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Influence of modified transdermal hormone replacement therapy on the concentrations of hormones, growth factors, and bone mineral density in women with osteopenia

Staniaław Stanosz[a,*], Ewa Żochowska[a], Krzysztof Safranow[b], Krzysztof Sieja[a], Małgorzta Stanosz[a]

[a]Department of Menopause and Andropause Pomeranian Medical University, PL-70-111 Szczecin, Poland
[b]Department of Biochemistry and Medical Chemistry Pomeranian Medical University, PL-70-111 Szczecin, Poland

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Abstract

The metabolic and therapeutic action of estrogens depends on their type, dosage, form, route of administration, and treatment-free interval during the therapeutic cycle. Hormone therapy is generally subclassified into 2 forms that differ in the type of hormones. In hormonal replacement therapy (HRT), estrogens and progesterone components do not differ in chemical structure and molecular mass from those naturally produced by the female organism. In hormonal supplementary therapy (HST), the estrogen and progestagen components do differ from the natural hormones in structure and mass. The aim of the study was to compare 2 kinds of hormonal therapy in early postmenopausal women with osteopenia. These forms of therapy are modified transdermal HRT and orally given HST. The objective of this study was the estimation of sex hormone, insulin-like growth factor I (IGF-I), prolactin (PRL), osteocalcin, and procollagen concentration in serum as well as the degree of mineralization of the lumbar spine in women in the early postmenopausal period with osteopenia under different kinds of hormonal therapy. The study was conducted in 75 women with an average age of 52.4 ± 3.5 years and with primary osteopenia, in the early postmenopausal period, who were randomly assigned to 3 groups depending on the form and route of administration of therapy: Group I (n = 25, control) was receiving placebo in the form of patches. Group II (n = 25) was treated with modified transdermal HRT. This group obtained micronized 17β-estradiol at increasing-decreasing doses and progesterone in the second phase of the therapeutic cycle. Group III (n = 25) was receiving orally given HST and obtained Cyclo-Menorette (Wyeth, Munster, Germany). The therapeutic cycle in each group lasted 21 days, followed by a 7-day medication-free interval. Estradiol concentration in serum was increased 5-fold and estrone (E_1) was increased about 11-fold in the group of women receiving orally given HST ($P < .0001$) compared with control group. Estrone and estradiol levels were increased about 3-fold in women receiving modified transdermal HRT compared with the baseline values. Basal PRL concentration and PRL level after metoclopramide stimulation test significantly increased after 3 and 12 months of treatment in the group receiving orally given HST. In women receiving modified transdermal HRT, increased IGF-I concentrations were statistically significant after 3 months of treatment. In the group of women receiving orally given HST, a significant decrease of IGF-I after 1 year therapy was found. During the entire time of treatment in this group, an increase of growth hormone was observed. No significant changes were shown in osteocalcin and in carboxyterminal propeptide of type I procollagen in all groups. Increase in bone mineral density L_2-L_4 was statistically significant in the group receiving modified transdermal HRT ($P < .01$) and was insignificant in women receiving orally given HST after 12 months of therapy as compared with baseline values. Following are the conclusions: (1) Low-dose modified transdermal HRT modulates concentration of hormones, growth factor, IGF-I, osteocalcin, procollagen, and bone metabolism. (2) The curve concentrations of estrogens and progesterone in serum are similar to the type observed in the physiologic menstrual cycle. (3) The lack of significant increase in bone mineral density of lumbar spine in women after HST may be a result of significantly lower concentration of IGF-I in serum and occurring hyperprolactinemia.

1. Introduction

The metabolic and therapeutic activity of estrogens depends on their type, dosage, form, route of administration, and treatment-free interval. The transdermal modified

* Corresponding author. Department of Menopause and Andropause Pomeranian Medical University, Unii Lubelskiej St 1, 71-256 Szczecin, Poland. Tel.: +48 91 486 13 20; fax: +48 91 425 33 06.
E-mail address: magnum@med.pam.szczecin.pl (S.ł Stanosz).

