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ΕΡΕΥΝΗΤΙΚΗ ΕΡΓΑΣΙΑ

Low dose estradiol valerate plus estriol can preserve bone loss in the forearm and attenuate climacteric symptoms in early postmenopausal women

OBJECTIVE **The aim of the study was to establish whether a combination of low dose estradiol valerate (EV) and estriol (E3) is able to alleviate climacteric symptoms and preserve bone in early postmenopausal women.** METHOD **A one-year prospective non-randomized study was conducted of two groups of women: control group (n=31) and hormone replacement therapy (HRT) group (n=35), treated with 1 mg EV and 2 mg E3, combined with sequential levonorgestrel 0.25 mg. The criteria for inclusion were: 9–18 months after last menstrual bleeding, FSH>25 IU/L, moderate climacteric symptoms, bone mineral density (BMD) of less than 2.5 SD below peak adult bone mass. None of the women had any pre-existing medical condition which could affect bone metabolism. BMD was estimated by single-energy X-ray absorptiometry on the distal and ultradistal areas of the forearm at the start of the study and after 1 year. The Kupperman menopausal index (KI), Hamilton anxiety scale (HAMA), and adverse effects were recorded at baseline and at the 3rd, 6th and 12th months.** RESULTS **No differences in age, height, menstrual history, parity, physical activity, exposure to sunlight, coffee intake, HAMA and distal BMD were observed between the groups. In the control group body mass index (BMI) and ultradistal BMD were higher and KI lower than in the HRT group. During the study KI and HAMA decreased significantly in the HRT group compared to initial values and to the control group. BMD increased significantly in the HRT group for both distal and ultradistal areas while in the control group a significant decrease in these parameters was observed.** CONCLUSIONS **Treatment with low dose EV+E3 is sufficient to reduce climacteric symptoms and prevent bone loss with acceptable tolerability in early menopause.**

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2000, 17(6):600–608

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Η χορήγηση μικρών δόσεων βαλεριανικής οιστραδιόλης και οιστριόλης προφυλάσσει τις μετεμμηνοπαυσιακές γυναίκες από την απώλεια οστικής μάζας και τα κλιμακτηριακά συμπτώματα

Περίληψη στο τέλος του άρθρου

Key words

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During the early postmenopausal period a number of unfavourable processes take place in the female organism. Adequate treatment could considerably improve the quality of life of postmenopausal women. The unfavourable effects of estrogen deficiency in the climacteric period can be divided into short-, medium- and long-term and comprise neurogenic and psychogenic symptoms. Several methods are now used to measure

the severity of the climacteric syndrome. Some of these, as for example, the Kupperman menopausal index (KI),[1] refer predominantly to neurogenic aspects, while others, such as the Hamilton anxiety scale (HAMA),[2] Selbstbeurteilungs-Depressions-Skala (SDS), profile of mood states (POMS), etc.,[3] stress on the psychological changes after menopause. Hormone replacement therapy (HRT) has proved to be effective in alleviating climacteric complaints.[4–6] The early postmenopausal period is also characterized by active bone loss, although this is asymptomatic. Taking control of bone loss could improve the long-term "bone perspective" in females. Estrogens can protect,[7,8] or even increase[9] bone mass.

Sufficient information has been accumulated concerning the beneficial effects of treatment with standard doses of estrogens, i.e. 0.625 mg conjugated equine estrogens (CCE), 1 mg 17-beta estradiol (E2) oral or 50 µg transdermal, 2 mg estradiol valerate (EV) daily, but the issue of the minimal effective doses of estrogens is still debated. The aim of this study was the estimation of the effect of treatment with a low dose of estrogens combined with progestin in a sequential regimen on bone mineral density (BMD) and on the degree of the expression of climacteric syndrome during the early postmenopausal period.

MATERIAL AND METHOD

A one-year prospective, non-randomized, open study of menopausal outpatients referred to the University Clinics of Gynecology and Endocrinology in Sofia Medical University was performed. The criteria for selection were as follows:

a. Early non-operative postmenopausal period, 9–18 months after the last menstrual period, increased FSH (>25 IU/L), and absence of previous HRT

b. Moderate climacteric syndrome, showing 20–35 points according to the KI

c. Clinical and biochemical data indicating absence of other conditions leading to secondary osteoporosis. Women suffering from diseases which are known to affect mineral metabolism were not included. It was also considered necessary for the selected patients to have had no intake of medicine with osteotropic action throughout the year prior to, and during the study. Patients with osteoporosis showing BMD greater than 2.5 SD below peak adult bone mass[10] on baseline investigation, which requires intensive treatment, and patients with BMD>0 SD were also excluded from the study. To ensure optimal calcium (Ca) intake all women took 600 mg Ca daily in pills during the study. All the women were examined by a gynecologist and a breast specialist. They were briefed on the advantages and the risks of HRT, following which each made her own choice about whether to start HRT or not, and signed an informed consent. The study was approved by the institutional review committee.

