CORRELATION OF BONE MINERAL DENSITY WITH BIOCHEMICAL MARKERS IN POST MENOPAUSAL WOMEN

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ABSTRACT

To evaluate the magnitude of bone loss in postmenopausal women and to study the effect of a selective estrogen Receptor Modulator, raloxifene, on bone loss by quantitative ultrasound of calcaneus and serum bone specific alkaline phosphatase (BAP). Postmenopausal women with osteopenia/osteoporosis were assigned randomly to receive placebo (n=30) or raloxifene (60mg/d, n=30) with calcium (500mg/day) and vitamin D (250 IU/day). The bone mineral density (BMD) and BAP levels were measured at the beginning of therapy and six months later. They were subjected to statistical analysis (t test, p value) using SPSS statistical package. 70% of postmenopausal women suffered from osteopenia/osteoporosis. After raloxifene therapy, there was improvement in the BMD but this was not statistically significant ($p>0.05$). There was a fall in the value of serum BAP by 26.6% ($p<0.05$). Raloxifene has a favourable effect on bone turnover as evident from changes in BMD and a significant fall in serum BAP.

KEY WORDS

Bone mineral density, Bone specific alkaline phosphatase, Quantitative ultra sonography, Dual X Ray Absorptiometry.

INTRODUCTION

Osteoporosis leads to considerable morbidity and mortality in postmenopausal women. In India, an estimated 12 million postmenopausal women suffer from osteoporosis and are at a lifetime risk of bone fracture. In a study conducted on 2100 women with osteoporosis in Andhra Pradesh, it was found that 1600 of them were post menopausal. Out of which 330 had severe osteoporosis, 262 had osteoporosis, 676 had osteopenia and 332 were normal. Early detection of bone loss by measurement of bone mineral density helps confirm the diagnosis of osteoporosis and assesses the future risk of osteoporotic fractures so that timely therapy can be instituted. Dual X-ray absorptiometry (DXA) is the gold standard to assess bone mineral density but is not always available to the general population (1). In developing countries besides

being inexpensive, Quantitative ultrasound (QUS) scanning of the calcaneus is a mobile and radiation free diagnostic alternative and a number of studies have shown that the predictive power for QUS is of the same order as that of DXA (2,3). In addition several new biochemical markers have been developed which are found to be sensitive indices of early changes in bone turnover in research protocols (4). One of these, serum BAP is a highly specific and sensitive marker that reflects the increased turnover associated with bone destruction of aging, menopause and various conditions affecting bone metabolism (5).

With the conventional hormone replacement therapy going into disrepute, Selective Estrogen Receptor Modulators (SERMs), especially raloxifene have provided a new dimension in the field of postmenopausal health. The benefits of raloxifene (lipid lowering, anti estrogenic action on breast and uterus) beyond its action on bone resorption make it an effective and well tolerated treatment option for the prevention and treatment of bone loss in post menopausal women (6).

MATERIALS AND METHODS

This study was carried out jointly in the Department of

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Obstetrics and Gynaecology and Department of Biochemistry at Lady Hardinge Medical College and Smt. Sucheta Kriplani Hospital, New Delhi after institutional ethical clearance. The study was conducted in two phases:

Phase-I: 150 healthy post menopausal women above the age of 40 years were enrolled from out patient department and wards of the hospital after written informed consent. 150 women were screened for BMD by means of QUS of the calcaneus.

Inclusion criteria: Patients in the age group 40-65 years who have undergone natural/surgical menopause (at least 6 weeks have elapsed after hysterectomy).

Exclusion criteria: Women receiving/having received any treatment for osteoporosis; having a secondary cause for osteoporosis; diagnosed breast/endometrial carcinoma; chronic diseases affecting bone; taking medications that influence bone (corticosteroids, anticonvulsants or thyroxine).

Phase-II : 60 women with low BMD were recruited in the study and equally divided into study and control groups, who visited the Menopause clinic of LHMC and SSK Hospital from March 2004 to August 2004 and were followed up for six months till February 2005 .

Inclusion criteria: All women found to have osteopenia/osteoporosis after Phase-I.

