg/ml) and estron (170-200 pg/ml) concentrations are achieved during the late follicular phase thereafter decreasing to their lowest concentration (estradiol, 40-60 pg/ml; estrone, 40-60 pg/ml) during the early follicular phase[2]. After menopause, estrone derived from the conversion of adrenal androstenedione becomes the predominant estrogen. Average estradiol and estron concentration are 5-20 pg/ml and 30-70 pg/ml, respectively, with an estradiol/estron ratio of less than one[3].

The two major uses of estrogens are as components of combination oral contraceptives and for menopausal hormone therapy (MHT). The pharmacological considerations for their use and the specific drugs and doses used differ in these settings. Historically, conjugated estrogens have been the most common agents for postmenopausal use (0.625 mg/day most often used)[4].

The use of estrogens in postmenopausal women is controversial. Many organizations advice that they should be used in as low a dose as possible for as short a time as possible. These recommendations are based primarily on results of the Women's Health Initiative, which found harmful side effects to the heart or breast cancer in women who started combination hormone replacement. Fracture rates, however, were significantly reduced with estrogen in all ages, races, with or without progestin. Every study about estrogen, from animal experiments to observational studies to clinical trials, has found that estrogen is beneficial to bone health, including a meta-analysis of 57 trials done before the Women's Health Initiative**.** The bones are stronger as long as estrogen is used. Further analysis of the Women's Health Initiative study has revealed that the side effects are different in women who start estrogen close to the time of menopause[4, 5].

Women aged 50-59 who took their estrogen (conjugated equine estrogen 0.625 mg/d) for 7 years had significantly fewer coronary calcifications than those who took placebo[6]**.** It is possible that women taking estrogens for extended periods of time may experience some of the same long-term side effects as women who have taken oral contraceptives for extended periods of time. These long-term problems may include the development of blood-clotting disorders, liver cancer or other liver tumors, high blood pressure, glucose intolerance (symptoms similar to diabetes) or worsening of the disease in diabetic patients, unusual sensitivity to the sun, and high blood levels of calcium[7].

This study was undertaken to observe the effect of conjugated equine estrogen 0.625 mg/d and in comparison with placebo on the lipid profile, BMI, blood sugar, blood pressure and

symptoms in healthy postmenopausal women for 2 month follow up.

Subjects and methods

This prospective cohort study was carried out during the period from July 2007 to February 2008 at the Out-patients clinic in Maternity Teaching Hospital, Erbil and Shahid Molazem Karim, Salahadin.

The study included 36 postmenopausal women, mean ± SD age of 53.3 ± 3 years; range 43 to 65 years; mean menopausal period, 5 years; range, 1 to 10 years who had been previously diagnosed by gynecologist as having sign and symptoms of postmenopausal and they complained about it and needed treatment. Each subject received oral conjugated equine estrogen (premarin®) 0.625 mg daily for two months.

Height and weight were measured while participants were wearing light clothing and no shoes. Blood pressures (BP) were recorded in the sitting position with a standard mercury sphygmomanometer after 10 minutes of rest. These patients had not undergone oophorectomy and hysterectomy. None of the subjects had menstruated for at least one year. None of them had a history of hypertension, diabetic mellitus or cardiovascular disease, and none was currently taking any medication known to influence lipoprotein metabolism, serum glucose level. None of the women was taking ERT before this study.

Twenty naturally postmenopausal women mean ± SD age, 57.3±2 years; ranges 45 to 65 were selected as a placebo group. They used daily starch capsule for two month follow up of women.

Three ml of blood samples were drawn from placebo group and patients in the morning after an overnight fast for 12 hours. Blood samples were obtained before starting treatment and rechecked at the end of two months. The serum was collected in a plain tube and kept frozen for analysis of serum glucose and lipid profile.

Data are presented as mean ± SE. Statistical analyses were carried out using ANOVA and Chi-square test. The least significant difference (LSD) was used for comparison between means. Paired student t-test was used to compare BMI between control and treated group. Correlation coefficient (r) was used to determine the relationship between BMI and the effects of estrogen on blood pressure, blood sugar and cholesterol. $P<0.05$ was considered significant.

Results

The effect of conjugated equine estrogen (CEE) on serum lipid profile of postmenopausal women

In postmenopausal women treated with CEE, serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were decreased significantly in comparison with the placebo group, while there was no significant change in the serum level of HDL-C in both groups as shown in Table 1.