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hormone replacement therapy (HRT) in menopausal women has been reported to have a beneficial effect on the coagulation process [1,2] and lipid metabolism [3-5]. This kind of therapy exerts a modulating effect on homocysteine level and decreases C-reactive protein [6] as well as induces repair of bone structure [7,8].

Estrogens have an influence on osteoblasts and osteoclasts through their receptors in bone tissue [9,10]. In osteoblasts, estrogens stimulate the synthesis of growth and differentiation factors transforming growth factor-beta [TGF-β], bone morphongenic protein 6 [BMP-6], insulin-like growth factor I [IGF-I]) and increase the expression of receptors for vitamin $1,25(OH)_2D_3$, growth hormone (GH), and progesterone. Estrogens inhibit the synthesis of proresorption cytokinins (interleukin [IL]-1a, IL-1b, IL-6, morphogene colony-stimulating factor [M-CSF], tumor necrosis factor–α) [8] and also increase the gene expression of osteoprotegrin [11]. Their effect on osteoclasts includes the inhibition of the osteoclastgenesis stages, stimulation of osteoclasts, apoptosis, and inhibition of lysosomal enzyme activities in those cells [8].

Hormone therapy is generally subclassified into 2 forms that differ in the type of applied hormones. In transdermal HRT, estrogen and progesterone components do not differ in chemical structure and molecular mass from the hormones naturally produced by the female organism. In orally given hormonal supplementary therapy (HST), the estrogen and progestagen components differ generally from the natural hormones in structure and mass. Oral HST is still commonly used despite its many adverse effects such as arterial hypertension, coagulation disturbances, increase in homocysteine and C-reactive protein levels, cardiological complications, and increased risk of breast and endometrial cancer.

2. Objective

The aim of the study was to compare 2 kinds of hormonal therapy in early postmenopausal women. These forms of therapy are the modified transdermal HRT and the orally given HST. The objective of this study was the estimation of sex hormone, IGF-I, prolactin (PRL), osteocalcin (OC), and procollagen concentration in serum as well as the degree of mineralization of the lumbar spine in women in the early postmenopausal period with osteopenia.

3. Material and methods

The study was conducted on women in the early postmenopausal period aged 45 to 58 years with primary osteopenia and no history of general diseases; there were no significant differences between groups in terms of age, body mass index, and parity. The women were divided into 3 groups based on randomized list, as follows: Group I (n = 25, control) consisted of women with an average age of 52.8 ± 3.0 years. They received placebo transdermal treatment in the form of patches produced by Janssen-Cilag (Baar, Switzerland). Group II (n = 25) consisted of women aged 52.3 ± 4 years who were treated with modified transdermal HRT: micronized 17β-estradiol (molar mass, 272.39 g/mol) in the form of patches (Systen, Janssen-Cilag) with subsequently increasing and decreasing doses (25, 50, 75, and 75 μg per dose) imitating the physiologic serum concentrations of estrogens throughout the therapeutic cycle as described by Stanosz et al [4], with concomitant oral intermittent progesterone administration (molar mass, 314.47 g/mol) (Lutein Firm; Adamed, Pienkow, Poland) in the second phase of the therapeutic cycle at doses of 50 mg daily for 6 days and, subsequently, 100 mg daily for the next 6 days. Such dosages allowed for the maintenance of the minimal level of progesterone required to evoke sequential transformation in endometrium leading to cyclic withdrawal bleeding. The use of fluctuating doses of hormones leads to receiving the physiologic concentrations of estrogens and progesterone in serum during the therapeutic cycle. In this group, the characteristic curve of hormonal levels in serum was similar to that observed in the physiologic menstrual cycle. Group III (n = 25) consisted of women with a mean age of 52.2 ± 3.0 years receiving orally given HST by taking Cyclo-Menorette (1 mg estradiol valerate [358.39 g/mol] + 2 mg estriol [288.39 g/mol] + 0.25 mg levonorgestrel [312.466 g/mol]; Wyeth, Munster, Germany) in the form of sugar-coated tablets during 21 days of the therapeutic cycle.

