e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(8); 13-19

Original Research Article

Hormone Replacement Therapy in the Diagnosis and Intervention of Postmenopausal Osteoporosis

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Received: 15-04-2022 / Revised: 20-05-2022 / Accepted: 05-06-2022
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Conflict of interest: Nil

Abstract

Reducing the frequency of vertebral and non-vertebral fractures (particularly at the hip), which are to blame for the morbidity associated with the illness, is the goal of treatment for postmenopausal osteoporosis. In early postmenopausal women, hormone replacement therapy is still an important tool for osteoporosis prevention. At various doses, hormone replacement treatment (HRT) quickly restores bone turnover and preserves bone mineral density (BMD) at all skeletal locations, resulting in a marked decline in both vertebral and nonvertebral fractures. A one-year follow-up was done by 84 postmenopausal women who were randomly assigned to one of four groups. The first group (n = 20) received conjugated estrogens (CE; 25 days/month) at a rate of 0.625 mg/day. The third (n = 17) received 50 p g/day of transdermal 179-estradiol cyclically (24 days/month) while the second (n = 23) received 0.625 mg/day of CE continuously. The fourth group (n = 24) served as a treatment-free control group, whereas all of these groups additionally received 2.5 mg of medroxyprogesterone acetate consecutively throughout the final 12 days of hormone replacement therapy. Dual photon absorptiometry was performed prior to treatment and again after a year. Prior to treatment and six and twelve months later, measurements of serum calcium, phosphate, and osteocalcin levels as well as urinary calcium/creatinine and hydroxyproline/creatinine ratios were made. The amount of bone mineral increased across the board in all treatment groups. This rise was greater in the transdermal group (7.1 percent, P <0.01) and the continuous CE therapy group (4.4 percent, P <0.05). Concomitant biochemical effects at 6 and 12 months, including decreases in blood calcium, phosphate, and osteocalcin, as well as decreases in urine calcium and hydroxyproline, were consistent with the effects on bone mineral reported.

Keywords: Hormone Replacement Therapy, Osteoporosis, Postmenopausal, Prevention, Treatment

Background

Women's bone mass essentially stays constant up until menopause. The amount of bone mineral starts to decrease as soon as ovarian activity stops, and fractures become more common [1-3]. Additionally, premenopausal and perimenopausal women's bone mass is dramatically decreased by bilateral oophorectomy [4,5]. However, despite the numerous studies demonstrating the preventive impact of

estrogens against bone loss during the menopause, it is also well known that once oestrogen therapy is discontinued, the process is reactivated [6,9,10]. The majority of these studies [11,12] evaluate the effectiveness of the dosage and the treatment. This study compares the effects of various hormone replacement therapy regimens and delivery methods on bone metabolism.

Materials and Methods

Patients

To take part in the study, 99 healthy women with recent menopause (less than 24 months) and early menopause (younger than 50 years old) who had not used any kind of sex hormone replacement treatment were required. 84 of the study's 99 postmenopausal participants finished the 1-year follow-up. Patients were divided into one of four groups at random:

Group 1: (n = 20) conjugated equine estrogen cyclically 0.625 mg/day (24 days/month).

Group 2: (ii = 23) conjugated equine estrogen continuously 0.625 mg/day (each day/month).

Group 3: (n = 17) transdermal 17a-estradiol cyclically. 50 mg/day (24 days/month).

Group 4: (n =24) free-treatment control group. All treated groups received 2.5 mg of medroxyprogesterone acetate (MPA) sequentially for the last 12 days of estrogen therapy.

Analysis

In 2-h samples, urine calcium, creatinine, and hydroxyproline were measured [13]. The morning following an overnight fast and cigarette abstinence, blood samples were obtained. The measurement of creatinine used picric acid photocolorimetry. The ultrafiltered sample was converted to phenyl isothiocyanate before being subjected to high-resolution liquid chromatography analysis to measure the amount of hydroxyproline (Waters, Millipore Corp., Milford, MA, USA). Atomic absorption techniques were used to measure calcium in urine, while ortocresolftalein photocolorimetry was used to measure calcium in serum. Using molibdate ammonium photocolorimetry and UV light, serum phosphate was quantified. All prior measurements were adjusted to a discontinuous flow auto-analyzer, with the exception of urine calcium and hydroxyproline. Serum osteocalcin was determined by radioimmunoassay. Basal, 6-month and twelve-month samples were taken.