In this way, two groups were formed: a control group who received no treatment (n=31) and a treatment (HRT) group (n=35) to whom low doses of estrogens were administered orally in a sequential regimen: 11 days 1 mg EV and 2 mg estriol (E3), followed by 10 days 1 mg EV, 2 mg E3 and 0.25 mg levonorgestrel (Cyclo-Menorette, Wyeth-Lederle). The next course of tablets was started on the 28th day.

The following data were also recorded for each participant: age, height, weight, BMI, duration of time after the last menstrual period, mean interval and mean duration of menstrual cycle during the fertility period, parity, and the number of coffees per day. At the beginning of the study and on the 3rd, 6th and 12th months all women completed a questionnaire covering the 11 symptoms determining KI: hot flushes (with or without sweating), paresthesias, insomnia, nervousness, melancholia, vertigo, fatigue, arthralgia/myalgia, headache, palpitations, and formication. Each symptom was rated on a scale of 0–3 referring to slight, moderate, and severe complaints. To calculate the KI a multiplication factor was used as follows: 4 for hot flushes, 2 for paresthesias, insomnia, and nervousness, and 1 for all other symptoms. A total score of 15–20 indicated mild, 20–35 moderate and over 35 severe climacteric syndrome.[1] Simultaneously, the 14 symptoms of HAMA were recorded, including anxious mood, tension, fear, insomnia, intellectual, depressed mood, somatic (muscular), somatic (sensory), cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, autonomic symptoms, behaviour at interview. The severity of symptoms was assessed using the following scale: 0=not present, 1=mild, 2=moderate, 3=severe. A total score of HAMA up to 14 indicated mild, from 15 to 28 moderate and over 28 severe climacteric complaints.[2]

Physical activity was estimated by points at the beginning and end of the study:

– Sedentary work-style without additional physical exercise=0 points

– Sedentary work-style with physical exercise during the weekends=1 point

– Sedentary work-style with physical exercise at least 3 days weekly=2 points

– Work-style associated with physical activity and exercise=3 points.

Exposure to sun was also estimated by points:

– Work indoors without exposure to sun=0 points

– Work indoors but residing at the seaside in the summer=1 point

– The same with exposure to sun during the weekends also=2 points

– Work outdoors=3 points.

The BMD was measured by the same investigator at the beginning and at the end of the study on the forearm by single-

energy X-ray absorptiometry (densitometer DTX-100-Osteometer A/S-Denmark). Calibration with the standard phantom supplied by the producer was performed daily. BMD was recorded on the ulna and radius in g/cm^2 at the distal area (predominantly compact bone) and the ultradistal area (predominantly cancellous bone).[11] The region of measurement is automatically determined proximal and distal to the point at which the radius and ulna are separated by 8 mm. For more details concerning this method see reference 12.

The FSH was measured by the immunoenzyme method using commercial kits (Serozyme, Serono, Switzerland). The intra- and interassay coefficients of variation were 2.5% and 3.8%, respectively.

Women on HRT were followed-up for side effects, breast discomfort, bloating, nausea, headache, intermenstrual bleeding and their dynamics, if present.

On starting treatment the HRT-group numbered 37 women but afterwards two withdrew for reasons not related to the medicine. The control group initially consisted of 40 women but later 9 of them were excluded because of starting sedative therapy, improper compliance, etc.

Statistical analysis was performed using the SPSS 8.0 statistical package. All data are presented as the mean±SEM (standard error of mean). Differences at the beginning, during and at the end of the study period in each group were explored using Student's paired t-test. In the case of non-normally distributed data, the Mann-Whitney U test and Wilcoxon's test were used for unpaired and paired comparisons respectively. Pearson and Kendall correlation coefficients were calculated for relevant variables. Significance was assumed when $P<0.05$.

RESULTS

No substantial differences between the two groups were observed according to age, height, mean interval and duration of menstrual cycle, parity, number of the cups of coffee consumed daily, physical activity and exposure to the sun at the beginning and the end of the study (tabl. 1). The treatment group initially had a lower BMI.

The initial KI was significantly lower in the control group than is the treatment group (25.8±0.76 vs 29.1±0.58, $P<0.01$). At the end of the study period it decreased significantly in the controls ($P<0.001$) compared to the initial data. In the HRT group there was a highly significant decrease ($P<0.001$) even during the first 3 months and persisting between the 3rd and the 6th months. During the second half-year the KI kept on decreasing, though not reaching a significant difference from the 6th month. The differences between the groups were highly significant ($P<0.001$) starting from the 3rd month (tabl. 2, fig. 1). A similar pattern was observed concerning the HAMA (tabl. 3, fig. 2). No significant difference was found between the groups at the onset of the study. A significant decrease of the HAMA was observed in the control group ($P<0.001$) at the end of the study period compared to the initial data. In the treatment group the HAMA score fell significantly starting from the 3rd month ($P<0.001$) continuing to be low until the 12th month. The intergroup differences reached significance as early as the 3rd month ($P<0.001$).

The side effects reported in the treatment group are shown on table 4. Sixteen women (46%) had acceptable side effects (some of them more than one) on the 3rd month which did not present a sufficient argument for discontinuation of the treatment and their number had

Table 1. Main investigated basal parameters in HRT and control groups.

