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HRT and exercise: effects on bone density, muscle strength and lipid metabolism. A placebo controlled 2-year prospective trial on two estrogen–progestin regimens in healthy postmenopausal women

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Abstract

Objectives: To evaluate the effect of 1- or 3-monthly sequential combinations of estradiol valerate (E_2V) and medroxyprogesterone acetate (MPA) on menopausal symptoms, bone density, muscle strength and lipid metabolism in postmenopausal women. *Methods:* Changes in bone mineral density (BMD), isometric muscle strength, serum lipids and climacteric symptoms were evaluated in 78 women, 49–55 years of age, with a spontaneous menopause 0.5–3 years earlier. Treatment group I received 2 mg E_2V tablets for 11 days, followed by 2 mg E_2V + 10 mg MPA for 10 days and placebo for an additional 7 days; treatment group II received 2 mg E_2V for 70 days, 2 mg E_2V + 20 mg MPA for 14 days, and placebo for 7 days. The placebo group received placebo continuously for 24 months. Each group was further randomised to exercise and non-exercise subgroups. *Results:* Both hormone regimens significantly reduced menopausal symptoms, and prevented equally well the decrease of BMD both in the lumbar spine and proximal femur. A positive effect of exercise on BMD was observed in the placebo group. No synergistic effect of exercise and estrogen on BMD could be shown. Both hormone regimens increased the isometric strength of back extensor muscles. Serum total and LDL cholesterol decreased during the first year with both estrogen regimens. *Conclusions:* Estrogen–progestin regimens were equally effective in the control of menopausal symptoms and preventing bone loss, increasing muscle strength and lowering serum cholesterol. © 1997 Elsevier Science Ireland Ltd.

Keywords: Postmenopausal women; Osteoporosis; Muscle strength; Lipid metabolism; Quarterly progestin; Medroxyprogesterone acetate; Estradiol valerate

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1. Introduction

It is well known that postmenopausal estrogen replacement alleviates climacteric symptoms [1–6]. More recently, case-control and cohort studies have shown that hormone replacement therapy (HRT) reduces the risk of hip and forearm fractures in postmenopausal women [7]. Estrogen may also have anabolic effects on other skeletal tissues, especially on muscle, although very little is known of these effects [8].

Physical exercise has clear effects on bone during childhood and adolescence [9]. However, prospective studies in pre- and postmenopausal women have provided conflicting results, and data on the possible synergistic effect of exercise and HRT are still lacking [10,11].

A menopause-related increase in the risk of coronary heart disease has been verified, and several studies suggest that HRT protects against coronary heart disease in postmenopausal women [12–14]. This is thought to be partly related to the beneficial effects of estrogen on serum lipids [15]. Progestins, depending on their androgenic effects, may counteract the beneficial effects of estrogens [16]. It is thus of special importance that estrogen–progestin combinations used in long-term HRT maintain a beneficial or, at least, neutral balance in lipid metabolism.

Monthly bleeds during HRT are unwanted by many postmenopausal women and continuous HRT regimens are associated with frequent unscheduled bleeds [17,18].

The quarterly administration of progestin in HRT represents a compromise between the conventional 1-month cycles and the continuous combined regimens [19,20].

The present study was performed to investigate the effect of two regimens of estradiol valerate, combined with medroxyprogesterone acetate sequentially monthly or every 3 months, on menopausal symptoms, bone, skeletal muscle and lipid metabolism. In order to clarify the possible synergistic effect of exercise with estrogen on bone, half of the patients in each group were introduced to a moderate exercise program.

2. Materials and methods

2.1. Study design and patient selection

The study was a prospective, randomised, placebo controlled comparison of two estrogen–progestin regimens. Randomisation was stratified to evaluate the effects of hormone treatment and exercise. The trial was conducted at the Deaconess Institute of Oulu, Finland between January 1989 and April 1991. The protocol was approved by the ethical committee of the hospital and the study was conducted in accordance with the Declaration of Helsinki of the World Medical Assembly.

From a population of 100 000 inhabitants in the City of Oulu and its immediate surroundings in Northern Finland, all women aged 49–55 years were listed from public records and a questionnaire on menopause, previous medical history, use of hormones and other treatments was sent randomly to every third of these women ($N = 1179$).

Altogether 833 (71%) replied, and 93 presumably healthy women, 0.5–3 years postmenopausal, without previous HRT and without obvious contraindications for estrogen–progestin treatment were invited to an interview and medical examination. A further 15 women were excluded because of reluctance to participate in the trial [8], or because of various diseases [7]. After oral and written information from the investigators, written informed consent was obtained from all patients. Finally, 78 healthy women in early menopause, meeting all inclusion and exclusion criteria and willing to have HRT, were entered in the study. S-FSH was determined in all women at the onset of the study to confirm the menopausal status.

