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BMD Profile – A Follow up After Different Treatments in Postmenopausal Women

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OBJECTIVE – To compare the efficacy of different treatments for low bone mineral density (BMD) in women between 40 and 70 years of age based on the hypothesis that peri- and early post-menopausal women may respond better to combination therapy than to HRT alone. **METHODS** – The study was conducted at a private 'menopause clinic' on 100 randomly selected women aged 40 to 70 years. The effect of prescribed medication was observed on their bone mineral densities over one year, medications used were conjugated equine estrogens(CEE) with or without progestogen and bisphosphonates. **RESULTS** – Improvement in BMD was better achieved by using a combination of HRT and bisphosphonates as compared to that with either treatment alone in immediate post-menopausal period. HRT alone or with bisphosphonates does not affect BMD significantly in late post-menopausal women. **CONCLUSION** – Combination of HRT and bisphosphonates should be used in the immediate postmenopausal period for improving BMD.

Key words : bone mass density, bisphosphonate, hormone replacement

Introduction

Osteoporosis is a global problem which will increase in significance as the population of the world increases and ages. By definition, it is a condition of skeletal fragility characterized by reduced bone mass and architectural deterioration of bone tissue with a consequent increase in risk of fractures. According to recent WHO criteria, the term osteoporosis is also used to designate a bone mass value more than 2.5 SD below the young adult mean.

Bone is in a state of constant remodeling in the body. All changes in bone mass occur through adjustments in the balance between resorption by osteoclasts and formulation by osteoblasts. Bone mass and density reach their maximum values in women somewhere between menarche and the fourth decade. Adequate supply of nutrients and physical stress during growth and transition through menarche appear necessary to achieve genetically predetermined skeletal status. Bone mass and density remain fairly constant until the onset of ovarian failure, although at some skeletal sites there is a small premenopausal decline in bone mass. During this period of life, bone remodeling continues as a preventive maintenance program which is thought to be necessary for both metabolic and mechanical skeletal functions[1].

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This remodeling process is controlled, at least in part, by ovarian hormones, specifically estrogen. If endogenous supply of estrogen is interrupted, remodeling in bone in disrupted. There seems to be an increase in the rate at which new remodeling sites are activated. This phenomenon produces a transient decline in bone mass that is reversible when the activation rate is reduced to premenopausal levels. Increased activation can also cause permanent loss of bone within the cancellous bone envelop. As the woman ages, bone loss continues albeit at a relatively slower pace. This phase is influenced by various age related factors like vitamin D deficiency, reduced calcium absorption, secondary hyperparathyroidism etc.

Primary reduction in bone mass, therefore, occurs as part of involutional bone losses during natural menopause or normal human aging. Reduction in bone mass can also be due to numerous secondary causes which account for 20% of the incidence of osteoporosis in elderly women[2].

Extensive epidemiological data indicate that fracture risk increases two to three fold for every drop of one standard deviation in bone mass at any given site[3]. A 30% reduction in bone mass, common in osteoporosis, will decrease strength by 50%.

The above facts warrant an assessment of the effect of different therapeutic agents on bone mineral density (BMD) in different phases of life.

Material and Methods

The present study was conducted with the aim to assess

the change in BMD profile over a period of one year in patients on different treatment modalities.

One hundred women aged 40 to70 years were randomly selected after ruling out secondary causes of osteoporosis. These women were divided into two groups.

Group A – women aged 40 to 54 years

Group B – women aged 55 to 70 years

Fifty women were assigned to each group. Women in Group A were less than five years post-menopausal where as women in Group B were more than five years post menopausal.

BMD of all the women in both the groups was assessed at the hip and the spine by Dual Energy X-ray absorptiomethy (DEXA) using Hologic 4500 machine. Different treatments were prescribed based on clinical judgement, need of the patient and patient's choice as follows -

a) Conjugated equine estrogens (CEE) 0.625 mg daily with or without medroxy progesterone acetate 2.5mg daily.

b) Bisphosphonates 5 to 10 mg and CEE 0.625 mg daily.

c) Bisphosphonaters alone 5 to 10 mg daily.