Table 1. The effects of CEE and placebo on lipid profile of menopausal women. Data are represented by mean ± SE.

Parameters	C1 n=36	T	C2 n=20	Placebo	LSD	
					P<0.05	P<0.01
TC mg/dl	198.3 ±6.537	167.1 ±4.71	180.9 ±7.897	168.4 ±6.663	26.27	34.9
TG mg/dl	146.7 ±7	167.1 ±8	162.7 ±18	*139.7* ±10	43.6	57.9
HDL-C mg/dl	58.4 ±2.1	59.9 ±1.7	58.9 ±3.9	60.6 ±3.9	11	14.6
LDL-C mg/dl	110.38 ±6.7	71.22 ±4.8	89.3 ±8	80.9 ±6	26.97	35.8

C1= before treatment with CEE, T = after treatment with CEE, C2= before using placebo
LSD = least significant difference.

In postmenopausal women treated with CEE, serum level of LDL-C decreased significantly ($p<0.01$), in comparison with the placebo group (Table 1).

The effect of conjugated equine estrogen and placebo on blood sugar of postmenopausal women

serum sugar levels of postmenopausal women treated with CEE were decreased significantly ($P<0.05$) as compared with placebo group as shown in Figure 1

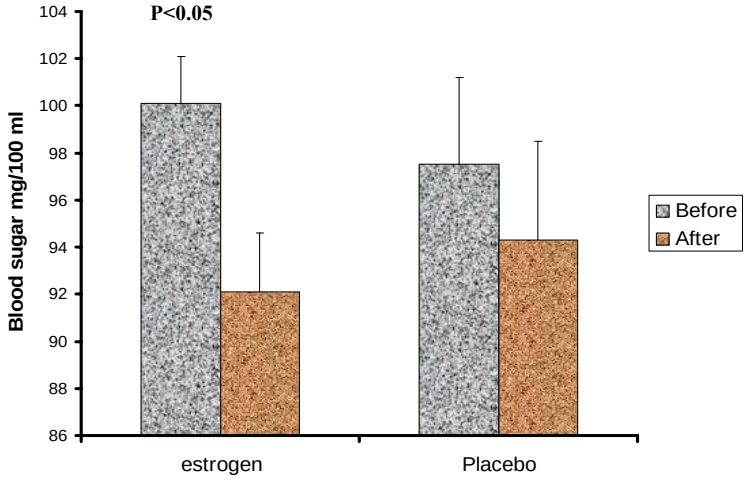

Figure 1. The effect of CEE and placebo (n_1=36, n_2=20) on serum sugar of postmenopausal women

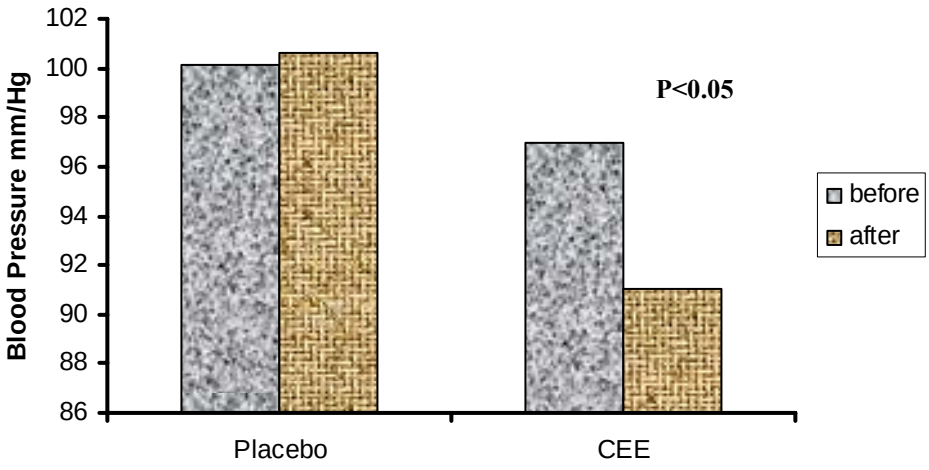

Figure 2. The effect of CEE and placebo (n_1=36, n_2=20) on blood pressure of postmenopausal women