The women were randomised to receive either treatment I, treatment II or placebo (Table 1), with 26 women in each group. The randomisation was stratified: 13 patients in each group received active guidance and encouragement to physical activities, while no special reference to exercise was made to the other half.

2.2. Recording of menopausal symptoms

Menopausal symptoms were recorded at baseline and at 12 further time points during the study using the Visual Analogue Scale (VAS) method [21]. The following symptoms were recorded: hot flushes, night time sweating, tension or anxiety, sleep disturbances, depressive mood, dizziness, headaches, dry vagina, palpitations, urinary incontinence, nausea, edema, fatigue and breast tension.

2.3. Measurement of bone mineral density (BMD)

BMD of the lumbar spine and proximal femur was measured by X-ray dual photon absorptiometry (Lunar DPX; Lunar Radiation Corporation, Madison, WI, USA), with a correction for interference from fatty tissue. The measurement sites were the lumbar vertebrae L2–L4 in the spine, femoral neck, Ward's triangle and trochanter major area in the proximal left femur, with coefficients of variation of 0.9–1.0%, 1.2–2.0%, 2.6–3.1 and 1.5–2.4%, respectively [22]. The measurements were performed at baseline and at 3, 6, 9, 12, 18 and 24 months.

2.4. Clinical laboratory measurements

Blood and urine samples for measurement of calcium metabolism were taken at same time points as the BMD measurements. All other tests were performed at 0, 6, 12, 18, and 24 months. To demonstrate maximal progestin effect the samples were always collected during the last 4 days of the estrogen–progestin combination tablets (same calendar window in the placebo group). Standard methods were used for the following analyses: diuresis (24 h), creatine and creatine 24 h, calcium and calcium 24 h, hydroxyproline, hydroxyproline 24 h, B-hemoglobin, S-creatine, fS-calcium, S-albumin, fS-phosphate, S-alkaline phosphatase, S-alanine aminotransferase, fS-glucose and tartrate resistant acid phosphatase (TRAP), fS-cholesterol, fS-HDL-cholesterol, fS-VLDL-cholesterol, fS-triglyceride. fS-LDL-cholesterol was calculated using the Friedewald formula [23]. Commercial radioimmunoassay kits were used to measure serum osteocalcin, procollagen-1 (PICP), FSH and estradiol.

2.5. Muscle strength and anaerobic threshold

The anaerobic threshold and maximal isometric strength measurements for both back extensor and flexor muscles, were performed at baseline and at 12 and 24 months. The maximal isometric extension and flexion strength of the back were measured in a standing position with the Muskeli® apparatus (Digitest, Muurame, Finland). The subject was fixed with a belt in the device below the anterior superior iliac spine and humeroscapular joint level, after which she was asked to perform maximal flexion and extension torque of the back against a bar for 5 s; the best result of three successive attempts was accepted [24]. The anaerobic threshold was found with the bicycle ergometer test by increasing the load step by step after the aerobic threshold was reached and blood lactate started to increase linearly with respect to work [24].

2.6. Exercise program

The exercise program consisted of a guided 1-h loading exercise per week in a fitness centre, with particular loading on the lumbar and femoral areas. The women in the exercise groups were instructed to exercise for an additional 2 h per week. All women in the study kept a diary of their daily activities.

2.7. Bleeding pattern and endometrial changes

Endometrial biopsies (Pistolet aspiration) [25] and cervical smears were obtained at baseline, 12 and 24 months. The specimens were collected during the last 4 days of the estrogen–progestin phase, and reviewed by the same pathologist with no prior knowledge of the treatment group. Bleeds were evaluated from the patients' bleeding diaries. Withdrawal bleeding was classified as regular if it occurred at any time during the combination tablet phase or the hormone-free week (during placebo tablets), and unscheduled if it occurred at any time during the estrogen tablet

Table 1
Summary of demographic data (mean ± SD), and study treatments

	Group I (N = 26)	Group II (N = 26)	Placebo (N = 26)	All (N = 78)
Age (years)	52.7 ± 1.4	52.5 ± 1.6	52.5 ± 1.6	52.5 ± 1.5
Age at menopause (years)	50.3 ± 1.6	50.2 ± 1.7	50.1 ± 1.2	50.2 ± 1.5
Body Mass Index	24.4 ± 3.7	25.8 ± 3.0	26.4 ± 3.5	25.6 ± 3.4
Time since last spontaneous bleeding (years)	2.7 ± 1.0	2.6 ± 1.3	2.6 ± 1.3	2.6 ± 1.2
Study treatment, on tablet daily	11 days: E_2V 2 mg 10 days: E_2V 2 mg and MPA 10 mg 7 days: placebo[a]	70 days: E_2V 2 mg 14 days: E_2V 2 mg and MPA 10 mg 7 days: placebo[b]	Placebo	

[a]Divina® (Orion Pharma, Finland).
[b]Divitren® (Orion Pharma, Finland).

phase. For the placebo group, all bleeds were classified as unscheduled.

