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New aspects of postmenopausal osteoporosis treatment with micronized estradiol and progesterone

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ABSTRACT

Objectives: The aim of the study was to assess the effectiveness of postmenopausal osteoporosis treatment with natural sex hormones.

Material and methods: The single-blind study included 210 women, randomly allocated to three different groups, with various methods of treatment: Group I (70 controls) received transcutaneous placebo for the course of one year, Group II (70 females, aged 52.2 ± 3.1 years) used oral hormone supplementary therapy (HST), and Group III (70 females, aged 51.9 ± 3.5 years) received transcutaneous modified hormone replacement therapy (MHRT), supplemented with intravaginal lutein, dietary minerals, and 1000 IU of vitamin D_3/day.

Results: No increase in bone mineral density was observed in the control group. However, mineral density of the vertebral bodies was significantly higher after 3 and 5 years in the HST group ($p < 0.05$), and after 1 year in the MHRT group ($p < 0.01$). This increase was even more significant ($p < 0.001$) after 3 and 5 years in the MHRT group.

Conclusions: Transcutaneous hormone therapy with micronized estradiol and progesterone is the treatment of choice in postmenopausal osteoporosis, as evidenced by bone mineral density and biochemical markers.

Key words: postmenopausal osteoporosis, prolactin, estrogens, growth hormone, alkaline phosphatase, mineral density

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INTRODUCTION

Postmenopausal osteoporosis belongs to the group of primary involutional pathologies and is responsible for as many as 80% of the cases of metabolic bone disease. Its etiology has been linked with estrogen deficit [1–5], and dysfunction of the thyroid gland [6–10], adrenals [11, 12], or the hypothalamic-pituitary axis [13–17]. Estrogens play a key role in maintaining bone mass and stabilizing bone metabolism through inhibition of the resorptive activity of osteoclasts and stimulation of osteogenesis by osteoblasts. Osteoblasts suppress the secretion of resorptive cytokines IL-1, IL-6, and TNF-α, which act as paracrine regulators of osteoblasts. Since the 1960s, estrogens have been used to treat osteoporosis owing to their enhancement of the expression of vitamin D_3 receptors, growth hormone receptors, and the osteoprotegerin gene [18], and their regulatory action on the thyroid gland [19]. Estrogens, like testosterone, stimulate bone metabolism [20]. Moreover, estrogens promote the uptake of microelements in the gastrointestinal system, thus maintaining a positive metabolic balance in the bones [21]. Estrogen action depends on their type, dose, and route of administration. The oral route is commonly used, although it is associated with adverse effects in the form of arterial hypertension, stroke, myocardial infarction, as well as tumors of the uterus, ovaries and glands of the mucous membranes. These adverse effects were the reason behind the decision to administer a modified hormone therapy with a 50% smaller dose of estrogens as compared to the dose recommended by the manufacturer.

OBJECTIVE

The study was undertaken to assess the effects of oral hormone supplementary therapy (HST) and transcutaneous modified hormone replacement therapy (MHRT) on

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biochemical and clinical aspects of postmenopausal osteoporosis, using the following parameters: concentrations of gonadotropins, estrogens, progesterone, prolactin, markers of bone turnover (bone-specific alkaline phosphatase, procollagen, osteocalcin), insulin-like growth factor, and growth hormone, as well as the mineral densities of L1–L4 vertebral bodies, body mass index, and arterial blood pressure.