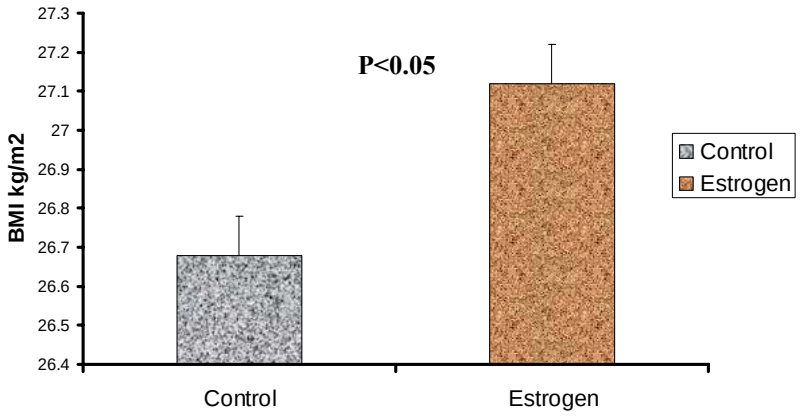

Figure 3. Effect of CEE on BMI of postmenopausal women (n_1=36)

The effect of conjugated equine estrogen and placebo on blood pressure of postmenopausal women

There were slight but statistically (P<0.05) fall in mean blood pressure of menopausal women treated with CEE, while no detectable changes were found in the mean blood pressure of women in the placebo group Figure 2.

The effect of conjugated equine estrogen and placebo on BMI (body mass index) of postmenopausal women

In postmenopausal women treated with CEE, BMI was significantly increased as shown in Figure 3.

The relationship between BMI and TC and LDL-C of postmenopausal women treated with CEE

Significant positive correlation was found between the BMI and total blood cholesterol whereas significantly negative correlation was found between the BMI and LDL-C of treated postmenopausal women (Figures 4 & 5).

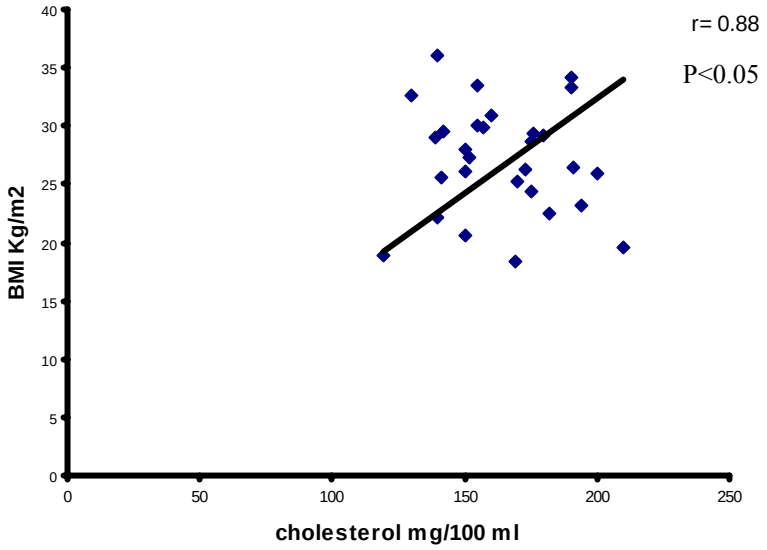

Figure 4. The relationship between BMI and cholesterol of menopausal women treated with estrogen

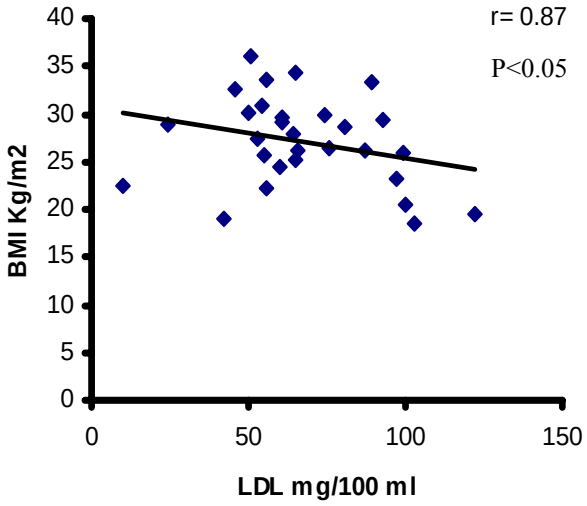

Figure 5. The relation between BMI and LDL of menopausal women treated with estrogen