2.8. Statistical methods

An analysis of covariance (ANCOVA) including two factors, medication and exercise, and the baseline values as a covariate, was used as the basic method for the statistical analysis. When the response consisted of successive measurements, a repeated measurements factor was included in the model. Multiple comparisons were carried out by t-tests, using the Bonferroni correction for protection of the overall risk level. For serum and urinary variables average changes from baseline to 12 and 24 months were compared between the treatment groups by Tukey's HSD method.

3. Results

3.1. Patients

There were no differences between the randomised treatment groups regarding patient characteristics at the baseline (Table 1). During the 2-year study period, 9 women altogether (11.5%) discontinued the study, 7 during the first year and 2 during the second year (Table 2). There were 3 discontinuations in treatment group I, 5 in treatment group II and, rather surprisingly, only 1 in the placebo group. The number of discontinuations was not statistically different between groups. The efficacy analyses thus includes 76 women, 25 in group I and in the placebo group, and 26 in group II.

There were no statistically significant changes in height, weight, Body Mass Index or blood pressure between the treatment groups and placebo group during the study period. The same was true for laboratory safety parameters, including B-hemoglobin, fS-glucose, S-ALAT (data not shown).

3.2. Hormonal status and menopausal symptoms

Serum FSH concentrations were clearly elevated in each group at the baseline (62.77 ± 4.78 IU/l, 57.41 ± 2.83 IU/l and 52.85 ± 3.44 IU/l in groups I, II and placebo, respectively), which confirmed the postmenopausal status of the study subjects. Serum estradiol levels increased, as expected, in both hormone groups during treatment. The severity of menopausal symptoms was markedly reduced in groups I and II. Compared with placebo, a significant reduction was seen in the average scores for hot flushes ($P < 0.001$) and night sweats ($P < 0.05$), when comparing symptom scores in patients who experienced these symptoms at baseline. Symptom scores also decreased for all other menopausal symptoms that were recorded, but statistically significant differences could not be detected between the placebo group and the hormone groups. There was no difference in amelioration of symptoms between hormone groups.

Table 2
Reasons for discontinuation by study group

Treatment group	Patient number	Time point (months)	Reason
I 3/26 (11.5%)	16	2	Personal reason (no follow-up data)
	21	3	Various psychological symptoms
	45	16	Thrombosis in leg after hip operation
II 5/26 (19.2%)	4	9	Death (acute myocarditis)
	19	6	Ischemic papillopathy in left eye
	34	5	Breast cancer
	61	6	Long withdrawal bleeding, BP 182/100 mmHg
	65	16	Long, painful withdrawal bleedings, strange feeling
Placebo 1/26 (3.8%)	30	Not known	Lost to follow-up

3.3. Bleeding pattern and endometrial histology

Regular withdrawal bleeds occurred in 88% and 96% of the women in groups I and II, respectively. During the first 6 months of the trial, mean duration of bleeding was significantly longer in group II (7.6 days) than in group I (5.5 days) ($P < 0.001$), but after 6 months no significant differences remained in this respect.

Initial endometrial samples demonstrated atrophy in the great majority of the patients, well in accordance with their hormonal status. A significant number of samples was insufficient for histologic diagnosis at the baseline in all three groups, probably reflecting the atrophic status of the endometrium as the frequency of insufficient samples subsequently decreased in both hormone treatment groups, but did not change in the placebo group (Table 3). At 12 and 24 months, 63% and 70% of women in the treatment group I revealed secretory endometrial histology. Corresponding figures for group II were 73% and 86%, respectively. In the placebo group, atrophy prevailed also at 12 and 24 months. Hyperplastic changes were incidental and were detected in all groups with similar frequency. Endometrial histology and cervical smears revealed no malignancies during the 2-year study period in any of the groups.

3.4. BMD

Compared with placebo, BMD values increased in groups I and II significantly over time in the spine ($P < 0.001$), femoral neck ($P < 0.001$), Ward's triangle ($P < 0.05$), and trochanter ($P < 0.05$) (Fig. 1aFig. 1bFig. 1cFig. 1d). There were no significant differences between the hormone groups.