Bone mass measurement

Dual photon absorptiometry was used to compare the lumbar spine's (L2-L4) bone mineral density before and after treatment (at 12 months) (Lunar DP3 system). Precision (<3%) and radiation exposure (<10 mrem) are both excellent. Because age margins were small and remarkably consistent across all four groups, no age-matched values were employed.

Statistical analysis

The mean + S.D. was used to express the results. Pairwise Student's i-test was used to determine statistical differences between baseline and treatment values within the groups, and analysis of variance was used to investigate differences between the groups. Wilcoxon and Kruskal-Wallis ranked-pairs tests were applied where needed. P< 0.05 was deemed significant. The Statistical Analysis Package was used to analyse the results (Walonick Ass., Minneapolis, USA).

Results

15 of the 99 participants that were referred for the study withdrew. In Table I, the causes of default are listed.

Table 1: Reasons for Defaulting From Study

Reason	Group	n
Abnormal uterine bleeding	Continuous CEE	3
Erythema in patch applica tion area	Transdermal	3
Poor relief of climacteric symptoms	Transdermal	2
	Cyclic CEE	3
Endometrial hyperplasia	Cyclic CEE	2
	Transdermal	3

Clinical parameters (Table II) and baseline results did not show significant differences between the four studied groups.

Table 2: Clinical data

Group	n	Age (years)	Mean elapsed time since menopause (mcinths)	Weight (kgs)
1	21	45.1 + 6.3	20.7 + 14.3	66.0 + 3.5
2	22	47.4 + 4.3	17.3 + 11.9	68.2 + 4.6
3	18	45.6 + 7.7	23.3 + 22.2	63.3 + 6.9
4	24	49.3 + 2.4	17.1 + 9.8	d3.2 + 7.3

After 6 months, serum calcium and phosphate levels significantly decreased in all treatment plans, whereas the control group showed no differences. Osteocalcin levels in all replacement therapy groups were considerably lower at the 6-month follow-up, but they rose in the control group (Table III).

Table 3: Urine analysis and Serum Analysis

Urine Analysis				
	Conjugated estrogens		Transdermal	Control
	continuous	cyclical	17β-estradiol	
Calcium/creatinine				
0	0.166 ± 0.02	0.174 ± 0.01	0.173 ± 0.02	0.175 ± 0.02
6	0.129 ± 0.03	0.159 ± 0.02	0.119 ± 0.01 **	0.176 ± 0.01^{NS}
12	0.131 ± 0.05	0.161 ± 0.02	0.122 ± 0.01 **	0.198 ± 0.02 ^{NS}
Hydroxyproline				
0	131.9 ± 8.8	130.5 ± 7.6	135.7 ± 3.6	136.1 ± 5.1
6	125.6 ± 9.1 **	128.0 ± 9.8 ^{NS}	125.8 ± 8.7 **	140.3 ± 9.4 ^{NS}
12	127.1 ± 7.6 *	128.5 ± 6.7 ^{NS}	127.7 ± 9.5 **	141.9 ± 4.9 ^{NS}
Serum Analysis				
	Conjugated estrogens		Transdermal	Control
	continuous	cyclical	17β-estradiol	
Phosphate				
0	3.91 ± 0.08	3.82 ± 0.11	3.78 ± 0.13	3.63 ± 0.13
6	3.69 ± 0.10*	3.63 ± 0.09 *	3.61 ± 0.08 *	3.65 ± 0.14^{NS}
12	3.71 ± 0.06	3.65 ± 0.08 *	3.67 ± 0.08 *	3.65 ± 0.09^{NS}
Calcium				
0	9.66 ± 0.09	9.82 ± 0.08	9.72 ± 0.05	9.54 ± 0.13
6	9.43 ± 0.09 *	9.50 ± 0.09	9.4.3 ± 0.06 *	9.56 ± 0.12 ^{NS}
12	9.43 ± 0.06 *	9.52 ± 0.08	9.47 ± 0.08 *	9.59 ± 0.11 ^{NS}

In all three hormone replacement groups, the levels of calcium, phosphate, and osteocalcin were found to be significantly lower after a year of treatment than at baseline, although they did not differ from values discovered at six months. The increase seen at six months for all metrics was remained present in the control group after a year. When compared to the baseline and 6-month values, this increase in osteocalcin was substantial (Table III). No differences were found among the therapy groups when comparing the changes in osteocalcin levels between groups at 6 months, but there appeared to be a trend toward a significant difference between the treated and control groups (P <0.07). At the 12-month follow-up, this difference became statistically significant (P <0.05).