MATERIAL AND METHODS

Our single-blind, placebo-controlled study enrolled 210 female city dwellers without a history of chronic illness or hereditary disease. Group I comprised 70 women who received placebo (Janssen-Cilag Baar, Switzerland) in the form of transcutaneous plasters administered over the course of one year. Group II included 70 women (aged 52 ± 3.1 years) who received oral HST with Cyclo-Menorette (Wyeth-Munster), containing 1 mg estradiol with a molecular weight of 343.39 g, 2 mg estradiol with a molecular weight of 288.38 g, and 0.25 mg levonorgestrel with a molecular weight of 312.4 g, with therapeutic cycles of 22 days, followed by a treatment-free interval of 7 days to induce menstruation. Group III included 70 women (aged 51.9 ± 3.5 years) who received transcutaneous modified HRT (MHRT) developed by Stanosz [22] and based on Systen 50 (Janssen-Cilag Baar, Switzerland), containing 17β-estradiol with a molecular weight of 272.39 g, supplemented from day 11 with micronized lutein (molecular weight: 314.47 g) from Adamed Pienkow (Poland). The dose of lutein was 50 mg/24h for the first and 100 mg/24h for the next 6 days. Therapeutic cycles of 22 days were followed by a treatment-free interval of seven days to induce menstruation. All participants followed a mineral-rich diet and received 1000 IU/24 h of vitamin D_3 (Vitrum) during the autumn-spring season. Bromocriptine (5 mg/24 h) was administered for 12 days in women with hyperprolactinemia. Oral Metformax (850 mg/24 h; Teva) was administered for 12 days to women with hyperinsulinism. Venous blood was collected in the morning. Concentrations of gonadotropins, estrogens, progesterone, prolactin, growth hormone, osteocalcin, procollagen, and insulin-like growth factor were determined with Elisa (IBL). Alkaline phosphatase activities were measured with test kits from DRG. Bone mineral density (BMD) of the lumbar vertebral bodies was determined with the DEXA DPX-TQ densitometer from Lunar Corporation. Assessment of bone density was done according to the WHO recommendations. Clinical and sonographic (Siemens Adara, USA) examinations of the breasts, ovaries, and the endometrium were performed during a 5-year follow-up. Local Ethics Committee approved of the study (№ BN-001/05).

Statistical analyses

Statistical analyses were performed using Statistica 9. Distributions of serum concentrations for most hormones deviated significantly from the norm, as determined with the Shapiro-Wilk test, in which case nonparametric tests were applied. The significance of change in hormone concentration during follow-up was assessed with Friedman's ANOVA and the Wilcoxon matched-pairs test. The significance of the differences between the groups was determined with the Kruskal-Wallis ANOVA test and the Mann-Whitney U-test. The significance of change in BMD during follow-up was evaluated with Student's paired samples t-test in each group of patients. The significance of differences in BMD between the three groups of patients was assessed with ANOVA and Tukey's post-hoc test. Statistical significance in the case of percentage values was determined with the chi-square test. The p-value of < 0.05 was considered as statistically significant.

RESULTS

The results are shown in Tables 1–7. Table 1 demonstrates that the participants were homogenous as to age, body weight, parity, residence, and age at menopause; no statistically significant differences were found.

Table 2 contains mean values and standard deviations for all parameters in the group of patients on placebo at the start and after one year of follow-up. BMD of L3 and L4 vertebral bodies was significantly lower after one year of placebo ($p < 0.05$).

Table 3 shows the results in groups II and III before treatment; no significant differences were noted. After one year of HST and MHRT (Table 4), the concentrations of gonadotropins (FSH, LH) decreased significantly ($p < 0.001$), while the concentrations of estrogens increased significantly ($p < 0.001$). HST patients demonstrated significantly higher concentrations of prolactin, body mass index, and systolic blood pressure ($p < 0.05$). In this group, concentrations of bone-forming factors were insignificantly reduced. Patients on MHRT presented with higher concentrations of the growth hormone, progesterone, IGF-1, and activities of the bone-specific alkaline phosphatase ($p < 0.05$).

Table 5 demonstrates that the concentrations of gonadotropins (FSH, LH) and estrogens after three years of oral HST and transcutaneous MHRT were significantly lower ($p < 0.001$) and significantly higher ($p < 0.001$), respectively. HST patients presented with significantly higher concentrations of prolactin ($p < 0.01$), growth hormone ($p < 0.01$), and BMI ($p < 0.01$). In this group, significantly reduced concentrations of IGF-1 ($p < 0.01$) and bone-forming factors ($p < 0.05$) were noted. MHRT patients demonstrated elevated concentrations of progesterone, IGF-1, and procollagen ($p < 0.05$). Activities of the bone-specific alkaline phosphatase were reduced ($p < 0.01$). No significant differences in BMI and arterial blood pressure values were found.