Within groups I and II, there were no significant differences between exercising and non-exercising women. In the placebo group, a positive effect of exercise could be seen in Ward's triangle (average change 0–24 months 0.009 g/cm^2 with exercise and -0.018 g/cm^2 in the non-exercise group; $P < 0.05$) and the trochanter (average change 0–24 months 0.002 g/cm^2 with exercise and -0.017 g/cm^2 in the non-exercise group; $P < 0.05$). When data from all women were pooled together and the BMD values in the exercise and non-exercise groups were compared, a statistically significant difference ($P < 0.05$) was seen in the femoral neck, but no effect was observed in the spine.

3.5. Muscle strength and anaerobic threshold

There was a highly significant inverse association between initial isometric back extensor and flexor strength and the extent of change during the trial in the hormone-treated groups ($P < 0.001$) and a significant response of isometric extensor strength to both hormone combinations

Table 3
Endometrial histology findings during treatment by study group

Sample	Baseline			12 months			24 months		
Histological class	I	II	P	I	II	P	I	II	P
Atrophy	15	20	18	1	0	16	1	1	17
Proliferative	0	2	0	6	2	0	2	0	0
Secretory	0	0	1	15	16	0	16	18	0
Hyperplasia, simple[a]	0	0	0	2	0[b]	1[c]	1	0	0
Hyperplasia, complex[a]	0	0	0	0	0	0	2	0	1
Insufficient sample[d]	11	4	7	0	3	4	1	0	5
No sample	0	0	0	0	1	4	0	2	2
Total	26	26	26	24	22	25	23	21	25

[a]No hyperplastic findings with atypia.
[b]One patient had cystic-glandular hyperplasia at 6 months.
[c]The same patient had complex hyperplasia at 6 months.
[d]Insufficient samples at baseline in all groups and throughout the study in the placebo group reflect endometrial atrophy.

($P < 0.05$) after correction for initial strength in group I (Fig. 2a). The main response occurred during the first year. When data from all women were pooled together and flexion strength in the exercise and non-exercise groups was compared, a significant effect of exercise was observed (Fig. 2b).

Significant lowering of the anaerobic threshold was observed during the 2 years of follow-up (from 20.76 ± 4.37 ml/kg per min, $N = 76$, to 18.56 ± 4.10 ml/kg per min, $N = 51$), and no effect of hormone treatment or exercise could be demonstrated.

3.6. Calcium metabolism

Results form serum indexes reflecting bone metabolism are summarised in Table 4. Fasting serum calcium remained unchanged during the first year of treatment in groups I and II, but increased in the placebo group. During the second year no differences were seen between the three groups. Serum alkaline phosphatase, osteocalcin and PICP decreased significantly ($P < 0.001$) in both treatment groups compared with the placebo group during the first year of treatment, and remained at a decreased level also during the second year. No statistically significant changes were observed in serum TRAP activities between the groups. Significantly less calcium and hydroxyproline was secreted into urine over time in both treatment groups compared to the placebo group. No effect of exercise could be seen in the serum or urine parameters.

3.7. Lipid metabolism

Serum total cholesterol decreased in both hormone groups compared with placebo during the first year (Table 4). However, during the second year this decrease was observed only in group II. Similar changes were noticed in LDL cholesterol levels between groups. Only minor changes were observed in HDL cholesterol, VLDL cholesterol and triglycerides during the trial, and these changes were not statistically significant between hormone groups and placebo group (VLDL and triglyceride data not shown).

3.8. Adverse drug reactions and adverse events

Estrogenic adverse drug reactions, like breast tenderness and feeling of swelling, were reported at the beginning of the study, but there were no differences between 1- and 3-month regimens. Adverse events leading to discontinuation of the study are listed in Table 2.