The therapeutic cycle in each group lasted 21 days, with a treatment-free interval of 7 days. Peripheral blood for analyses was taken on days 18 to 20 of the therapeutic cycle. In all 3 groups, the following hormones were analyzed by immunoenzymatic methods 3 times during 1 year of therapy (ie, before treatment [at baseline], after 3 months of treatment, and after 12 months of treatment):

1. Folliculotropic hormone (FSH), luteinizing hormone (LH), estradiol (E_2), progesterone, basal prolactin (PRL_I), and prolactin after metoclopramide (MCP) test (PRL_{II}) (kit from bioMerieux, Craponne, France).
2. Estrone (E_1) by using radioimmunoassay (DSL-8700; Diagnostic System Laboratories, Webster, TX).
3. Prolactin concentration was analyzed in the morning hours (basal conditions, PRL_I) and 60 minutes after taking 10 mg of MCP orally (PRL_{II}, concentration after stimulation test; MCP/PRL).
4. Bone growth factors: IGF-I by using immunoenzymatic assay (OCTEIA; Boldon IDS, Tyne and Wear, United Kingdom) and GH by using radioimmunoassay (kit from Immunotech, Marseille, France).
5. Bone formation markers: carboxyterminal propeptide of type I procollagen (PICP) (kit from Orion Diagnostica, Nivelles, Belgium) and OC (by radioimmunoassay) (kit from DRG, Madison, WI).

Bone mineral density (BMD L_2-L_4) was determined at baseline (before treatment) and at 12 months by a dual-energy x-ray absorptiometry scanner (Lunar DPX-IQ) that uses hydroxyapatite level in grams per square centimeter as an expression of the degree of bone mineralization. The

results of BMD L_2-L_4 were interpreted according to the World Health Organization criteria [12].

The protocol was approved by the Bioethical Committee of the Pomeranian Medical University in Szczecin.

Statistical calculations were performed using the Statistica 6.188 PL package made by StatSoft (Tulsa, OK). Nonparametric tests were used for the analysis of serum hormone concentrations because most of their distributions deviated from the reference range (Shapiro-Wilk test). Significance of changes in the hormone concentrations during this study was assessed in each group of patients using Friedman analysis of variance (ANOVA) and Wilcoxon signed-rank test. Differences among the 3 groups of patients were analyzed with Kruskal-Wallis ANOVA followed by Mann-Whitney test. Bone mineral density values were not significantly different from normal distribution in any group of patients; therefore, parametric tests were used. Statistical significance of BMD changes during this study was assessed using Student *t* test for paired variables. Differences among the 3 groups of patients were assessed with ANOVA followed by Tukey post hoc test [13]. *P* less than .05 was considered as statistically significant. Results are presented as mean values ± SD.

4. Results

The results are shown in Fig. 1 and Tables 1 to 3.

The concentration of estrogens in serum of women being given modified transdermal hormonal therapy is dependent on the applied doses of estrogens (Fig. 1). The baseline (before treatment) study levels of hormones and bone markers did not differ significantly in the groups of women undergoing different methods of hormonal therapy (Table 1). As shown in Table 1, after 3 and 12 months of treatment in group II (modified transdermal HRT) and group III (orally given HST), significantly decreased FSH and LH levels were found. In group II, increased E_2 and E_1 concentrations in serum were observed ($P < .001$ and $P < .0001$, respectively). The concentrations of E_2 and E_1 in group III were also increased ($P < .0001$ and $P < .0001$). The LH concentrations were significantly decreased after 3 months of therapy in both groups ($P < .001$). After 1 year of treatment, the decrease in LH was statistically significant in the group of women receiving modified transdermal HRT ($P < .05$) and was on the verge of statistical significance in the group receiving orally given HST ($P = .06$). Estradiol concentration was increased 10-fold ($P < .0001$) in women after orally given HST (group III). In this group, E_1 level was already increased 11-fold after 3 months of therapy and remained so throughout the whole year of treatment. These changes were highly significant ($P < .0001$). Estrone level in the group receiving modified transdermal HRT (group II) was 3-fold increased as compared with the baseline level ($P < .0001$). Estradiol level in this group was also increased 3-fold ($P < .0001$). After 12 months of HRT treatment, the concentration of E_2 ($P < .001$) and E_1 ($P < .00001$) was significantly increased. In the group receiving orally given HST, E1 and E2 were significantly increased ($P < .00001$)