Table 6 shows that five years of oral HST and transcutaneous MHRT produced significantly lower concentrations

Table 1. Clinical data of women receiving placebo (group I), oral HST (group II), and transcutaneous modified MHRT (group III) (mean ± standard deviation)

Parameters	Group I (placebo) n = 70	Group II (HST) n = 70	Group III (MHRT) n = 70	p#
Age	50.8 ± 3.4	52.1 ± 3.1	59.9 ± 3.5	NS
BMI	24.7 ± 3.9	24.2 ± 1.1	23.8 ± 1.2	NS
Systolic blood pressure [mm Hg]	120.5 ± 22.1	127.28 ± 13.24	126.52 ± 16.55	NS
Diastolic blood pressure [mm Hg]	74.9 ± 6.1	75 ± 9.4	93 ± 11.7	NS
Parity	2.4 ± 0.9	2.1 ± 0.7	1.9 ± 0.9	NS
Number of abortions	1.5 ± 0.85	1.7 ± 0.2	1.4 ± 1.9	NS
Age at menopause (yrs)	49.1 ± 1.6	49.7 ± 2.3	49.3 ± 1.9	NS
Postmenopausal age (yrs)	3.9 ± 1.4	3.5 ± 1.8	3.4 ± 2.1	NS
Smokers (%)	17.9	18.7	20.5	NS

mm Hg = 0.1333 kPa
Group I — transcutaneous placebo; Group II — oral HST; Group III — transcutaneous MHRT; NS — not significant; n — number of women in the group; p — level of significance; #Mann-Whitney U test or chi-square test

Table 2. Concentrations of gonadotropins (FSH, LH), estrogens (E1, E2), progesterone (P), prolactin (PRL), bone-specific alkaline phosphatase (bALP), procollagen (PICP), osteocalcin (OC), growth hormone (GH), insulin-like growth factor (IGF-1), body mass index (BMI), systolic and diastolic blood pressures in group I (placebo)

Markers	Group I n=70 Placebo (before treatment)	Group I n=70 Placebo (after treatment)
FSH [mIU/mL]	69.1 ± 8.4	72 ± 11
LH [mIU/mL]	37.3 ± 11.0	35.0 ± 9.7
E1 [pg/mL]	22.1 ± 3.1	20.1 ± 1.5
E2 [pg/mL]	19.71 ± 7.2	17.3 ± 4.3
P [ng/mL]	0.21 ± 0.7	0.2 ± 0.03
PRL [ng/mL]	18.7 ± 2.4	23.3 ± 4.1*
bALP [ng/mL]	31.7 ± 4.2	30.1 ± 3.2
PICP [ng/mL]	133.0 ± 22.0	135.0 ± 19.7
BGP [ng/mL]	18.4 ± 3.1	17.9 ± 3.2
IGF-1 [ug/L]	97.4 ± 11.3	94.1 ± 3.7
GH [mIU/L]	1.5 ± 0.7	1.3 ± 0.4
BMI [kg/m^2]	25.9 ± 3.1	23.8 ± 4.1
Systolic blood pressure [mm Hg]	124.1 ± 9.7	135 ± 6.2*
Diastolic blood pressure [mm Hg]	71.1 ± 6.2	75.0 ± 4.1

mm Hg = 0.1333 kPa
n — number of women; p — level of significance; *p < 0.05, Wilcoxon matched-pairs test

of gonadotropins (FSH, LH) ($p < 0.001$) and significantly higher concentrations of estrogens ($p < 0.001$). In case of HST patients, bone-forming factors (bALP, PICP, OC) decreased significantly ($p < 0.05$). Concentrations of IGF-1 were significantly lower as well ($p < 0.01$). Significantly higher concentrations of the growth hormone, BMI, and blood pressure values were observed ($p < 0.01$). MHRT patients presented with significantly higher concentrations of progesterone ($p < 0.01$), osteocalcin ($p < 0.01$), IGF-1, growth hormone ($p < 0.001$), and procollagen ($p < 0.01$). BMI increased significantly ($p < 0.05$) and no change in arterial blood pressure values was found.

Table 7 demonstrates that one year of placebo resulted in significant reductions in BMD of L1–L4 vertebral bodies ($p < 0.05$), as well as in the respective percentage values ($p < 0.05$). In group II, L1–L4 BMD values were greater after one year ($p < 0.05$), without a tendency to higher values after three and five years of the follow-up. Patients using transcutaneous MHRT presented with greater BMD of L1–L4 vertebral bodies after one year ($p < 0.05$) and higher values after three ($p < 0.01$) and five years of follow-up ($p < 0.001$).