The effect of Conjugated equine estrogen and placebo on hot flush, night sweat, vaginal dryness and bone pain

There was significant reduction in frequency of night sweat and hot flush in women treated with CEE as compared with placebo group (67%) (Table 2) The improvement of vaginal dryness in women were treated with estrogen (47%) is statistically significant had good response (Table 3). With regard to bone pain, effect of estrogen on bone pain was not significant (16-20%) (Table 4).

Discussion

An increase of both serum TC and LDL-C have been observed during menopause. Additionally, a shift to smaller, denser and potentially more atherogenic LDL particle sizes has been related to menopause[8]. However data on HDL-c have been inconsistent, as HDL-C has been reported to remain unaffected[9], a part from a decline of HDL-C has been also observed[10]. An increase of plasma TG concentration has also been reported after menopause[11]. These parameters were in agreement with base line measurement of lipid

Table 2. The effect of placebo and CEE on hot flash of postmenopausal women

Hot flush	No response		Response		Good response	
	No	%	No	%	No	%
Placebo	18	90	2	10	0	0
CCE	2	5	10	28	24	67

Pearson Chi-square: 54.7 (P<0.001

Table 3: The effect of placebo and CEE on vaginal dryness of postmenopausal women

Vaginal Dryness	No response		Response		Good response	
	No	%	No	%	No	%
Placebo	19	95	1	5	0	0
CCE	5	14	14	39	17	47

Pearson Chi-square: 34.69 (P<0.001)

Table 4. The effect of CEE on bone pain of postmenopausal women

Bone pain	No response		Response		Good response	
	No	%	No	%	No	%
Placebo	10	50	6	30	4	20
CCE	21	58	9	25	6	16

Pearson Chi-square: 0.361 (P<0.835

profile of postmenopausal women in the present study.

In our study CEE decreased the level of serum TC and LDL-Cl in women . These results are in agreement with other studies[12-14].

In this study, level of HDL-C remain unchanged or slightly increase comparing to placebo, this finding may be related to short term therapy of this research. Mean while wakatsuki et al.[13] found that 0.625 mg CEE daily for 3 month but not 0.312mg increased the plasma HDL-C, which disagrees with the present study.

After one year research Kukcu et al.[15] observed that oral CEE increased HDL-C significantly. These effects of oral CEE in increasing HDL-C and decreasing LDL-C levels demonstrated its beneficial effects on lipid profiles. Moreover Rabbani et al.[14] found that follow up of postmenopausal women who used 0.625mg of oral CEE for one month increased HDL-C significantly which disagree with the present study related to short time follow up.

In the present attempt, triglyceride level increased which is in consistent with other studies[16,14]. Plasma triglyceride concentrations were elevated by 0.625mg and not by 0.3125 mg of CEE[17]. This finding suggests that higher dose oral CEE may be atherogenic, whereas lower doses may prevent the development of atherosclerosis.

The effects of estrogens on serum lipids and lipoproteins are most widely studied regarding cardiovascular risk factors. Favorable changes in the lipoprotein profile have previously been estimated to account for 25-50% of the cardio protective effects observed in postmenopausal women during the Estrogen Replacement and Atherosclerosis (ERT)[18]. But there are controversial results on cardioprotective effect of oral hormone replacement therapy (HRT) and ERT. The heart and Estrogen/Progestin Replacement study (HERS)[19] and ERA Trial –showed that (HRT) did not reduce the risk of coronary heart disease (CHD) in postmenopausal women with established coronary disease. In addition, the women's Health Initiative (WHI) in healthy postmenopausal women without CHD demonstrated that HRT was associated with an initial increased risk of cardiovascular disease (writing group)[20] .

A reduction in the plasma concentrations of estrogen leads to enhanced activity of lipoprotein lipase, which may increase the plasma LDL concentration[21]. In addition, have suggested that hypercholesterolemia in postmenopausal women results from impairment of the LDL receptor[22]. The decrease LDL receptor activity has been observed in hypercholestrolemic postmenopausal women. whereas estrogen has been shown to increase the rate of LDL catabolism [23,24].