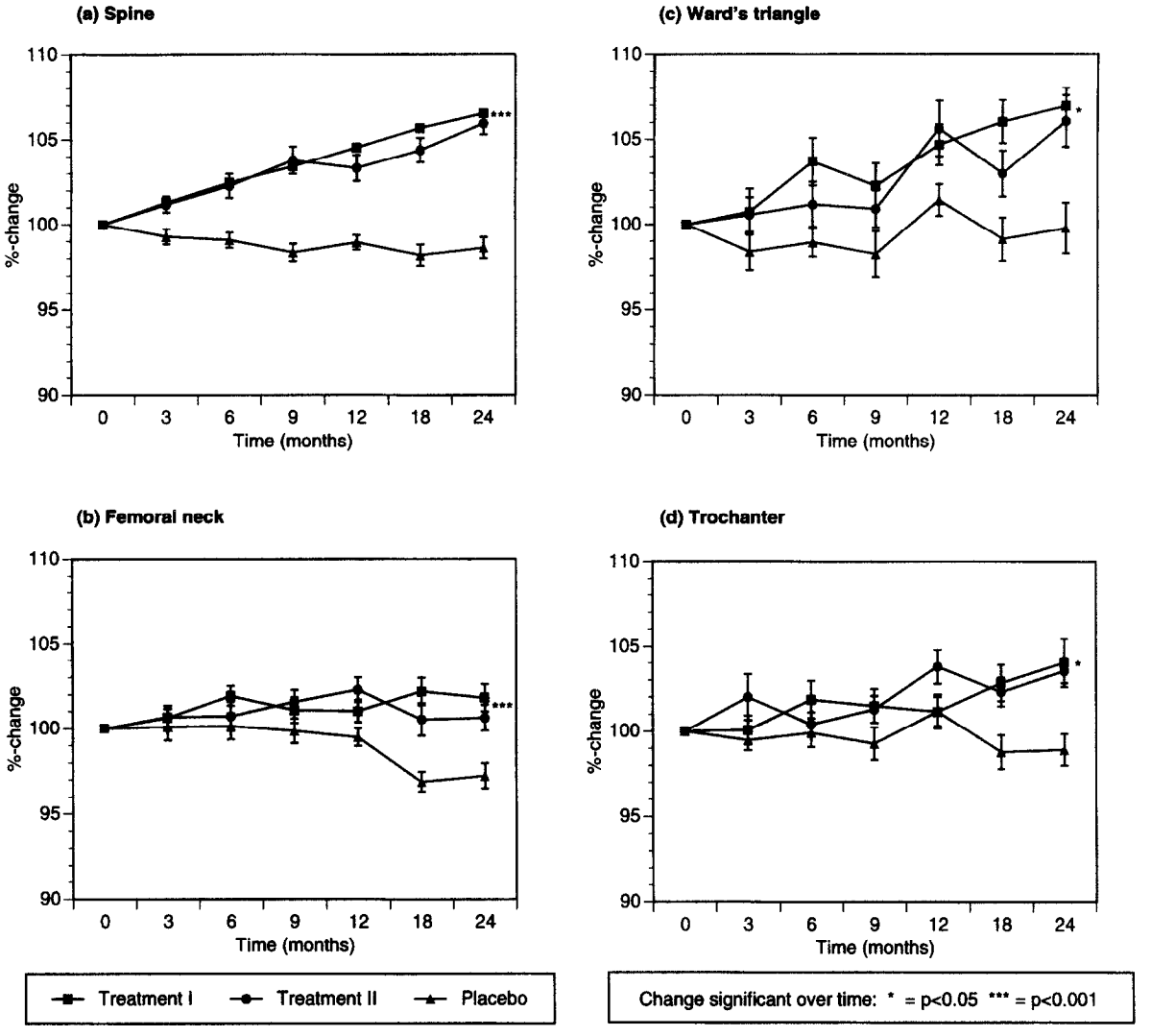

Fig. 1. (a–d) Percentual changes (mean ± S.E.M.) in bone mineral density in: (a) spine, (b) femoral neck, (c) Ward's triangle, and (d) trochanter.

4. Discussion

In a prospective, placebo controlled trial over 24 months, we compared two HRT regimens and studied the effect of exercise in 78 postmenopausal women who had not had any previous HRT for menopausal symptoms. The results showed that both hormone regimens reduced typical menopausal symptoms, especially hot flushes and night-time sweating. According to laboratory safety parameters and endometrial histology these two regimens did not differ from each other. In the beginning of the study, some women had long bleeding times with regimen II. During the 2-year follow-up period we obtained no evidence of increased endometrial or other abnormalities in either of the hormone groups, suggesting that both regimens can be used in the treatment of menopause. Hyperplastic changes were detected with similar frequency in all groups, including one complex hyperplasia in the placebo group, which should underscore the importance of diligent en-

dometrial monitoring in this age group regardless of the therapy mode.

Several studies have shown that both cyclic and continuous estrogen treatments prevent postmenopausal bone loss [26–29]. In the present study, both estrogen–progestin regimens significantly increased BMD in the spine and femoral neck when compared with placebo. There were no differences between groups I and II, suggesting that 3-month cyclic treatment is as effective on bone as 1-month regimens. Serum and urine parameters confirmed decreased bone turnover. This is in agreement with results showing that low dose continuous estrogen treatment without progestin is also effective on bone [30]. However, there is not enough documentation on this type of treatment to replace conventional cyclic treatment. Nevertheless, many women prefer less frequent bleedings, and to them 3-monthly cycles can be recommended [17,20].