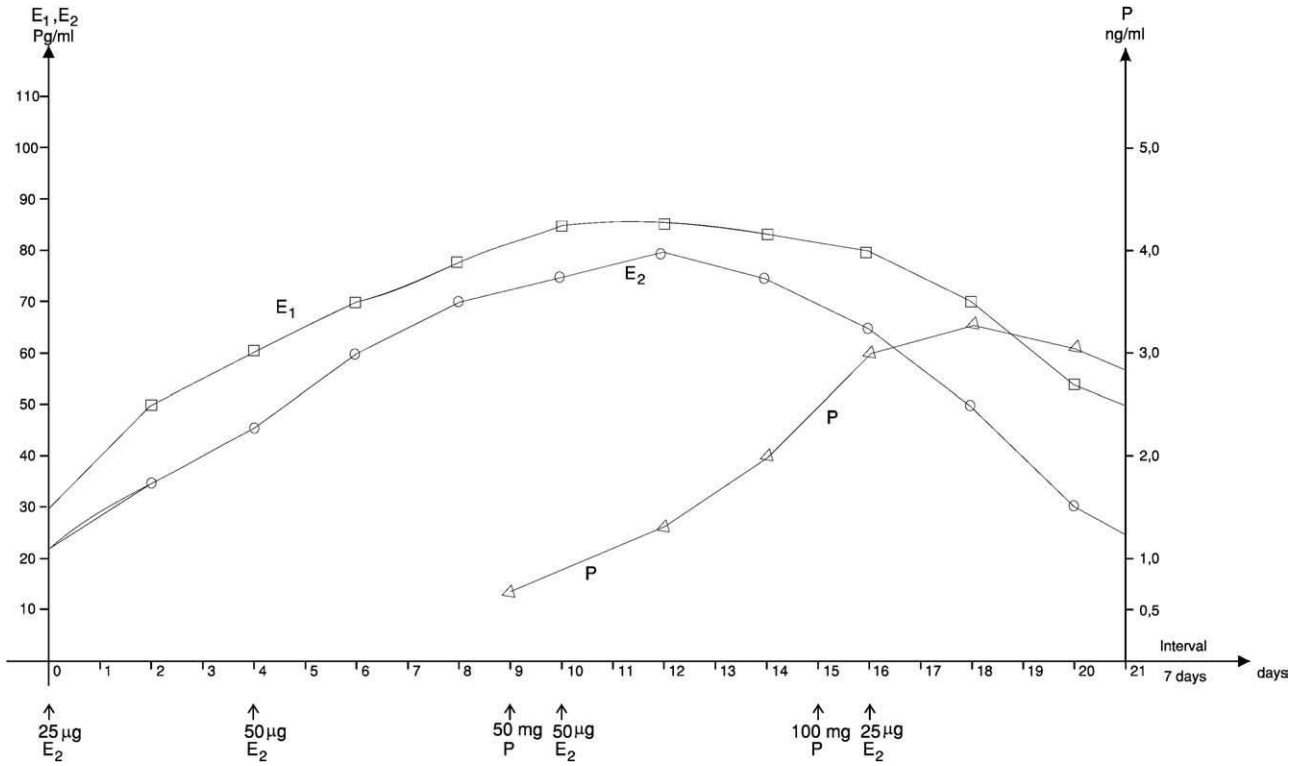

Fig. 1. Concentrations of estrogens and progesterone during modified transdermal HRT.