The criteria for choosing different treatments were as follows -

40 – 70 years	-	Estrogen deficiency. Osteopenia / Osteoporosis No contraindication for estrogens. Patient willing to take HRT.	Conjugated estrogens with / without progestogen + Bisphosphonates
40-55 Years	-	No estrogen deficiency, Osteopenia / Osteoporosis No contraindication for estrogens. Patient willing to take HRT.	Conjugated estrogens with / without progestogen + Bisphosphonates
40-45 years	-	No estrogen deficiency. Osteopenia / Osteoporosis. Estrogens contraindicated. Patient not willing for HRT.	Bisphosphonates
55-70 years	-	Osteopenia / Osteoporosis No estrogen deficiency	Bisphosphonates

Table I : Results of Treatment

Treatment by CEE / CEE In Group A (n=50)			Treated by B+CEE / B In Group B (n=50)		
Favourable	**Unfavourable**	**NS**	**Favourable**	**Unfavourable**	**NS**
28 (56%)	2 (4%)	20 (40%)	23 (46%)	5 (10%)	22 (44%)

NS – Non Significant change (<2% variation) B – bisphosphonate CEE – conjugated equine estrogens

Table II : Analysis of Favourable Results

Group A (n=50)		Group (B n=50)	
B+CEE	**CEE**	**B+CEE**	**B**
20 (71.42%)	8 (28.57%)	12 (52.17%)	11 (47.82%)

B – bisphosphonate CEE –conjugated equine estrogens

Table III : Age Group wise and Response wise Comparison of Treatment

Age Group (Yrs.)	Response to medication	Medicine used	n	Mean increase in BMD after one Year	SD	t	degree of freedom	p-value
40-54	Favourable	B+CEF	20	0.0628	0.0226	3.4166	26	<.01
		CEE	8	0.0337	0.0121			
40-54	Unfavourable	B+CEE	2	-0.0610	0.0116	-	-	-
55-70	Favourable	B+CEE	12	0.676	0.0373	-0.0382	21	NS
		B	11	0.0682	0.0376			
55-70	Unfavourable	B+CEE	8	-0.0795	0.0302	0.03821	19	NS

B – bisphosphonate, CEE – conjugated equine estrogen

BMD was repeated at the end of one year in all women and pattern of change in BMD was noted. Also, a co-relation between change in BMD with treatment prescribed was studied.

Results

On reassessing the BMD after one year, it was observed that in Group A, 56% patients showed a favourable change of 4-11% in BMD, 4% showed an unfavourable change and 40% showed no significant change. In Group B, 46% showed a favourable change of 4-6% in BMD, 44% showed no significant change and 10% showed an unfavourable change. (Table I)

It was further seen that in Group A, out of the women exhibiting favourable change in BMD, 71.42% were on a combination of bisphosphonates and CEE and 28.57% were on CEE alone (Table II). In Group B, out of the women showing favourable change in BMD, 52.17% were on a combination of bisphosphonates + CEE and 47.82% were on bisphosphonates alone (Table II).

Further analysis and co-relation of women showing insignificant change in BMD with treatment was done in Group B. It was seen that 72.72% of these patients were taking CEE and 27.27% were on a combination of bisphosphonates + CEE.

Table III summarises the results of treatments given. On the basis of this study, it can be concluded that improvement in bone mineral density can be better achieved by a combination of HRT and bisphosphonates as compared to either of the treatments alone in immediate postmenopausal period. Also HRT alone or addition of HRT to bisphosphonates does not significantly affect bone mineral density in late postmenopausal period.

Discussion

Verifying the patient's response to medication is widely believed to encourage compliance with treatment. In the interpretation of follow-up scans, clear rules must be followed for determining whether the measured changes in BMD indicate a statistically significant response to treatment or whether BMD is unchanged or is continuing to fall.

Studies of long term precision give a value of approximately 1.5% for spine BMD and 2.5% for femoral neck BMD[4]. These results give a smallest measurable change of 4.5% for the spine and 7.5% for the femoral neck.

Most currently available therapeutic approaches to osteoporosis are effective by virtue of reduction in bone remodeling. However, these agents may interact at different points in the remodeling cycle, either reducing the recruitment of osteoclasts or the activity of mature osteoclasts or affecting osteoclast activity only indirectly. Consequently, there is a possibility that each one of the available anti-resorptive agents may add to or detract from the effects of estrogen on the skeleton.

Prevention of early postmenopausal bone loss has been successfully achieved by the use of drugs which reduce or inhibit bone resorption. Estrogen and bisphosphonates are considered safe and effective in maintaining mineral density of trabecular and cortical bone at pre-menopausal levels by counteracting the exacerbated activity of obsteoclasts induced by the sharp postmenopausal decrease in circulating estrogens[5,6].