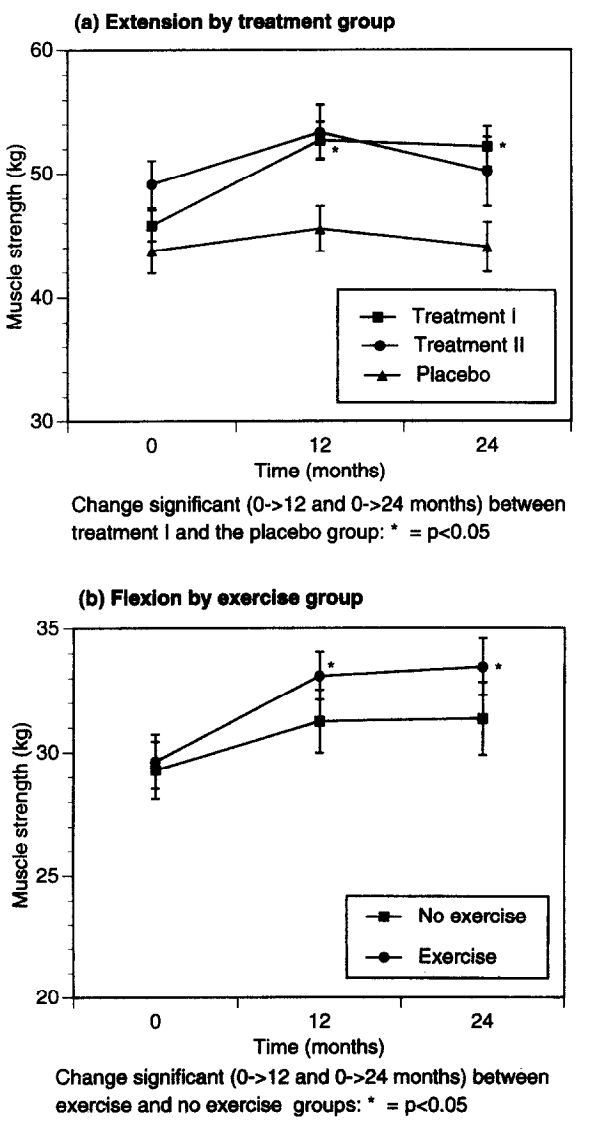

Fig. 2. (a,b) Isometric muscle strength: (a) extension by treatment group, and (b) flexion by exercise group.

It has been shown that MPA therapy alone prevents bone loss in postmenopausal women [31], and limited data suggest that, in combination therapy, progestins do not diminish the bone-preserving effect of estrogens [32]. On a cellular level, the effects of progestins on bone turnover are currently know to a much lesser extent than the effects of estrogens.

A positive effect of exercise on BMD in the proximal femur was observed during the 2-year period in the placebo group. However, no synergistic effect of exercise and hormone treatment could be seen. When all patients were combined, and exercise and non-exercise groups compared, a positive effect of exercise on BMD in the femoral neck was noted. This suggests that even easy exercise programs, which are feasible in everyday life for long periods, could be beneficial to slow down bone loss in the femoral neck. Recent animal studies strongly support this result and show further that moderate exercise is at least as effective as heavy exercise to prevent ovariectomy induced bone loss [33]. Since there are no known contraindications for low and moderate intensity exercise, it should also be recommended regularly for the prevention of bone loss in the elderly.

Serum and urine parameters clearly confirmed that both regimens were effective to decrease bone turnover. This is in agreement with bone density measurements and supports the anti-resorptive effect of both regimens used. Thus, it seems that other parameters and possible adverse drug reactions as well as women's own preference are more important criteria than effects on bone when different HRT regimens are assessed in clinical practice.

In addition to bone, our results showed that estrogen treatment has a beneficial effect also on

Table 4
Serum parameters reflecting lipid and bone metabolism

	Group	Time point (months)			Average changes			
		0	12	24	0–>12	*P*	0–>24	*P*
fS-chol (mmol/l)	I	6.46	5.70	6.34	−0.61		0.04	
	II	7.10	6.15	6.23	−0.77		−0.75	<0.05[a]
	Placebo	6.35	6.37	6.32	0.03	<0.01[b]	−0.03	
fs-chol-HDL (mmol/l)	I	1.56	1.58	1.57	0.01		−0.01	
	II	1.66	1.63	1.63	−0.10		−0.08	
	Placebo	1.58	1.64	1.55	0.06		−0.02	
fs-chol-LDL (mmol/l)	I	4.36	3.56	4.19	−0.65		−0.02	
	II	4.86	3.95	3.97	−0.67		−0.72	<0.05[a]
	Placebo	4.22	4.14	4.15	−0.09	<0.05[b]	−0.07	
fs-Ca (mmol/l)	I	2.28	2.25	2.37	−0.04		0.08	
	II	2.32	2.25	2.36	−0.06		0.04	
	Placebo	2.31	2.36	2.42	0.05	<0.05[b]	0.11	
dU-Ca (mmol/l)	I	3.18	2.68	2.96	−0.52		−0.31	
	II	2.62	2.38	2.21	−0.31		−0.43	
	Placebo	3.32	3.47	3.16	0.15		−0.16	
S-AFOS (U/l)	I	173.1	128.0	125.1	−45.4		−49.1	
	II	148.3	107.7	110.2	−35.5		−31.2	
	Placebo	153.1	171.0	169.2	17.9	<0.001[b]	16.0	<0.001[b]
S-PICP (mg/l)	I	135.8	95.2	106.1	−41.0		−30.4	
	II	120.6	80.1	89.0	−37.9		−28.7	
	Placebo	113.6	118.7	120.4	5.0	<0.001[b]	4.5	<0.01[b]
S-BGP (U/l)	I	11.25	8.01	9.90	−3.05		−1.17	
	II	10.38	7.01	8.30	−3.45		−2.05	
	Placebo	9.99	10.20	13.45	0.20	<0.001[b]	3.46	<0.001[b]
S-TRAP (mmol/l)	I	5.06	6.37	6.13	1.36		1.19	
	II	5.20	5.34	6.45	0.06		1.34	
	Placebo	5.43	7.10	6.80	1.65		1.44	

