THE IMPACT OF VITAMIN D_3 METABOLITE TO HORMONE REPLACEMENT THERAPY ON BONE DENSITY IN EARLY POSTMENOPAUSAL WOMEN

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ABSTRACT

Objective: The purpose of this prospective study is to investigate the impact of adding active vitamin D metabolite to hormone replacement therapy (HRT) in the treatment of osteoporosis in early postmenopausal women.

Methods: Fifty-two naturally postmenopausal women receiving either 0.625 mg conjugated estrogen with 2.5 mg medroxyprogesterone acetate daily for 12 months or 0.50 µgr one alpha cholecalciferol in addition to 0.625 mg conjugated estrogen with 2.5 mg medroxyprogesterone acetate daily for 12 months.

Results: Bone mass density (BMD) increases significantly in both treatment groups at 12 months not only in proximal femur but in the lumbar spine as well. In the HRT + alpha calcidiol group, the percentage of change in BMD for the proximal femur was 17.32 ± 22.41 and 15.02 ± 10.05 for the lumbar spine. In the HRT alone treatment group the percentage of change in BMD was 12.21 ± 12.81 and 9.44 ± 8.01 for the proximal femur and the lumbar spine respectively.

Conclusion: Addition of vitamin D metabolite seemed to potentiate the BMD elevating effect of HRT even though the positive trend in the BMD change was not statistically significant in one year.

Key Words: Alpha calcidiol, Bone Density, Hormone Replacement Therapy.

INTRODUCTION

Osteoporosis is a systemic skeletal disease characterised by low bone mass and microarthitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. The positive effect of hormone replacement therapy on reducing bone loss in estrogen deficient women is well defined and non controversial.

Vitamin D deficiency is common in elderly people, in whom it causes decreased intestinal calcium absorption and secondary hyperparatyroidism, which may result in increased bone turnover, bone loss and fractures or even osteomalacia (1). Supplementation with vitamin D and calcium may reduce bone loss and may decrease hip fractures especially among elderly women (2). Hence, vitamin D supplementation has been recommended for prevention of osteoporosis in the elderly. However, the literature is very scarce on the bone effects of vitamin D supplementation in early postmenopausal women. Alpha calcidiol which is a synthetic anologue of active vitamin D in the form of one-alpha- hydroxycholecalciferol, is attracting considerable interest in the prevention of osteoporosis. The purpose of the present study is to investigate the impact of adding active vitamin D metabolite to HRT in the treatment of osteoporosis in early postmenopausal women.

METHODS

Fifty two postmenopausal women who presented to the Marmara University Hospital Menopause clinic between December 1995 and February 1997 were recruited for this prospective study after informed consent was obtained. All subjects were natural menopausal women and 2-11 years had elapsed since their last menstruation. The study was approved by the Institutional Review Board of the Marmara University School of Medicine. Patients were free of any systemic disease and none of them had used any medication in the previous 6 months. Each patient underwent a complete physical and gynecological examination, in addition, hepatic and renal functions analyses were made and baseline serum TSH, PTH, T_3, T_4, total calcium, phosphate, total protein and albumin were measured. Anthropometric measurements were recorded initially (height, weight, waist, hip). The bone mineral density at the lumbar spine (L_2-L_4) and at the left femoral neck was determined by the trained personnel using dual energy X ray absorptiometry (Dexa, Lunar DPX, Madison, WI, U.S.A.). Coefficients

of variation for the instrument were 1% for the spine and 2.2% for the proximal femur in vivo. Scans were analyzed with 1.3 version software. These tests were repeated at the end of one year. Patients were randomly assigned using a computer program to receive either 0.625 mg conjugated estrogen with 2.5 mg medroxyprogesterone acetate or 0.50 µgr one alpha cholecalciferol in addition to 0.625 mg conjugated estrogen with 2.5 mg medroxyprogesterone acetate daily for 12 months. All patients received 500 mg calcium lactate gluconate daily. Values were expressed as means ± SD. Paired and unpaired Student's t tests were used for statistical analyses.