Parameters	HRT group n=35	Control group n=31
Age (years)	48.11±0.54	49.39±0.51
Height (cm)	163.83±0.69	165.16±0.70
BMI (kg/m^2)	24.10±0.30	25.40±0.40*
FSH (IU/L)	73.77±4.44	70.19±4.63
Mean interval of MC (days)	28.43±0.64	28.13±0.70
Mean duration of MC (days)	5.09±0.19	5.48±0.27
Parity (number of deliveries)	1.69±0.13	1.74±0.16
Number of coffees per day	1.29±0.20	1.13±0.21
Physical activity (points)	1.80±0.15	1.48±0.13
Exposure to sunlight (points)	1.29±0.13	1.13±0.11

*$P<0.05$

Table 2. The Kupperman menopausal index in HRT and control groups.

Groups	Basal		3rd month		6th month		12th month
Control group	25.8±0.76	NS†	25.5±1.0	NS†	23.2±1.21	NS†	21.1±1.24#
	P<0.01*		P<0.001*		P<0.001*		P<0.001*
HRT group	29.1±0.58	P<0.001†	15.3±0.55	P<0.001†	11.6±0.49	NS†	10.3±0.70#

#Comparison between basal and 1 year points within each group, $P<0.001$

†Comparison between two subsequent periods within each group

*Comparison between groups for corresponding periods

NS: No significant differences

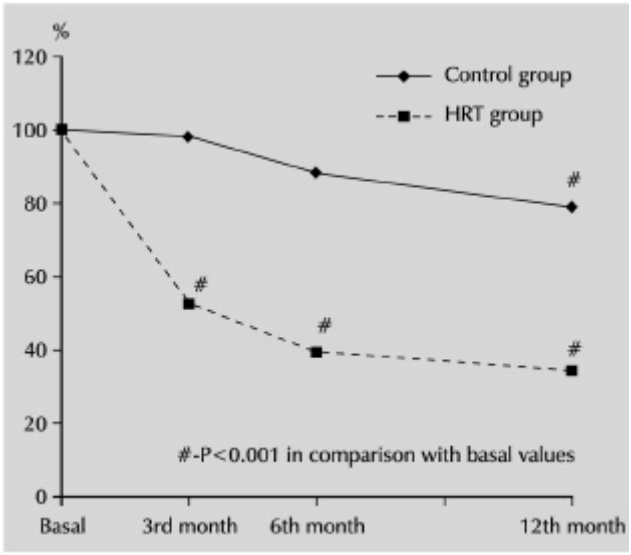

Figure 1. Percentage changes in the Kupperman menopausal index during the study period.

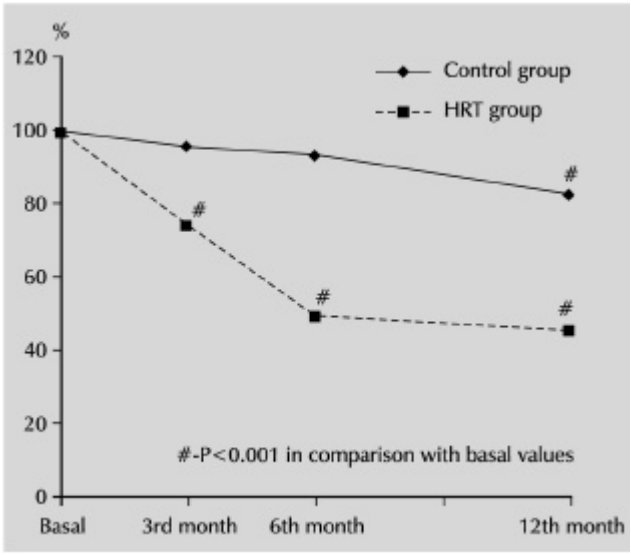

Figure 2. Percentage changes in Hamilton anxiety scale during the study period.

decreased to 3 (8.6%) by the end of the study. Thus, on the 12th month only 2 women reported 1 adverse effect and 1 woman had two. No overt climacteric symptoms occurred during the 7-day drug free period.

Initially there was no significant difference in BMD at the distal area between both groups (tabl. 5). Throughout the study a 1.6±0.23% decrease was established in the control group whereas in the treatment group distal BMD increased by 0.6±0.15% (fig. 3). The BMD dynamics were more pronounced in the ultradistal part. Initially the BMD was substantially lower in the treatment group than in the control group, but it rose significantly by 1.9±0.41% in the course of the treatment, while in the control group it diminished considerably by 3.4± 0.23% (P<0.001) (tabl. 5, fig. 3).

Correlation coefficients of the main initial parameters in all women participating in this study are shown on table 6. A highly significant positive correlation between KI and HAMA at the beginning of the study (r=0.69) as well as during the whole study period in both groups was observed. The percentage decrease of KI and HAMA at the end of the study was also significantly correlated (r=0.94 in the HRT group; r=0.80 in the control group). The distal and ultradistal BMD were also significantly correlated with physical activity (r=0.34; r=0.37, respectively) and exposure to sunlight (r=0.33; r=0.39, respectively). During the treatment a significant positive correlation was established between the percentage increase in ultradistal BMD and the percentage decrease of KI (r=0.59) and HAMA (r=0.56). The increase in distal BMD was not significantly correlated with the above variables.