[a]Between estrogen groups.
[b] Between both estrogen groups and placebo.

the skeletal muscle. It is of particular interest that the effect on muscle strength was especially pronounced in women who had low muscle strength in the beginning of the study. An explanation for this is not readily available, but the anabolic effect of estrogen on skeletal muscle seems definite. Since it is most likely that increased muscle strength improves mobility and decreases the probability of falling in the elderly, it may be that estrogen protects against osteoporotic fractures also by other mechanisms than just by preventing bone loss. Seeley and co-workers have previously reported negative findings on the association of estrogen therapy to muscle strength and falling, but the value of this observation is much limited by the cross-sectional design of their study [8].

Serum cholesterol decreased during the first year with both hormone regimens. During the second year, the cholesterol levels in group I showed a tendency to return to initial values. The reason for the difference between the regimens could be the higher amount of estrogen in group II, or its longer cycles, or both, and may indicate that continuous or long-cycle estrogen is more beneficial to lipids than cyclic estrogen–progestin. Furthermore, the results suggest that the positive effect of estrogen on the serum parameters of lipid metabolism could be to some extent transient, at least at low doses.

Initial observations on the effects of different progestins suggested that 17-α-OH-progesterone derivatives would have a more favourable effect

on lipid metabolism than the 19-nortestosterone derivatives [16], but in subsequent studies the results have been variable [34,35]. In this study, serum samples were always collected towards the end of the combination tablet phase to observe maximal progestin effects, but still the changes in HDL-cholesterol were insignificant.

In conclusion, the present 2-year study confirmed the positive effect of estrogen on menopausal symptoms and bone density. Furthermore, our results demonstrated the anabolic effect of estrogen on skeletal muscle, suggesting that a protective effect of estrogen on osteoporotic fractures could be the sum of its beneficial effects to all skeletal tissues. As regards bone density, exercise did not offer any additional benefits to women on hormone treatment, but was beneficial to women on placebo. The positive effect of estrogen treatment on some serum parameters of lipid metabolism was confirmed, but at the same time it was suggested that this positive effect could be, at least partly, dose dependent and transient.