Table 1
Concentrations of gonadotrophins, estrogens, progesterone, and PRL in serum in early postmenopausal women receiving modified transdermal HRT and orally given HST

Group	n	Time	Gonadotrophins (mIU/mL)		Estrogens (pg/mL)		Progesterone (ng/mL)	Prolactin (ng/mL)	
			FSH	LH	E_1	E_2		PRL	MCP/PRL
I	25	Baseline	74.3 ± 21	28.5 ± 11	19.0 ± 12	21.0 ± 10	0.45 ± 0.2	11.2 ± 5	186.4 ± 105
		3 mo	79.7 ± 23	27.6 ± 10	18.1 ± 14	20.0 ± 11	0.47 ± 0.1	10.4 ± 4	195.8 ± 103
		12 mo	83.3 ± 22	26.6 ± 80	16.2 ± 90	20.0 ± 10	0.46 ± 0.1	12.8 ± 7	197.5 ± 91
II	25	Baseline	68.0 ± 20	23.4 ± 6	21.4 ± 12	26.7 ± 24	0.43 ± 0.2	11.5 ± 5	149.5 ± 76
		3 mo	46.7 ± 16****	17.4 ± 6***	65.7 ± 57****	38.5 ± 29***	4.31 ± 4.6****	11.7 ± 6	183.0 ± 101
		12 mo	49.2 ± 15***	19.9 ± 6*	64.7 ± 52****	56.1 ± 71***	4.1 ± 3.0****	11.7 ± 7	190.0 ± 115
III	25	Baseline	70.0 ± 22	25.0 ± 7	19.7 ± 9	21.8 ± 10	0.48 ± 0.2	11.4 ± 6	176.0 ± 109
		3 mo	39.0 ± 18****	17.8 ± 8***	114.6 ± 65****	235.7 ± 165****	0.64 ± 0.7	19.4 ± 13**	282.4 ± 113**
		12 mo	45.1 ± 19****	20.5 ± 7°	97.5 ± 63****	243.9 ± 145****	0.55 ± 0.3	16.5 ± 14*	298.8 ± 107***
*P*x	I/II	Baseline	NS	NS	NS	NS	NS	NS	NS
		3 mo	<.001	<.001	<.001	<.001	<.001	NS	NS
		12 mo	<.001	<.01	<.001	<.001	<.001	NS	NS
	I/III	Baseline	NS	NS	NS	NS	NS	NS	NS
		3 mo	<.001	<.001	<.001	<.001	NS	<.05	<.05
		12 mo	<.001	<.05	<.001	<.001	NS	NS	<.05
	II/III	Baseline	NS	NS	NS	NS	NS	NS	NS
		3 mo	<.05	NS	<.001	<.001	<.001	<.05	<.01
		12 mo	NS	NS	<.01	<.001	<.001	NS	<.01

Data are shown as mean ± SD. *P* indicates level of significance; NS, not significant.
*$P < .05$, **$P < .01$, ***$P < .001$, and ****$P < .0001$—significance of difference in comparison with basal result (ANOVA Friedman + Wilcoxon signed-rank test; Kruskal-Wallis ANOVA + Mann-Whitney test).

after 12 months of treatment compared with the baseline level concentrations. Table 1 shows that the increase in progesterone in the course of therapy was significant only in group II ($P < .001$) and its concentration was higher than that in the 2 remaining groups ($P < .001$). Prolactin concentration in basal conditions (PRL_I) was significantly increased after 3

Table 2
Concentrations of IGF-I, GH, OC, and PICP in serum in early postmenopausal women receiving modified transdermal HRT and orally given HST