DISCUSSION

This study was designed to answer the question whether the combination of low doses of estrogens with progestin in a sequential regimen with a drug free inter-

Table 3. Hamilton anxiety scale in HRT and control groups.

Groups	Basal		3rd month		6th month		12th month
Control group	22.8±0.8	NS†	22.1±0.88	NS†	21.6±0.92	NS†	19.4±1.06#
	NS*		P<0.001*		P<0.001*		P<0.001*
HRT group	23.7±0.5	P<0.001†	17.8±0.79	P<0.001†	12.1±0.93	NS†	11.2±0.84#

#Comparison between basal and 1 year points within each group, P<0.001
†Comparison between two subsequent periods within each group
*Comparison between groups for corresponding periods
NS: No significant differences

Table 4. Side effects in the HRT group.

Side effects	3rd month	6th month	12th month
Breast discomfort	9 women (25.7%)	3 women (8.6%)	2 women (5.7%)
Bloating	5 women (14.3%)	2 women (5.7%)	1 woman (2.8%)
Nausea	5 women (14.3%)	1 woman (2.8%)	– –
Headache	2 women (5.7%)	1 woman (2.8%)	1 woman (2.8%)
Intermenstrual bleeding	2 women (5.7%)	–	–

The data are represented as number of patients possessing side effects and their percentage of the whole group

Table 5. BMD at the distal and the ultradistal area in HRT and control groups.

BMD	Basal		After 1 year	
	HRT group	Control group	HRT group	Control group
Distal (g/cm^2)	0.464±0.003	0.470±0.003	0.467±0.003**	0.463±0.004**
Ultradistal (g/cm^2)	0.331±0.003	0.341±0.003*	0.338±0.004**	0.330±0.004**

*P<0.05 (comparison between two groups)

**P<0.001 (comparison between basal and after 1 year values within each group)

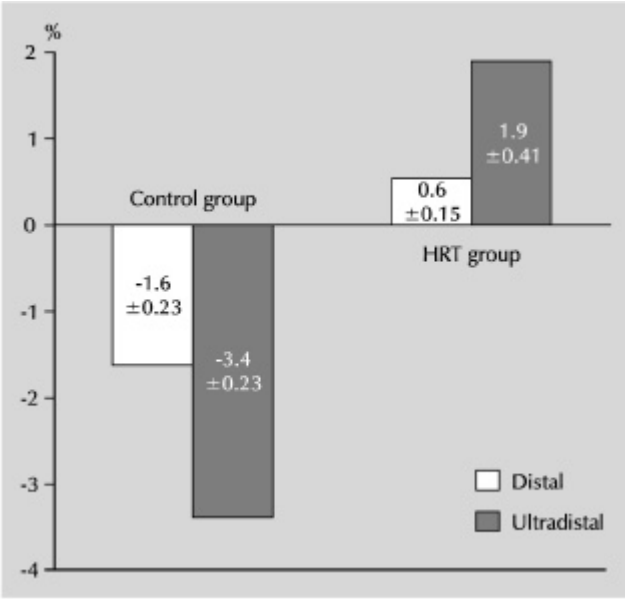

Figure 3. Percentage changes in BMD after 1 year compared to initial levels (100%).

val, started in the early postmenopausal period, is able to diminish climacteric symptoms and arrest bone loss.

The doses (minimal-effective, optimal, etc.) and the time to start treatment of neurogenic and psychological symptoms in order to reach an optimal benefit/risk ratio are still under discussion.[13–15] As in our study, a good effect from treatment with low doses of estrogens in women with moderately expressed climacteric syndrome was also established by Maclennan et al,[16] and others.[17,18] Gangar et al reported abolishment of menopausal symptoms after continuous administration of 1 mg EV+5 mg medroxyprogesterone acetate daily in patients treated with GnRH analogues.[19] Although considered a "weak" estrogen, E3 has proved its favorable effect on symptoms caused by urogenital atrophy[20] and on other menopausal complaints.[21,22] In some cases E3 is preferred because of its safety.[23]

Initially in this study the women who preferred to start HRT had significantly more marked neurological complaints as estimated by the KI and they displayed a trend towards more severe symptoms as indicated by the HAMA. The women in the control group generally showed spontaneous alleviation of the reported symptoms in the course of the study. After 1 year some of the control women failed to improve while in others the complaints had diminished considerably. In the treatment group the most pronounced improvement was reached during the first 3 months and this beneficial effect persisted till the end of the study. The percentage change in KI between the beginning and the end of the study was 20.3±1.02% in the control group and 65.4±2.25% in the HRT group. These data are similar to the results obtained by Marslew et al after the first year of treatment. In a two-year placebo-controlled study this group administered 2 mg EV continuously, combined with 1 mg cyproteron acetate continuously or with sequential levonorgestrel 75 µg, and achieved a reduction in KI of 72% and 78% respectively. In the placebo group the change was 19%. They found no difference between the two treatment regimens in reducing menopausal symptoms. The initial KI of their patients was lower than that of the groups in this study, perhaps because of the longer postmenopausal period (6 months to 3 years) before initiation of treatment.[24]