DISCUSSION

The present study has shown that the type of estrogen and the route of administration both exert an influence on hormone metabolism and therapy outcome. Significantly reduced concentrations of FSH and LH ($p < 0.001$) are linked with the route of administration [23, 24]. Hormone distribution is important in case of estrone and estradiol [25]. Oral estrogens in group II (HST) are partially (70%) metabolized by the liver, excreted with the bile together with other metabolites, and taken up again in the small intestine [26]. Oral hormone therapy is associated with hepatic conversion of estradiol to estrone and its conjugates with glucuronic and sulfuric acids [27]. Multiple passages of estrogens through the liver lead to an additive effect during subsequent therapeutic cycles [28]. Acting on hepatocytes, estrogens stimulate the synthesis of hormone-transporting proteins, thus reducing the fraction of free hormones and their tissue availability. Transcutaneous MHRT in group III

Table 3. Concentrations of gonadotropins (FSH, LH), estrogens (E1, E2), progesterone (P), prolactin (PRL), bone-specific alkaline phosphatase (bALP), procollagen (PICP), osteocalcin (OC), growth hormone (GH), insulin-like growth factor (IGF-1), body mass index (BMI), systolic and diastolic blood pressures in group II (HST) and group III (MHRT) before treatment

Markers	Group II (HST) n = 70	Group III (MHRT) n = 70	p
FSH [mIU/mL]	72.1 ± 17	65.4 ± 11.3	NS
LH [mIU/mL]	35.2 ± 12	33.5 ± 12.2	NS
E1 [pg/mL]	20.5 ± 2.81	14.31 ± 4.49	NS
E2 [pg/mL]	18.54 ± 2.84	20.89 ± 2.16	NS
P [ng/mL]	0.27 ± 0.9	0.29 ± 0.11	NS
PRL [ng/mL]	12.64 ± 2.95	11.44 ± 2.13	NS
bALP [ng/mL]	29.1 ± 5.3	30.2 ± 4.7	NS
PICP [ng/mL]	134.7 ± 22.1	124.4 ± 31.7	NS
BGP [ng/mL]	17.6 ± 5.3	15.3 ± 4.4	NS
IGF-1 [ug/L]	98.2 ± 30.7	99.2 ± 29.2	NS
GH [mIU/L]	1.1 ± 0.4	1.3 ± 0.9	NS
BMI [kg/m^2]	24.2 ± 0.9	23.9 ±1.4	NS
Systolic blood pressure [mm Hg]	127.28 ± 13.24	126.52 ± 16.55	NS
Diastolic blood pressure [mm Hg]	80.42 ± 7.21	76.5 ± 7.55	NS

mm Hg = 0.1333 kPa
n — number of women in the group; NS — not significant; p — level of significance, Mann-Whitney U-test

Table 4. Concentrations of gonadotropins (FSH, LH), estrogens (E1, E2), progesterone (P), prolactin (PRL), bone-specific alkaline phosphatase (bALP), procollagen (PICP), osteocalcin (OC), growth hormone (GH), insulin-like growth factor (IGF-1), body mass index (BMI), systolic and diastolic blood pressures in group II (HST) and group III (MHRT) after one year of treatment

Markers	Group II (HST) n = 70	Group III (MHRT) n = 70
FSH [mIU/mL]	52.1 ± 12.3****	45.4 ± 12.3***
LH [mIU/mL]	25.6 ± 11.6****	27.1 ± 10.1***
E1 [pg/mL]	226.6 ± 50.3****	209.6 ± 6.6***
E2 [pg/mL]	127.2 ± 27.9****	182.7 ± 17.7***
P [ng/mL]	0.21 ± 0.7	4.18 ± 0.22***
PRL [ng/mL]	16.15 ± 3.51*	12.41 ± 2.15
bALP [ng/mL]	25.3 ± 14.7	33.7 ± 6.1*
PICP [ng/mL]	131.3 ± 19.3	127.3 ± 29.3
BGP [ng/mL]	15.1 ± 6.2	19.4 ± 6.7*
IGF-1 [ug/L]	90.8 ± 17.4	118 ± 31.1**
GH [mIU/L]	1.4 ± 0.9*	2.5 ± 1.9**
BMI [kg/m^2]	25.7 ± 1.4	24.5 ± 1.1
Systolic blood pressure [mm Hg]	137.42 ± 8.85*	128.38 ± 8.07
Diastolic blood pressure [mm Hg]	87.57 ± 5.9*	77.57 ± 4.43

mm Hg = 0.1333 kPa
n — number of women in the group; p — level of significance; *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001 in comparison to initial values