Group	n	Time	IGF-I (μg/L)	GH (mIU/L)	OC (ng/mL)	PICP (μg/L)
I	25	Baseline	86.6 ± 24.3	1.0 ± 2.0	11.1 ± 8.9	164.1 ± 61.91
		1 mo	89.6 ± 25.7	1.3 ± 2.6	11.2 ± 8.7	165.1 ± 45.2
		3 mo	81.3 ± 17.4	1.2 ± 2.1	9.5 ± 8.6	165.3 ± 53
		12 mo	66.6 ± 18.6***	0.8 ± 1.0	9.8 ± 8.7	190.9 ± 66.2
II	25	Baseline	97.9 ± 54.2	2.1 ± 3.6	6.5 ± 4.8	129.8 ± 40.3
		1 mo	102.5 ± 19.8	2.7 ± 4.0	6.2 ± 4.6	160.6 ± 117.8
		3 mo	123.5 ± 33.0†	3.3 ± 4.2	7.6 ± 5.9	118.0 ± 30.2
		12 mo	105.2 ± 30.1	1.4 ± 2.6‡	7.0 ± 5.6	113.7 ± 36.2
III	25	Baseline	95.9 ± 33.8	1.2 ± 1.8	7.2 ± 5.9	134.9 ± 45.3
		1 mo	92.1 ± 17.5	3.8 ± 5.9*	7.3 ± 6.3	161.1 ± 84.6
		3 mo	106.7 ± 20.7	3.1 ± 2.5***	7.1 ± 6.8	147.1 ± 75.5
		12 mo	81.7 ± 16.0*	3.4 ± 3.9**	8.7 ± 6.1	142.6 ± 55.8
*P*x	I/II	Baseline	NS	NS	NS	NS
		1 mo	NS	NS	NS	NS
		3 mo	<.01	<.5	NS	<.01
		12 mo	<.001	NS	NS	<.001
	I/III	Baseline	NS	NS	NS	NS
		1 mo	NS	<.01	NS	NS
		3 mo	<.001	<.01	NS	NS
		12 mo	<.05	<.001	NS	<.01
	II/III	Baseline	NS	NS	NS	NS
		1 mo	NS	NS	NS	NS
		3 mo	NS	NS	NS	NS
		12 mo	<.001	<.01	NS	<.05

Data are shown as mean ± SD.
*$P < .05$, **$P < .01$, ***$P < .001$, †$P = .05$, and ‡$P = .07$—significance in comparison with basal result (ANOVA Friedman + Wilcoxon signed-rank test; Kruskal-Wallis ANOVA + Mann-Whitney test).

Table 3
Bone mineral density of the lumbar spine (BMD L_2-L_4) in women in early postmenopausal period receiving modified transdermal HRT and orally given HST

Group	n	Time	L_1 (g/cm^2)	L_2 (g/cm^2)	L_3 (g/cm^2)	L_4 (g/cm^2)	BMD L_2-L_4 (g/cm^2)	I BMD L_2-L_4 (%)
I	25	Baseline	0.892 ± 0.094	0.949 ± 0.092	0.982 ± 0.104	0.953 ± 0.079	0.961 ± 0.084	
		12 mo	0.883 ± 0.069	0.904 ± 0.11**	0.952 ± 0.105**	0.915 ± 0.091**	0.923 ± 0.96**	−3.0 ± 6.0
II	25	Baseline	0.878 ± 0.105	0.922 ± 0.096	0.933 ± 0.097	0.904 ± 0.089	0.920 ± 0.087	
		12 mo	0.889 ± 0.107	0.946 ± 0.112**	0.967 ± 0.11**	0.950 ± 0.112**	0.954 ± 0.106**,†	+3.8 ± 6.0 $P < .001$
III	25	Baseline	0.861 ± 0.062	0.922 ± 0.076	0.972 ± 0.067	0.953 ± 0.068	0.949 ± 0.057	
		12 mo	0.881 ± 0.071	0.945 ± 0.07*	0.992 ± 0.079*	0.969 ± 0.078	0.969 ± 0.065*,†	+2.2 ± 3.6 $P < .01$

L_1 indicates BMD of the first lumbar spine; L_2, BMD of the second lumbar spine; L_3, BMD of the third lumbar spine; L_4, BMD of the fourth lumbar spine; L_1-L_4, mean values of BMD in grams per square centimeter; BMD L_2-L_4, BMD of the lumbar spine L_2-L_4.
*$P < .05$ and **$P < .01$—significance of difference in comparison with baseline results (Student t test for paired variables); †$P < .01$—significance of difference in comparison with control group (ANOVA + Tukey post hoc test; Student t test).