Almost all studies using DEXA have demonstrated the prevention of bone loss in the spine with adequatedoses of oral estrogens. The effects on femoral neck bone mass

are generally less than those on the spine. Data on esterified estrogens suggest that a dosage of 0.3mg/day prevents bone loss over a 2 year period in the spine without producing much of an endometrial response[7].

All the bisphosphonates studied to date when given in sufficient doses seem to be effective in preventing bone loss in recently postmenopausal women and in increasing bone mass in women with postmenopausal osteoporosis[8].

Bone et al[9] enrolled 359 osteoporotic women between the ages of 60 and 85 years, assigned them to receive a placebo or one of three doses of alendronate daily (1mg. 2.5 mg. 5 mg) and observed them for 2 years. A dose of 1mg had no effect, 2.5 mg dose produced significant gains at the spine and total body and dose of 5 mg daily resulted in significant gains at all sites measured (spine, femoral neck, total body, distal forearm).

Liberman et al[10] studied osteo-porotic postmenopausal women treated orally with 10mg of alendronate daily. On an average, an increase of 4.5% required for detecting a significant change in spine was reached after 6 months of treatment. However, the mean change in femoral neck BMD did not approach the required figure of 7.5% even after 3 years.

Cummings et al[11] have drawn attention to the fact that in the alendronate study reported by Black et al[12], the increase in BMD in the treatment group accounted for only 40% of the reduction in fracture incidence.

The early postmenopausal intervention cohort (EPIC) is an on going study to assess the efficacy of alendronate in the prevention of the accelerated phase of bone loss that occurs in early menopause. Weiss et al[13] have infered that treatment with alendronate in recently menopausal women may be effective only as long as it is given. Although bone loss begins when treatment is stopped, the initial gains and possibly a slower rate of loss should still confer long-term benefits.

There is considerable interest in the effects of the addition of bisphosphonate to HRT. Lindsay et al[14] studied 428 postmenopausal women with osteoporosis, for more than 5 years and found that alendronate and ongoing HRT in postmenopausal women with osteoporosis stimulated increases in bone mass at both 6 and 12 month follow up that were significantly higher at the lumber spine and hip trochanter. Combined therapy was well tolerated.

Further studies are required to evaluate the effects of different drugs on BMD in different groups of women based on their age and postmenopausal status.

References

1. Bonjor JP, Rizzoli R. Bone acquisition in adolescence. In: Marcus R. Feldman D, Kelsey J, eds. Osteoporosis. *San Diego, Academic Press. 1996: 465-76.*
2. Harper KD, Weber TJ. Secondary Osteoporosis. Diagnostic considerations. *Endocrinol Metab Clin North Am 1998;27:325-48.*
3. Heaney RP. Pathophysiology of osteoporosis. *Endocrinol Metab Clin North Am 1998;27:255-65.*
4. Patel R, Blake GM, Rymer J et al. Long-term precision of DXA scanning assessed over seven years in forty postmenopausal women. *Osteoporos Int 2000;11:68-75.*
5. Christiansen C, Lindsay R. Estrogens, bone loss and preservation. *Osteoporosis Int 1990;1:7-13.*
6. Reginster JY, Taquet AN, Gosset C. Therapy for osteoporosis. Miscellaneous and experimental agents. *Endocrinol Metab Clin North Am 1998;27:453-63.*
7. Genant H K, Lucas J, Weiss S et al. Low dose Esterified Estrogen therapy. *Arch Intern Med 1997; 157: 2609-15.*
8. Watts NB. Treatment of osteoporosis with bisphosphonates. *Endocrinol Metab Clin of North Am. 1998;27:419-39.*
9. Bone HG, Downs RW Jr., Tucci JR et al. Dose response relationships for alendronate treatment in osteoporotic elderly women. *J Clin Endocrinol Metab 1997;82:265-74.*
10. Liberman UA, Weiss SR, Brok J. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med 1995; 333: 1437-43.*
11. Cummings SR, Black DM. Vogi TM. Changes in BMD substantially underestimate the anti-fracture effects of alendronate and other anti-resorptive drugs. *J Bone Miner Res 1996;11 (suppl 1):S102.*
12. Black DM. Cummings SR, Karpf DB et al. Randomized trail of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet 1996; 348: 1533-41.*
13. Weiss S, McClungM, Gilchrist N. Five year efficacy and safety or oral alendronate for prevention of Osteoporosis in early postmenopausal women. *J Bone Miner Res 1997;12:S144*
14. Lindsay R, Cosman F, Lobo RA et al. Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoprosis: a randomized, controlled clinical trial. *J Clin Endocrinol Metab 1999;84:3076-81.*