Table 5. Concentrations of gonadotropins (FSH, LH), estrogens (E1, E2), progesterone (P), prolactin (PRL), bone-specific alkaline phosphatase (bALP), procollagen (PICP), osteocalcin (OC), growth hormone (GH), insulin-like growth factor (IGF-1), body mass index (BMI), systolic and diastolic blood pressures in group II (HST) and group III (MHRT) after three years of treatment

Markers	Group II (HST) n = 70	Group III (MHRT) n = 70
FSH [mIU/mL]	27.3 ± 7.1****	24.6 ± 11.2***
LH [mIU/mL]	16.4 ± 7.4****	12.4 ± 8.4***
E1 [pg/mL]	209.58 ± 10.8****	70.66 ± 12.23****
E2 [pg/mL]	122.77 ± 16.66****	63.5 ± 10.11***
P [ng/mL]	0.2 ± 0.06	4.49 ± 0.31***
PRL [ng/mL]	20.81 ± 4.13**	12.1 ± 1.8
bALP [ng/mL]	21.2 ± 6.1	37.1 ± 8.1**
PICP [ng/mL]	130.1 ± 33.1	130.8* ± 27.2
BGP [ng/mL]	14.1 ± 4.9	29.4 ± 6.1
IGF-1 [ug/L]	84.0 ± 20.3*	128.7 ± 30.0***
GH [mIU/L]	2.1 ± 1.8**	3.4 ± 2.1***
BMI [kg/m^2]	27.2 ± 1.8**	25.3 ± 1.2
Systolic blood pressure [mm Hg]	137.92 ± 8.85*	126.38 ± 8.7
Diastolic blood pressure [mm Hg]	84.57 ± 5.98	77.57 ± 4.43

mm Hg = 0.1333 kPa
n — number of women in the group; p — level of significance; *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001 in comparison to initial values

precluded the primary passage through the portal system of the liver, resulting in serum concentrations of estrogens which are sufficient to alleviate menopausal symptoms and improve bone metabolism. MRHT women presented with a three-fold increase in the concentrations of estrogen and a normal E1:E2 ratio (1:1). The concentration curve resembled a sinusoid, as in physiologic menstrual cycles. Serum concentration of progesterone increased five-fold and provided for optimal secretory activity of the endometrium during the second phase of the therapeutic cycle. Synthesis of the insulin-like growth factor is induced in osteoblasts by estrogen and the growth hormone [29], stimulating the precursor of osteoclasts and bone formation [30, 31]. The liver is the main source of circulating IGF-1 [32, 33].

Numerous studies have confirmed that the effect of estrogens on the concentration of GH, IGF-1, and bone-forming factors depends on the route of administration. Significantly higher concentrations of estrone and estradiol in women using oral HST are linked with the chemical structure and distribution. The effect of estrogens on the liver is due to two mechanisms of turnover of the inactive substrate to the active hormone, and is associated with the binding to hepatocyte receptors, leading to stimulation of protein synthesis and modulation of biochemical processes. It has frequently been noted that oral estrogens produce an effect on lipid metabolism, as well as on the synthesis of renin, blood-clotting factors, and the sex hormone-binding globulin (SHBG). Enhanced synthesis of SHBG is associated with reduced concentrations of free estradiol acting on tissue receptors. In turn, impaired availability produces significantly smaller concentrations of the bone-specific alkaline phosphatase, osteocalcin, procollagen, IGF-1, as well as BMD values seen after one, three, and five years of HST. Transcutaneous MHRT provided for optimal mean concentrations of E1 and E2, which fully prevented bone mass loss as confirmed with densitometry. Even though the dose of estrogens in MHRT has been reduced by 50 %, menopausal symptoms and metabolic disorders could still be alleviated. One year of balanced transcutaneous hormone therapy (MHRT) has stabilized concentrations of bone-forming factors, thus producing significantly higher BMD, as well as maintaining arterial blood pressure and BMI values seen

Table 6. Concentrations of gonadotropins (FSH, LH), estrogens (E1, E2), progesterone (P), prolactin (PRL), bone-specific alkaline phosphatase (bALP), procollagen (PICP), osteocalcin (OC), growth hormone (GH), insulin-like growth factor (IGF-1), body mass index (BMI), systolic and diastolic blood pressures in group II (HST) and group III (MHRT) after five years of treatment