Urinary calcium and hydroxyproline/ creatinine ratios displayed a similar pattern to the changes in serum levels (Table III). At the 12-month follow-up, all hormone replacement therapy groups had higher bone mineral content (Table III). As anticipated, the control group, however, displayed a substantial decline (P <0.05). Women on cyclic conjugated estrogens experienced the lowest rise overall, I.3 No (14 mg/cm^2), while patients taking a continuous regimen experienced a greater (4.4 percent, 39 mg/cm^2) and significantly higher increase (P <0.05) increase. However, individuals who received transdermal treatment saw the greatest gain in bone mass, at 7.1% (71 mg/cm^2) (P <0.01). The control group's average bone mass loss was calculated to be 31 mg/cm^2.

Discussion

The data from the control group show a clear rise in both resorption and formation rates during the first few years following the onset of menopause. While the rise in osteocalcin levels indicates an increase in bone production, the rise in the urinary calcium/creatinine ratio shows a net increase in resorption. The assumption that bone loss occurs in an early stage of menopause is supported by the increase in these bone turnover rates in our patients with first menopause and densitometric results further support the notion that the age-related decrease of bone mineral content does indeed start at this time.

The optimum strategy is still up for debate, despite the fact that estrogens obviously have a preventive effect against osteoporosis in menopausal women and numerous articles have recommended administering the lowest effective dose From a therapeutic perspective, it would undoubtedly be extremely interesting to be able to determine the dose and delivery method of the minimal estrogens that can prevent osteoporosis and do not result in hypertrophic changes in the endometrium. Determining the progestin dosage and delivery method that inhibits endometrial proliferation while having minimal effects on lipid metabolism may also be helpful. This dose was established in earlier research at 2.5 mg of medroxyprogesterone acetate and 0.625 mg of conjugated estrogens [12,16]. Progestins are also known to have preventive effects against bone loss [17,19]. These doses were investigated in the current investigation using oral medications, and the effectiveness of continuous vs. cyclic delivery was assessed. Although the dosage of medroxyprogesterone is not the focus of the current investigation, our findings (Table I) show that 2.5 mg of MPA per day is insufficient to prevent endometrial hyperplasia, especially when transdermal estradiol is used.

The Christiansen group argued for the value of ongoing routines [20]. Our data allow us to suggest that continuous medication is more effective because it seems to reduce bone turnover and raise bone mineral content more than intermittent administration. Although cyclic administration causes a modest increase in bone mass (1.3%), this rise is less than the accuracy of the method (3%)

and cannot be definitively linked to the increase. With a cyclical regime, there is no increase in bone mineral content, which conflicts with other authors' findings [21,22].

Percutaneous [23-25] and transdermal [26] estradiol treatment reduced bone loss in postmenopausal women, according to a number of studies. Stevenson [27] did not discover any differences between oral and transdermal hormone replacement treatment in a randomised investigation. Nevertheless, the administration of 50 pg/day of 17a-estradiol was the most effective pattern in the study subjects, and our data demonstrate the value of the transdermal route in preventing bone loss associated with menopause. The greatest increase in bone mass was seen in this group.

Conclusion

The holy grail compound that can alleviate menopausal symptoms, such as vasomotor symptoms and vaginal dryness, maintain or increase BMD, lower the risk of fractures at all skeletal sites, as well as lower the risk of cardiovascular disease, dementia, genitourinary issues, and breast, endometrial, and ovarian cancer, has not yet been discovered. Routine use of HRT in postmenopausal women is not advised due to the availability of newer and safer medicinal treatments for osteoporosis and its prevention. However, short-term use of HRT, raloxifene, and/or tibolone is currently allowed to reduce symptoms in some postmenopausal women with early menopause or postmenopausal symptoms. Although osteoporosis prevention is an approved indication for estrogen-based hormone therapy, they shouldn't be used as the first line of treatment for asymptomatic women because there are alternatives available. Serum Before beginning any other treatment for the prevention of bone loss, vitamin D deficiency should be ruled out, and appropriate calcium intake should be made before managing osteoporosis. It is particularly intriguing to note the stabilization of these annual results when compared to values after 6 months, despite the fact that all treatment groups have bone turnover markers that are much lower than baseline levels after 12 months. This supports the idea that the impact of replacement therapy on bone metabolism is greater in the initial months of treatment and then rather stable after that.

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