Estrogen lowers plasma concentrations of LDL particles by stimulating hepatic synthesis of LDL-receptors while increasing plasma concentrations of HDL via inhibition of hepatic TG lipase activity [25].

A dose dependent increase of plasma TG levels seems to be related to the enhanced hepatic production of large TG-rich VLDL particles, and not to impaired VLDL catabolism [26]. Estrogen induced changes in plasma TG correlation negatively with the size of LDL particles [25, 27]. The mechanism of the estrogen-induced decrease in LDL particle size could be that: estrogen induced hypertriglyceridemia enhances lipid transfer reactions, resulting in TG-

rich and cholesterol ester poor LDL particles; subsequent hydrolysis may increase the formation of LDL particles that are smaller than normal[28].

In this study, blood pressure were decreased in postmenopausal women treated with CEE as compared with placebo, this result goes with the studies[29,30] who observed that estrogen replacement therapy lowered blood pressure of menopausal women. Howerer, August and Oparil[31], showed increase in blood pressure during HRT.

In agreement with our study Sanada[19] observed that, administration of oral CEE 0.625mg daily for three months increased NO-mediated endothelium-dependent vasodilatation and plasma levels of ACE activity were significantly reduced from baseline after 3 months of estrogen treatment. The fall in blood pressure induced by CEE therapy could be attributed to short term vasodilatation caused by increased release of nitric oxide or changes in ion channel function (non-genomic effect). Estrogen causes a rapid, transient vasodilatation by ER-α mediated activation of endothelial nitric oxide synthase enzyme, resulting in increase formation and release of nitric oxide without altering gene expression. Vasodilatation may also be partly due to the activation of potassium channels or the inhibition of calcium currents[18;32]. Part of estrogen-induced vasorelaxation could be related to beneficial changes in lipoproteins, such as an increase of HDL cholesterol [33]. A decrease of endothelin-1 level, a vasoconstrictor, has also been observed during ERT[34].

One can find that fasting blood sugar decrease as compared with placebo, this result was consistent with other workers[28,29]. Epidemiological studies, showed that, postmenopausal estrogen use was associated with reducing fasting glucose and insulin levels. However, fasting blood glucose levels are not altered with estrogen replacement and do not increase with the addition of progestin. Also it must be noted that estrogen either oral or transdermal, improve insulin sensitivity and increase insulin secretion at usual doses[35].

BMI of the present menopausal women treated with CEE was increased which could be related to salt and water retention by estrogen or it could be due to women life style (such as dietary intakes) and increase in appetite and mood improvement..

At the present study, there was no change between the effect of CEE and placebo on bone pain, which is the important symptom of osteoporosis. Lindsay et al.[36] suggested that follow up of menopausal women after two years of study, that took CEE 0.625mg, 0.45mg, and 0.3 mg daily with and without medroxyprogestrone,

Hot flush is one of the most consistent and bothersome symptoms that women face as they enter the menopausal transition and subsequent menopause. Hot flushes result from estrogen deficiency and a resetting of the hypothalamic thermoregulatory set point[37]. Also alterations in the concentration and sensitivity of catecholamine or serotonin receptors can be induced by changes in gonadal hormone levels as both these neurotransmitters believed to be involved in temperature regulation mediated by the hypothalamus, decreasing levels of estrogen may initiate a cascade of events that culminates in a hot flush[38]. In this study, oral administration of CEE was significantly effective in alleviating hot

flushes and night sweat. These results were correlated well with Utian and Colleagues[39], who noticed that at the third week of therapy, the mean daily numbers of hot flushes in all CEE and CEE/MPA was significantly lower when compared with the numbers at baseline or in the placebo group.

Vaginal dryness is one of vulvovaginal atrophy symptoms that improved in treated women with CEE in comparison to the placebo group. This result was consistent with other study[40], who found that standard doses of ET/HT improved vaginal atrophy and subsequent symptoms associated with this condition.

Conclusion

CEE decreased the level of TC and LDL-C cholesterol, increased plasma triglyceride level with no effect on HDL-C in the treated menopausal women. CEE lowered blood pressure and decreased fasting blood sugar. CEE elevated body mass index (BMI) of menopausal women. CEE effectively alleviated bothersome symptoms of postmenopausal.

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