Summarising the results of numerous studies it may be concluded that the yearly postmenopausal loss of bone mass ranges between 1% and 10%, 2–3% on the average, and it is more marked during the first years and in the cancellous bone.[25,26] The administration of HRT results, according to some authors,[27,28] in a 5–7% increase of bone mass in the space of 12 to 18 months, followed by a plateau. Other authors find no difference in bone

density throughout the treatment period and some report a decrease.[29] These differences may be related to various factors, including the continuation and the scheme of treatment, the hormone and the dose applied, the site of measurement, ethnic and geographical factors, etc.

The various studies have not yet solved the problem of the minimal estrogen dose required to preserve bone. It is accepted that the minimum effective dose with osteoprotective effect for CEE is 0.625 mg, for E2 1 mg oral, 50 µg transdermal and for EV 2 mg daily.[30,31] The report of Ettinger et al,[32] and more recent studies[33,34] showed that a dose of 0.3 mg CEE daily protects bone as does 0.625 µg if adequate calcium intake is available. Edmonds established significant reduction in bone loss during GnRH analogue treatment when a 25 µg E2 patch is applied.[35] Evans and Davie found no difference between the bone preserving effect of low (25 µg) and standard (50 µg) doses of transdermal E2 after 3 years of treatment.[36] There is scanty information concerning the effect of low-dose EV on bone. Duursma et al in a 3.7-year study compared the effect of 1 mg EV daily to 0.625 mg CCE by using dual photon absorptiometry.[37]

Data about the effect of E3 on bone are contradictory. Lindsay et al[38] and recently Hart et al, and Devogelaer et al[39,40] failed to establish any efficacy of the E3 treatment (1 and 2 mg respectively). Lately some Japanese centres have reported a powerful osteoprotective action of E3 in a dosage 2 mg daily cyclically or continuously. By using dual energy X-ray absorptiometry Nozaki et al[41] and Minaguchi et al[22] showed a significant increase of 1.66% and 1.79% respectively in the spine and a corresponding decrease in biochemical markers after an 1-year treatment of initially osteopenic women, coupled with improvement in KI and good tolerability. Itoi et al found a bone-preserving effect of E3 comparable to 0.625 CEE in early postmenopausal women after 2 years of treatment.[42] Nishibe et al in a 10-month study involving 29 women aged 70–84 years established that E3 is effective against senile osteoporosis, and low-turnover bones in elderly women are also responsive to E3.[43] Other studies (H. Mitsuhashi-unpublished data) also support a beneficial effect of E3 in Japanese women. According to the above data a speculative conclusion could be made about race differences in E3 action. In this study, 1 mg EV plus 2 mg E3 administered cyclically blocked early postmenopausal bone loss, measured on the forearm in Caucasian women.

The early postmenopausal period is of particular interest because it marks the highest rate of bone loss, although activation of bone turnover starts in the premenopausal period.[44] The study showed a decrease in BMD in the control group which was statistically more marked in the cancellous bone, 3.4%, whereas in the treatment group BMD increased significantly by 1.9%. This can be related to more active role of trabecular bone in maintaining calcium balance which is well-known.[45] Gambacciani et al, investigating bone density of the distal radius with dual-photon absorptiometry in the early postmenopausal period (6–12 months after the last bleeding) found a 4.6% loss in the control group and a 4.2% increase in group treated with 50 µg E2 transdermally after an 1-year follow-up.[46] Other authors[47] report a less severe bone loss per year on the distal forearm after the menopause, 2% in controls and 0.5% in patients treated with conventional doses of oral estrogens.

This study established a positive correlation between BMD and BMI, stature, physical activity and exposure to sunlight, and a negative correlation between BMD and both FSH levels and menopausal KI and HAMA scores (tabl. 6). Short stature, low BMI, insufficient physical activity and sunlight are well known risk factors for osteoporosis.[10] In obese women there is a beneficial effect of the even small quantity of estron generated from suprarenal steroids in the fatty tissue. This, in addition to the higher mechanical load on the skeleton, is of substantial importance for women with higher BMI. Bone loss has

Table 6. Pearson correlation of some baseline parameters in all participants.

Height							
BMI	0.22	BMI					
Distal			Distal				
BMD	0.46**	0.47**	BMD				
Ultradistal				Ultradistal			
BMD	0.35**	0.61**	0.77**	BMD			
FSH	0.23	–0.46**	–0.61**	–0.74**	FSH		
KI	–0.21	–0.43**	–0.56**	–0.76**	0.68**	KI	
HAMA	–0.24*	–0.36**	–0.52**	–0.70**	0.63**	0.69**	HAMA

*Correlation is significant at the 0.05 level

**Correlation is significant at the 0.01 level

been shown to correlate positively with climacteric symptoms[48] and FSH[49] and this study confirmed these data. During the treatment the increase in BMD in more metabolically active cancellous bone was correlated with fast improvement in climacteric symptoms.