($P < .01$) and 12 months ($P < .05$) of treatment in the group receiving orally given HST. Prolactin level after MCP stimulation test (PRL_{II}) was also increased in group III during the entire course of treatment ($P < .01$ after 3 months and $P < .001$ after 12 months).

During the period of study, no statistically significant changes in PRL concentration were observed in group II (modified transdermal HRT) and group I (control) (both in basic conditions and after the MCP stimulation test).

Table 2 presents data concerning IGF-I and GH measurements. In the control group, IGF-I concentration was significantly decreased after 1 year of therapy ($P < .001$); but no significant changes in GH levels in serum were found. In women receiving modified transdermal HRT, increased IGF-I concentrations were found during the whole therapy (statistically significant after 3 months of treatment, $P = .05$). In this same group (group II), decreased levels of GH were shown after 1 year of therapy, although these were statistically insignificant ($P = .07$). The IGF-I levels after 1 year of treatment were significantly higher in group II (women receiving modified transdermal HRT) than in group III (women receiving orally given HST) ($P < .001$) and in the control group ($P < .001$).

In the group of women receiving orally given HST (group III), a significant decrease of IGF-I was observed ($P < .05$) after a year of therapy. In this group, during the whole time of treatment, GH concentration was increased significantly in comparison with values at the beginning of therapy ($P < .05$ after 1 month, $P < .001$ after 3 months, and $P < .05$ after 12 months). Growth hormone concentration in group III was significantly higher than that in the control group throughout the whole period of treatment ($P < .01$). Growth hormone concentration in serum in group III was, after 1 year of treatment, also significantly higher ($P < .01$) than that in group II.

No significant changes were observed in OC and PICP concentrations in the course of the 12-month study in all 3 groups (Table 2). The PICP concentration in the serum was significantly lower in the group receiving modified transdermal HRT after 3 months ($P < .01$) and 12 months ($P < .001$) of therapy than in the control group. The PICP concentration was also decreased in this group compared with the group receiving orally given HST ($P < .05$) after 1 year of treatment. Furthermore, the PICP concentration was significantly lower after 1 year of therapy in group III than in group I (control group) ($P < .01$). No significant differences were observed in OC concentrations in all groups (I, II, and III).

The results of BMD L_2-L_4 of the lumbar spine at baseline and after 12 months of treatment are presented in Table 3. Significantly elevated BMD L_2-L_4 was observed in groups II ($P < .01$) and III ($P < .05$). After 12 months of application of transdermal HRT (group II), the BMD of lumbar vertebrae L_2-L_4 was significantly higher ($P < .001$) in comparison with that of the control group (group I) and that of the group orally given HST ($P < .01$). No changes in BMD L_1 were observed in groups I, II, and III. In the control group (group I), after 1 year of therapy, BMD was significantly reduced in L_2-L_4 ($P < .01$). The increase in BMD L_2-L_4 was statistically significant in women receiving modified transdermal HRT (group II) ($P < .01$) and also in women undergoing orally given HST (group III) ($P < .05$). The mean increase in BMD after a year of treatment was 3.8% in the women in group II (modified transdermal HRT) and 2.2% in the women in group III (orally given HST), and the mean decrease was −3.0% in group I (Table 3). The mean increase of BMD L_2-L_4 was 20 mg/cm^2 in group III ($P < .01$) and 34 mg/cm^2 in group II ($P < .001$), and the mean decrease was 38 mg/cm^2 in the control one ($P < .05$). Bone mineral density L_2-L_4 was significantly elevated in groups II ($P < .001$) and III ($P < .01$) compared with the control group after 12 months of therapy.