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References

[1] Gambrell RD, Jr. Update on hormone replacement therapy. Am Fam Physician 1992; 46 (Suppl. 5): 87S–96S.
[2] Barrett-Connor EL. The risks and benefits of long-term estrogen replacement therapy. Public Health Rep 1989; 104: 62–65.
[3] Mishell DR, Jr. Estrogen replacement therapy: an overview. Am J Obstet Gynecol 1989; 161: 1825–1827.
[4] Smith R, Judd JWW. Hormone replacement therapy: a review. J Drug Dev 1992; 4: 235–244.
[5] Tosteson AN. Hormone replacement therapy: benefit, risk and cost considerations. J Clin Pharmacol 1994; 34: 719–722.
[6] Whitcroft SI, Stevenson JC. Hormone replacement therapy: risks and benefits. Clin Endocrinol 1992; 36: 15–20.
[7] Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med 1992; 117: 1016–1037.
[8] Seeley DG, Cauley JA, Grady D, Browner WS, Nevitt MC, Cummings SR. Is postmenopausal estrogen therapy associated with neuromuscular function or falling in elderly women? Study of Osteoporotic Fractures Research Group. Arch Intern Med 1995; 155: 293–299.
[9] Heinonen A, Oja P, Kannus P, et al. Bone mineral density in female athletes representing sports with different loading characteristics of the skeleton. Bone 1995; 17: 197-203.
[10] Gleeson PB, Protas E, LeBlanc A, Scheider VS, Evans HJ. Effects of weight lifting on bone mineral density in premenopausal women. J Bone Miner Res 1990; 5: 153–158.
[11] Sinaki M. Exercise and osteoporosis. Arch Phys Med Rehabil 1989; 70: 220–229.
[12] Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease: the Framingham study. Ann Intern Med 1976; 85: 447–452.
[13] Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease [see comments]. N Engl J Med 1989; 321: 641–646.
[14] Zavaroni I, Bonora E, Pagliara M, et al. Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance [see comments]. N Engl J Med 1989; 320: 702–706.
[15] Bush TL, Barrett-Connor E, Cowan LD, et al. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. Circulation 1987; 75: 1102–1109.
[16] Hirvonen E, Mälkönen M, Manninen V. Effects of different progestogens on lipoproteins during postmenopausal replacement therapy. N Engl J Med 1981; 304: 560–563.
[17] Barentsen R, Groeneveld FP, Bareman FP, Hoes AW, Dokter HJ, Drogendijk AC. Women's opinion on withdrawal bleeding with hormone replacement therapy. Eur J Obstet Gynecol Reprod Biol 1993; 51: 203–207.
[18] Staland B. Continuous treatment with a combination of estrogen and gestagen - a way of avoiding endometrial stimulation. Clinical experiences with Kliogest®. Acta Obstet Gynecol Scand 1985; 131: 29–35.
[19] Hirvonen E, Salmi T, Puolakka J, et al. Can progestin be limited to every third month only in postmenopausal women taking estrogen? Maturitas 1995; 21: 39–44.
[20] Ettinger B, Selby J, Citron JT, Vangessel A, Ettinger VM, Hendrickson MR. Cyclic hormone replacement therapy using quarterly progestin. Obstet Gynecol 1994; 83: 693–700.
[21] Aitken RC. Measurement of feelings using visual analogue scales. Proc R Soc Med 1969; 62: 989–993.
[22] Kröger H, Heikkinen J, Laitinen K, Kotaniemi A. Dual-energy x-ray absorptiometry in normal women: a cross-sectional study of 717 Finnish volunteers. Osteoporosis Int 1992; 2: 135–140.
[23] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of preparative ultracentrifuge. Clin Chem 1972; 18: 499–502.

[24] Kyllonen ES, Väänänen HK, Heikkinen JE, Kurttila-Matero E, Martikkala V, Vanharanta JHV. Comparison of muscle strength and bone mineral density in healthy postmenopausal women. Scand J Rehab Med 1991; 23: 153–157.
[25] Wyss R, Vassilakos P, Riotton G. Eme neue Aspirationsmethode mit PISTOLET. Geburtshilfe Frauenheilkd 1975; 35: 846–853.
[26] Grey AB, Cundy TF, Reid IR. Continuous combined oestrogen/progestin therapy is well tolerated and increases bone density at the hip and spine in post-menopausal osteoporosis. Clin Endocrinol 1994; 40: 671–677.
[27] Stevenson JC, Hillard TC, Lees B, Whitcroft SI, Ellerington MC, Whitehead MI. Postmenopausal bone loss: does HRT always work? Int J Fertil Menopausal Stud 1993; 38: 88–91.
[28] Castelo-Branco C, Martinez de Osaba MJ, Pons F, Gonzalez-Merlo J. The effect of hormone replacement therapy on postmenopausal bone loss. Eur J Obstet Gynecol Reprod Biol 1992; 44: 131–136.
[29] Christiansen C. Hormonal prevention and treatment of osteoporosis-state of the art 1990. J Steroid Biochem Mol Biol 1990; 37: 447–449.
[30] Holland EF, Leather AT, Studd JW. The effect of 25 mg percutaneous estradiol implants on the bone mass of postmenopausal women. Obstet Gynecol 1994; 83: 43–46.
[31] McNeeley SG, Jr, Schinfeld JS, Stovall TG, Ling FW, Buxton BH. Prevention of osteoporosis by medroxyprogesterone acetate in postmenopausal women. Int J Gynaecol Obstet 1991; 34: 253–236.
[32] Naessén T, Persson I, Adami H-O, Bergstrom R, Bergkvist L. Hormone replacement therapy and the risk for first hip fracture. A prospective, population-based cohort study. Ann Intern Med 1990; 113: 95–103.
[33] Peng Z, Tuukkanen J, Vaananen HK. Exercise can provide protection against bone loss and prevent the decrease in mechanical strength of femoral neck in ovariectomized rats. J Bone Miner Res 1994; 9: 1559–1564.
[34] Marslew U, Rus BJ, Christiansen C. Desogestrel in hormone replacement therapy: long-term effects on bone, calcium and lipid metabolism, climacteric symptoms, and bleeding. Eur J Clin Invest 1991; 21: 601–607.
[35] Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. [see comments]. J Am Med Assoc 1995; 273: 199–208.