The sum effect of the treatment in this study cannot be precisely estimated because of the non-random patient selection, but the positive change of BMD in treated patients implies a marked favorable effect. Adverse effects during the study period were mild and temporary, and did not cause its discontinuation.

In conclusion, treatment with 1 mg EV combined with 2 mg E3 and 0.25 mg levonorgestrel is sufficient to reduce the climacteric symptoms and prevent bone loss with acceptable tolerability in early postmenopausal women. Longer, prospective and randomised studies are necessary to determine the long-term efficacy of this treatment as well as its potency in osteoporotic patients.

ΠΕΡΙΛΗΨΗ

Η χορήγηση μικρών δόσεων βαλεριανικής οιστραδιόλης και οιστριόλης προφυλάσσει τις μετεμμηνοπαυσιακές γυναίκες από την απώλεια οστικής μάζας και τα κλιμακτηριακά συμπτώματα

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ΣΚΟΠΟΣ Η διερεύνηση της δυνατότητας ανακούφισης των μετεμμηνοπαυσιακών γυναικών από τα κλιμακτηριακά συμπτώματα και πρόληψης της απώλειας οστικής μάζας, με τη χορήγηση συνδυασμού μικρών δόσεων βαλεριανικής οιστραδιόλης (EV) και οιστριόλης (E3). **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Έγινε προοπτική μη τυχαιοποιημένη μελέτη δύο ομάδων γυναικών: μιας ομάδας 31 μαρτύρων και μιας ομάδας 35 γυναικών, που υποβλήθηκαν σε θεραπεία υποκατάστασης με 1 mg EV και 2 mg E3 σε συνδυασμό με 0,25 mg λεβοργεστρέλης (HRT). Τα κριτήρια συμμετοχής στη μελέτη ήταν: πάροδος 9–18 μηνών από την τελευταία έμμηνο ρύση, FSH >25 IU/L, μέτρια κλιμακτηριακά συμπτώματα και οστική πυκνότητα (bone mineral density, BMD) μικρότερη των 2 SD κάτω από τη μέγιστη τιμή οστικής μάζας στους ενήλικες. Καμία από τις γυναίκες της μελέτης δεν είχε ιστορικό νοσήματος που επηρεάζει το μεταβολισμό των οστών. Η μέτρηση της BMD έγινε με ατομική απορρόφηση (single-energy X-ray absorptiometry) στην άπω και στην απώτατη περιοχή του πήχεος, κατά την έναρξη της μελέτης και μετά από 1 έτος. Καταγράφηκε, επίσης, ο εμμηνοπαυσιακός δείκτης Kupperman (Kupperman menopausal index, KI) και η εκτίμηση της κλίμακας άγχους Hamilton (Hamilton anxiety scale, HAMA) κατά την έναρξη και κατά τον 3ο, 6ο και 12ο μήνα της μελέτης. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Μεταξύ των δύο ομάδων δεν παρατηρήθηκαν διαφορές ως προς την ηλικία, το ύψος, το ιστορικό εμμηνόπαυσης, τον αριθμό των τοκετών, τη φυσική δραστηριότητα, την έκθεση στο ηλιακό φως, την πρόσληψη καφέ, τον HAMA και την άπω BMD. Στην ομάδα των μαρτύρων, ο δείκτης μάζας σώματος (body mass index, BMI) και η απώτατη BMD ήταν μεγαλύτεροι, ενώ ο KI ήταν μικρότερος, απ' ό,τι στην ομάδα HRT. Κατά τη διάρκεια της μελέτης, ο KI και η HAMA παρουσίασαν σημαντική ελάττωση, σε σχέση με τις αρχικές τιμές τους και σε σύγκριση με την ομάδα των μαρτύρων. Η BMD, τόσο στην άπω, όσο και στην απώτατη περιοχή του πήχεος, στην ομάδα HRT αυξήθηκε σημαντικά, ενώ ελαττώθηκε σημαντικά στην ομάδα των μαρτύρων. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Η χορήγηση μικρών δόσεων EV και E3 μειώνει τα κλιμακτηριακά συμπτώματα και προλαβαίνει την απώλεια οστικής μάζας, κατά τη διάρκεια της πρώιμης εμμηνόπαυσης, με ικανοποιητική ανεκτικότητα.

Λέξεις ευρετηρίου: Εμμηνοπαυσιακός δείκτης Kupperman, Κλίμακα άγχους Hamilton, Ορμονική θεραπεία υποκατάστασης, Οστική πυκνότητα, Πρώιμη εμμηνόπαυση