Markers	Group II (HST) n = 70	Group III (MHRT) n = 70
FSH [mIU/mL]	23.3 ± 8.1****	21.3 ± 8.4****
LH [mIU/mL]	19.5 ± 0.1****	18.5 ± 5.3****
E1 [pg/mL]]	210.1 ±11.4****	78.3 ± 8.4***
E2 [pg/mL]	123.1 ± 14.1****	72.4 ± 9.7****
P [ng/mL]	0.11 ± 0.05	4.3 ± 0.51****
PRL [ng/mL]	21.3 ± 5.1**	12.9 ± 1.6
bALP [ng/mL]	20.8 ± 6.4**	35.0 ± 6.1*
PICP [ng/mL]	125.8 ± 11.7*	140.5 ± 21.3**
BGP [ng/mL]	18.1 ± 6.9*	25.5 ± 5.9**
IGF-1 [ug/L]	93.1 ± 14.1**	131.5 ± 11.3***
GH [mIU/L]	2.9 ± 1.4**	3.8 ± 2.2***
BMI [kg/m^2]	28.9 ± 1.2*	24.9 ± 1.3
Systolic blood pressure [mm Hg]	138.28 ± 5.8**	128.38 ± 7.42
Diastolic blood pressure [mm Hg]	88.0 ± 4.05	82.3 ± 3.67

mm Hg = 0.1333 kPa
n — number of women in the group; p — level of significance; *p<0.05; **p<0.01; ***p < 0.001; ****p < 0.0001 in comparison to initial values

Table 7. Mineral densities of L1-L4 vertebral bodies depending on the method of treatment

Group	n	Examination	L1 [g/cm^2]	L2 [g/cm^2]	L3 [g/cm^2]	L4 [g/cm^2]	BMI % L1–L4
I Placebo	70	Initial	0.883 ± 0.091	0.935 ± 0.077	0.917 ± 0.065	0.955 ± 0.071	–
		After one year	0.868 ± 0.051	0.900 ± 0.066	0.880 ± 0.052	0.910 ± 0.046	–3.53
II HST	70	Initial	0.883 ± 0.091	0.935 ± 0.087	0.917 ± 0.065	0.952 ± 0.071	–
		After one year	0.908 ± 0.071	0.956 ± 0.081	0.959* ± 0.056	0.952* ± 0.067	+4.38
		After three years	0.917* ± 0.071	0.975* ± 0.062	0.967* ± 0.060	0.991* ± 0.083	+3.98
		After five years	0.92* ± 0.067	0.963* ± 0.074	0.957* ± 0.068	0.992* ± 0.091	+4.15
III MHRT	70	Initial	0.872 ± 0.066	0.921 ± 0.059	0.957 ± 0.41	0.942 ± 0.071	–
		After one year	0.902* ± 0.086	0.954* ± 0.091	0.971* ± 0.067	0.947* ± 0.061	+4.4
		After three years	0.997** ± 0.071	1.094*** ± 0.084	1.021*** ± 0.066	1.019***	+7.4
		After five years	1.011*** ± 0.088	1.019*** ± 0.091	1.013*** ± 0.076	1.016*** ± 0.081	+10.83

n — number of women in the group; p — level of significance; *p < 0.05; **p < 0.01; ***p < 0.001 in comparison to initial values

after one, three, and five years of treatment. Five years of HST have been associated with hyperprolactinemia in 25%, arterial hypertension in 11%, elevated serotonin concentration in 11.5%, mammary cysts in 9.8%, mammary fibrocystic lesions in 11.3%, and benign endometrial hyperplasia in 9.7% of the cases. In contrast, mammary cysts were seen in just 2.3% of women receiving transcutaneous MHRT.

CONCLUSIONS

Transcutaneous hormone therapy with micronized estradiol and progesterone is the procedure of choice in postmenopausal osteoporosis.

Transcutaneous hormone therapy with micronized estradiol and progesterone in rising doses, with a seven-day interval between therapeutic cycles, provides for a physiologic rhythm in estrogen and progesterone concentrations, with sinusoidal concentration curves resembling those during normal menstrual cycles.

Significantly lower concentrations of biochemical markers and mineral density values in L1–L4 vertebral bodies of women using oral supplementary therapy with synthetic hormones may be attributed to chemical structure, metabolism, and hyperprolactinemia.

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