RESULTS

The characteristics of the 52 postmenopausal women are shown in Table I. There is no statistically significant difference in demographic characteristics between patients taking HRT and those taking HRT plus alfa calcidiol. The serum calcium, phosphorus, creatinin, total protein, albumin, alkaline phosphatase (ALP), thyroid stimulating hormone (TSH) and parathyroid hormone (PTH) baseline levels and 12 months levels after initiation of treatment in both groups are shown in Table II. None of the parameters were significantly different between the groups. BMD at L2-L4 and proximal femur before and after 12 months of treatment in both groups are demonstrated in Table III. BMD increased significantly in both treatment groups at 12 months not only in proximal femur but at lumbar level as well. In the HRT + alfa calcidiol treatment group the percentage of change in BMD for the proximal femur was 17.32 ± 22.41 and 15.02 ± 10.05 for the lumbar spine. In the HRT alone treatment group, the percentage of change in BMD were 12.21 ± 12.81 and 9.44 ± 8.01 for the proximal femur and the lumbar spine respectively. The percentage of change in BMD in both groups is shown in Table IV. The percentage of change in BMD at the end of 12 months was not significantly different between the treatment groups both at the femur and lumbar site. However, there was a trend towards a better response with alpha calcidiol + HRT treatment group which did not achieve significance.

Table I. Demographic characteristics of the patients.

PATIENTS		CONTROL GROUP	TREATMENT GROUP	P VALUE
Age(years)	Mean	51.84±2.8	51.73±2.6	p>0.05
	Range	44-59	42-62	
Years for menopause	Mean	6.2±1.87	5.8±1.59	p>0.05
	Range	2-10	2-11	
BMI (Body Mass Index) (kg/m2)	Mean	38.3±3.8	37.6±3.7	p>0.05
	Range	24.6-45.4	22.4-48.2	
Values expressed as mean±deviation.				

Table II. Comparison of bone turnover related serum markers

	HRT GROUP (n:26)		HRT + ALFA CALCIDIOL GROUP (n:26)	
	Baseline	after 12 months	Baseline	after 12 months
Calcium mg/dl	9.12 ± 0.69	9.23 ± 0.69◆	9.36 ± 0.58	9.48 ± 0.63◆
Phosphorus mg/dl	3.35 ± 0.59	3.32 ± 0.27◆	3.15 ± 0.44	3.24 ± 0.40◆
Creatinin mg/dl	0.671 ± 0.20	0.694 ± 0.22◆	0.673 ± 0.19	0.703 ± 0.18◆
Tot. prot mg/dl	8.05 ± 0.95	8.21 ± 0.67◆	7.85 ± 1.0	8.10 ± 0.98◆
Albumin mg/dl	4.1 ± 0.67	4.05 ± 0.95◆	4.26 ± 0.82	4.18 ± 0.79◆
ALP mg/dl	62.54 ± 32.54	62.06 ± 32.27◆	61.33 ± 35.04	62.10 ± 34.75◆
TSH mIU/ml	1.17 ± 1.6	1.32 ± 0.88◆	1.06 ± 1.42	1.19 ± 1.37◆
PTH µg/ml	38.64 ± 19.71	41.24 ± 19.84◆	42.24 ± 20.32	39.56 ± 19.56◆
Values are the mean with standard deviations ◆: not significant				

Table III. Comparison of bone mass densities of groups at baseline and after 12 months

	HRT GROUP (n:26)		HRT + ALFA CALCIDIOL GROUP (n:26)	
	Baseline	after 12 months	Baseline	after 12 months
Proximal Femur gr/cm^3	0.790 ± 0.130	0.867 ± 0.128♣	0.771 ± 0.136	0.881 ± 0.130♣
Lumbar Vertebrae gr/cm^3	0.900 ± 0.123	0.961 ± 0.125♣	0.919 ± 0.128	1.025 ± 0.135♣

values are the mean with standard devations
♣: significant

Table IV. Percentage of increase in bone mass densities within groups after 12 months