References

1. KUPPERMAN HS, MEYER FG, BLAT J, WIESBADER H, FILLER W. Comparative clinical evaluation of estrogenic preparations by the menopausal and amenorrheal indices. *J Clin Endocrinol* 1953, 13:688–703
2. HAMILTON M. Standardised assessment and recording of depressive symptoms. *Psychiatr Neurol Neurochir* 1969, 72:201–205
3. DITKOFF EC, CRARY WG, CRISTO M, LOBO RA. Estrogen improves psychological functioning in asymptomatic postmenopausal women. *Obstet Gynecol* 1991, 78:991–995
4. GENAZZANI AR. Neuroendocrinology of the climacteric period and HRT. In: Wren B (ed) *Progress in the Management of the Menopause*. The Parthenon Publ Group Ltd, Casterton Hall, Carnforth, UK, 1997:380–384
5. BELCHETZ PE. Hormonal treatment of postmenopausal women. *N Engl J Med* 1994, 330:1062–1071
6. GRADY D , RUBIN SM, PETITTI DB, FOX CS, BLACK D, ETTINGER B ET AL. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992, 117:1016–1037
7. CHRISTIANSEN C, CHRISTIANSEN MS. Pathophysiological mechanisms of estrogen effect on bone metabolism. Dose-response relationship in early-postmenopausal women. *J Clin Endocrinol Metab* 1982, 55:1124–1130
8. ETTINGER B, GENANT HK, CANN CE. Long term estrogen replacement therapy prevents bone loss and fractures. *Ann Intern Med* 1985, 102:319–324
9. LINDSAY R, THOME J. Estrogen treatment of patients with established postmenopausal osteoporosis. *Obstet Gynecol* 1990, 76:1–6
10. KANIS JA, MELTON LJ III , CHRISTIANSEN C, JOHNSTON CC, KHALTAEV N. The diagnosis of osteoporosis. *J Bone Miner Res* 1994, 9: 1137–1141
11. NILAS L, NORGAARD H, PODENPHANT J, CHRISTIANSEN C. Bone composition in the distal forearm. *Scand J Clin Invest* 1987, 47:1–6
12. KELLY TL, CRANE G, BARAN DT. Single X-ray absorptiometry of the forearm: precision, correlation, and reference data. *Calcif Tissue Int* 1994, 54:212–218
13. BURGER HG. Diagnostic role of FSH measurements during the menopausal transition–an analysis of FSH, estradiol and inhibin. *Eur J Endocrinol* 1994, 42:130–138
14. BURGER HG, DUDLEY EC, HOPPER JL, SHELLEY JM, GREEN A, SMITH A ET AL. The endocrinology on the menopausal transition: a cross-sectional study of a population-based sample. *J Clin Endocrinol Metab* 1995, 80:3537–3545
15. TEEDE H, BURGER HG. The menopausal transition. In: Studd J (ed) *The Management of the Menopause*. *Annual review 1998*. The Parthenon Publ Group Ltd, Casterton Hall, Carnforth, UK, 1998: 1–12
16. MACLENNAN AH, MACLENNAN A, NEILL S, KIRKGARD Y, WENZEL S, CHAMBERS HM. Oestrogen and cyclical progestogen in postmenopausal hormone replacement therapy. *Med J Aust* 1992, 157: 167–170
17. DALY E, GRAY A, BARLOW D, McPHERSON K, ROCHE M, VESSEY M. Measuring the impact of menopausal symptoms on quality of life. *Br Med J* 1993, 307:836–840
18. LIMOUZIN-LAMOTHE M, MAIRON N, JOUCE CR, LE GAL M. Quality of life after the menopause: influence of hormone replacement therapy. *Am J Obstet Gynecol* 1994, 78:991–995
19. GANGAR KF, STONES RW, SAUNDERS D, ROGERS V, RAE T, COOPER S ET AL. An alternative to hysterectomy? GnRH analogue combined with hormone replacement therapy. *Br J Obstet Gynaecol* 1993, 100:360–364
20. CARDOZO L, BACHMAN G, McCLISH D, FONDA D, BIRGERSON L. Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: second report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol* 1998, 92(Pt 2):722–727
21. PEROVIC D, KOPAJTIC B, STANKOVIC T. Treatment of climacteric complaints with estriol. *Arzneim Forsch* 1975, 25:962–964
22. MINAGUCHI H, UEMURA T, SHIRASU K, SATO A, TSUKIKAWA S, IBUKI Y ET AL. Effect of estriol on bone loss in postmenopausal Japanese women: a multicenter prospective open study. *J Obstet Gynaecol Res* 1996, 22:259–265
23. HEAD KA. Estriol: safety and efficacy. *Altern Med Rev* 1998, 3: 101–113
24. MARSLEW U, OVERGAARD K, RIIS BJ, CHRISTIANSEN C. Two new combinations of estrogen and progestogen for prevention of postmenopausal bone loss: long-term effects on bone, calcium and lipid metabolism, climacteric symptoms, and bleeding. *Obstet Gynecol* 1992, 79:202–210
25. ETTINGER B Preventing postmenopausal osteoporosis with estrogen replacement therapy. *Int J Fertil* 1986, (Suppl):15–20
26. KANIS JA. *Osteoporosis*. Blackwell Science, 1994:46–47
27. ETTINGER B, GENANT HK, CANN CE. Postmenopausal bone loss is prevented by treatment with low-dose estrogen with calcium. *Ann Intern Med* 1987, 106:40–43
28. PRINCE RL, SMITH M, DICK IM. Prevention of postmenopausal osteoporosis. A comparative study of exercise, calcium supplementation and hormone-replacement therapy. *N Engl J Med* 1991, 325:1189–1195
29. ERIKSEN EF. Clinical aspects of estrogens and osteoporosis. In: Wren B (ed) *Progress in the Management of the Menopause*. Parthenon Publ Group Ltd, Casterton Hall, Carnforth, UK, 1997: 137–141
30. AVIOLI LV, KRANE SM. *Metabolic Bone Disease*. Academic Press, 1998
31. KOMULAINEN M, KROGER H, TUPPURAINEN MT, HEIKKINEN AM, ALHAVA E, HONKANEN R ET AL. Prevention of femoral and lumbar bone loss with hormone replacement therapy and vitamin D3 in early postmenopausal women: a population based 5-year randomized trial. *J Clin Endocrinol Metab* 1999, 84:546–552
32. ETTINGER B, GENANT HK, CANN CE. Postmenopausal bone loss is prevented by treatment with low dose estrogen with calcium. *Ann Intern Med* 1987, 106:40–45
33. MIZUNUMA H, OKANO H, SODA M, KAGAMI I, MIYAMOTO S, TOKIZAWA T ET AL. Prevention of postmenopausal bone loss with minimal uterine bleeding using low dose continuous estrogen/progestin therapy: a 2-year prospective study. *Maturitas* 1997, 27:69–76
34. BARRETT-CONNOR E. HRT and osteoporosis: practical implications of new research findings. *Eur Menopause J* 1997, 4:68–72