5. Discussion

Our own study revealed that the therapeutic effects and serum concentrations of estrogens depend on their kind and route of administration. Estrone and E_2 levels in the course of modified transdermal HRT were increased 3-fold, with appropriate E_1/E_2 ratio like 1:1 ensuring optimal physiologic estrogenic function. However, in women receiving orally given HST, E_1 concentration in serum increased 11-fold, E_2 increased 5-fold, and the E_1/E_2 ratio was more than 2:1 during the entire treatment, with a tendency to increase. These results coincide with reports of other authors [14-18].

Ten percent of estrogens administered transdermally and 70% of those administered orally are metabolized through the hepatic portal system and, with metabolites, are secreted in bile. They are subsequently reabsorbed in the intestines, resulting in multiple-pass metabolism through the hepatic system. Estradiol is converted to E_1 in the liver and intestines under the activity of E_2 17β-hydroxysteroid dehydrogenase that is in turn activated by enzyme sulfotransferase. The latter enzyme catalyzes the esterification of estrogens and their metabolites with glucuronic and sulfuric acids that are excreted in urine and partially in the bile. Estrogen sulfotransferase activity in postmenopausal women is very low, consequently causing the disturbances in the conjugation of estrogens with glucuronic acid. Progressive increase of estrogen concentrations in women receiving orally given HST may be caused by multiple passes of their metabolites. The occurrence of a more than 11-fold increase in E_1 concentration in women receiving orally given HST may be a result not only of the greater conversion of E_2 to E_1, but also of the longer half-life time of E_1 and its weaker affinity to sex hormone–binding globulin.

The highly significant increase in estrogens ($P < .0001$) in serum in the women receiving orally given HST corresponds with latent or overt hyperprolactinemia. The mechanism of PRL secretion in hyperprolactinemia is not as yet fully understood. It was suggested that the high level of estrogens in women receiving orally given HST stimulates the hypothalamic PRL-releasing hormone and decreases the activity of PRL-inhibiting factor affecting the release of PRL by the lactotropic cells of the pituitary gland. Hyperestrogenism and hyperprolactinemia in women receiving orally given HST predispose to fibrocystic changes of the breast and breast cancer [19] and activate the renin-angiotensin-aldosterone system [20]. Modified transdermal HRT ensures optimal levels of estrogens and progesterone, whose characteristic curves in the therapeutic cycle are comparable with those in the physiologic menstrual cycles. Variable estrogens and progesterone concentrations do not only improve the quality of life but also protect the progress of arteriosclerosis and of cardiovascular and breast diseases [4,6]. The significant increase in BMD L_2-L_4 ($P < .001$) after 12 months of modified transdermal HRT may be caused by an elevated level of IGF-I and estrogens and by a decreased PRL level [21]. On the contrary, in women receiving orally given HST for 12 months, the observed lack of significant increase in BMD L_2-L_4 may be associated not only with elevated PRL level ($P < .01$), but also with significant decrease in IGF-I ($P < .05$) in serum [21]. Low IGF-I concentration may be an indication of diminishing bone mass and of the risk factor of osteoporotic fractures in postmenopausal women [22].

The results of our study are in agreement with the reports of other authors who showed that orally given hormonal therapy causes increased GH and decreased IGF-I levels [16,21]. On the basis of the analysis of PICP concentration changes in women with osteopenia in the early postmenopausal period, it is also probable that estrogens administered transdermally slow down bone turnover to a greater degree than orally given estrogens.

6. Conclusions

1. Low-dose modified transdermal HRT modulates concentration of hormones, growth factor, IGF-I, OC, procollagen, and bone metabolism.
2. The curve concentrations of estrogens and progesterone in serum are similar to the type observed in the physiologic menstrual cycle.
3. Lower of significant increase in BMD of lumbar spine in women after HST may be a result of significantly lower concentration of IGF-I in serum and occurring hyperprolactinemia.

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