	HRT GROUP (n:26)	HRT + ALFA CALCIDIOL GROUP (n:26)	p value
Proximal Femur	12.21 (±12.81)%	17.32 (±22.41)%◆	p=0.21
Lumbar Vertebrae	9.44 (±8.01)%	15.02 (±10.05)%◆	p=0.15

values are the mean with standard deviations
◆ : not significant

DISCUSSION

Prevention of postmenopausal bone loss by HRT is widely accepted. Vitamin D supplementation is an accepted treatment of osteomalacia and has been suggested as a non hormonal alternative in the prevention of osteoporotic fractures in elderly people. Chapuy et al, demonstrated lower incidence of peripheral and femoral fractures in patients receiving 800 IU vitamin D_3 daily when compared to control group, in a 36 months follow up study (2). Lips et al, stated that 400 IU vitamin D3 daily produced a slight increase in femoral bone density, which did not show any influence on the incidence of hip fractures (3). The decline in estrogen levels during menopause, causes, a transient reduction in serum calcitriol concentrations and calcium absorption (4). It appears that, a direct reduction in 1 alpha hydroxylase capacity seems to be less involved than a reduction in the activity of factors that normally stimulate the conversion of 25(OD)D to 1,25 $(OH)_2D$ (5). Alfa calcidiol is a chemical precursor of calcitriol within the body and rapid transformation by liver via 25-hydroxylation in bone into the most active metabolite of vitamin D exemplifies the pro-drug technique (1). It has been confirmed previously in animal models that the half life of 1,25 $(OH)_2D_3$, is prolonged following alfa calcidiol administration (6).

The efficacy and safety of alfa calcidiol in treating postmenopausal osteoporosis were consistently and impressively demonstrated by several authors. In controlled clinical studies, it has been demonstrated that alfa calcidiol can increase vertebral bone mass between 2% and 6% after 2 years (7,8). Another prospective, placebo controlled, randomised study in 66 postmenopausal women demonstrated that alfa calcidiol combined with calcium increased radial bone density 2% whereas in placebo group BMD decreased by 7.8% at the end of 3 years (9). Francis et al, reported that neither vitamin D nor one alpha hyroxylated vitamin D_3 derivatives were effective in the treatment of postmenopausal osteoporosis (10). Heikkinen et al, stated that there was no significant difference in BMD between patients taking HRT and HRT plus vitamin D (8). In another study; Francis et al found that postmenopausal women treated over 7 days with 0.5 µgr alfa calcidiol daily display statistically significant superior increase in calcium absorption compared with women treated with 40 µgr 25(OH)D3 (11). Komulainen et al, reported that vitamin D supplementation with or without HRT could not prevent either lumbar or femoral bone loss in 464 non osteoporotic early postmenopausal women (12). Tuppurainen et al, in a 4 year prospective study showed that, addition of vitamin D to HRT increases

femoral neck BMD significantly, whereas lumbar spine BMD did not differ in comparison to HRT alone group (13). The vit D serum concentrations of the women were not measured in the present study. However, relative impairment of calcium absorption among early postmenopausal osteoporotic women is quite likely, which usually results in increased bone turnover. Addition of vitamin D to HRT might correct suboptimal serum concentrations of vitamin D. Our results showed that both HRT and HRT combined with alfa calcidiol increases bone densities at lumbar spine and femoral neck significantly at the end of 1 year. It appears that the addition of alfa calcidiol to HRT potentiates the BMD elevating effect of HRT even though the positive trend did not achieve significance. However, the additional cost of the treatment has to be considered. The limitations of this study are, having relatively smaller groups and shorter follow up periods. Future studies with larger groups and longer follow up periods will enlighten the efficacy of adding alfa calcidiol to HRT in preventing osteoporosis and reducing fractures in early postmenopausal women.

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