35. EDMONDS DK. Add-back therapy in the treatment of endome-triosis: the European experience. *Br J Obstet Gynaecol* 1996, 103 (Suppl 14):10–13
36. EVANS SF, DAVIE MW. Low and conventional dose transdermal estradiol are equally effective at preventing bone loss in spine and femur at all post-menopausal ages. *Clin Endocrinol (Oxf)* 1996, 44:79–84
37. DUURSMA SA, DE RAADT M, RAYMAKERS JA, HASPELS AA. Is 1 mg of estradiol valerate or 0.625 mg of conjugated estrogens suffi - cient for all women to prevent menopausal bone loss? *Gynecol Endocrinol* 1992, 6:205–209
38. LINDSAY R, HART DM, MACLEAN A, GARWOOD J, CLARK AC, KRASZEVSKI A. Bone loss during estriol therapy in postmenopausal women. *Maturitas* 1979, 1:279–285
39. HART DM, FARISH E, FLETCHER CD, BARNES JF, HART H, NOLAN D ET AL. Long-term effects of continuous combined HRT on bone turnover and lipid metabolism in postmenopausal women. *Osteoporos Int* 1998, 8:326–332
40. DEVOGELAER JP, LECART C, DUPRET P, DE NAYER P, NAGANT DE DEU-XCHAISNES C. Long-term effects of percutaneous estradiol on bone loss and bone metabolism in postmenopausal hysterectomized women. *Maturitas* 1998, 28:243–249
41. NOZAKI M, HASHIMOTO K, INOUE Y, SANO M, NAKANO H. Usefulness of estriol for the treatment of bone loss in postmenopausal women. *Nippon Sanka Fujinka Gakkai Zasshi* 1996, 48:83–88
42. ITOI H, MINAKAMI H, SATO I. Comparison of the long-term effects of oral estriol with the effects of conjugated estrogen, 1-alpha-hydroxyvitamin D3 and calcium lactate on vertebral bone loss in early menopausal women. *Maturitas* 1997, 28:11–17
43. NISHIBE A, MORIMOTO S, HIROTA K, YASUDA O, IKEGAMI H, YAMA-MOTO T ET AL. Effect of estriol and bone mineral density of lumbar vertebrae in elderly and postmenopausal women. *Nippon Ronen Igakkai Zasshi* 1996, 33:353–359
44. POUILLES JM, TREMOLLIERS F, RIBOT C. The effects of menopause on longitudinal bone loss from the spine. *Calcif Tissue Int* 1993, 52:340–343
45. RIGGS BL, WAHNER HW, MELTON LJ III, RICHELSONS S, JUDD HL, OFFORD KP. Rates of bone loss in appendicular and axial skeletons of women. *J Clin Invest* 1986, 77:1487–1491
46. GAMBACCIANI M, CAPPAGLI B, PIAGGESI L. Effects of transdermal estradiol administration on bone mass and bone metabolism in early postmenopausal women. *Eur Menopause J* 1996, 3:7–12
47. QUIGLEY ME, MARTIN PL, BURNIER AM, BROOKS P. Estrogen therapy arrests bone loss in elderly women. *Am J Obstet Gynecol* 1987, 156:1516–1523
48. NAESSEN T, PERSSON I, LJUNGHAL S, BERGSTROM R. Women with climacteric symptoms: a target group for prevention of rapid bone loss and osteoporosis. *Osteoporos Int* 1992, 2:225–231
49. EBELING PR, ATLEY LM, GUTHRIE JR, BURGER HG, DENNERSTEIN L, HOPPER JL ET AL. Bone turnover markers and bone density across the menopausal transition. *J Clin Endocrinol Metab* 1996, 81:3366–3371

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