Exclusion criteria: Hypersensitivity to raloxifene; past history of venous thromboembolic events; hepatic impairment; unexplained uterine bleeding; bed ridden patients and those with coagulation disorders.

All women were subjected to a detailed history taking and thorough clinical examination. A local examination was carried out to rule any lesion of genitalia. Baseline investigations includes - Complete blood count, Serum lipid profile (total cholesterol, serum triglycerides, HDL (high density lipoproteins), LDL (low density lipoproteins) and VLDL (very low density lipoproteins), Fasting blood sugar, LFT/KFT, Serum calcium and phosphorous (Beckman CX9 clinical chemistry analyzer), BAP quantification using enzyme immunoassay (EIA) with Metra BAP EIA kit, Pap smear, Transvaginal ultrasound for endometrial thickness and uterine volume.

Raloxifene 60 mg/d was administered to the study group. The control group received a placebo (Lactose tablet). Both groups were given 500 mg of calcium and 250 IU of vitamin D daily. The subjects were followed up monthly for six months. The acceptability of raloxifene was evaluated by clinical assessment on each visit. History regarding various side effects of raloxifene like hot flushes, breast pain, vaginal bleeding, leg cramps and peripheral edema was elicited. The

safety profile of Raloxifene was also studied. Gynecological safety was assessed by history of vaginal bleeding, repeat pap smear and transvaginal ultrasound at 3 and 6 months, Cardiovascular safety by lipid profile repeated at 3 and 6 months. Breast safety by local clinical examination on each visit followed by breast ultrasound or mammography, if indicated. Serum calcium, phosphorous and BAP levels were measured at 3 and 6 months. BMD was measured by QUS (calcaneus) at 3 and 6 months. All the data obtained was subjected to statistical analysis using SPSS statistical package.

RESULTS AND DISCUSSION

The quality of life of women after menopause is one of the key health issues today. The mean age at menopause was observed to be 49.66 years. The mean body mass index (BMI) in kg/m² was 25.695. It was also seen that the majority of women reported within 5 years of menopause. Of the 150 post menopausal women screened, 70% suffered from osteoporosis/osteopenia, the prevalence of which was found to be increasing with advancing age. 55% of women in the age group 40-50 years, 85% in the 50-60 years age group and 100% above 60 years had low BMD. Backache was the most common complaint, followed by easy fatigue and joint pains.

DXA is the current technique of choice to diagnose osteoporosis and to assess risk of future fracture. However, it is not always available to the general population due to high cost and hence there is a need for new inexpensive and easy methods are being sought. QUS of calcaneus appears promising in this regard. In our study it was found that the mean T scores obtained by QUS at the initiation and 6 months were statistically comparable to those by DXA scan of the spine in both study and control groups. This is in accordance with other studies (7-8). The increased bone turnover resulting from post-menopausal estrogen deficiency can be assessed by measuring serum and/ or urine biochemical markers of bone turnover (9). There is also now excellent evidence that the level of bone turnover is as strong a predictor of future fractures as is the level of BMD (10). Raloxifene administration is associated with increased bone mineral density, decreased bone turnover and maintenance of normal bone architecture (11). It was FDA approved for prevention of osteoporosis in December 1977. Its indication was extended to treatment of osteoporosis in October 1999.

In our study there was improvement in BMD with the use of Raloxifen but the improvement was not statistically significant (Table 1) whereas in the control group a significant decrease

was observed in the BMD. In the MORE study which was the largest clinical trial on raloxifene, 7705 postmenopausal women with osteoporosis were treated with raloxifene at a dosage of 60-120 mg/day or with a placebo for 3 years, showed that after 1 year, raloxifene 60 mg/day decreased the risk for new clinical vertebral fractures for 68% compared with placebo in the overall study population and by 60% in women with prevalent vertebral fractures, who are at greater risk for subsequent fractures. Several other studies have demonstrated similar effects of raloxifene on bone loss (12). Raloxifene induces a decreases in biochemical markers of bone turnover that correlate with a subsequent increase in bone mineral density (BMD).

Table 1: Effect of Raloxifene on bone mineral density (by QUS calcaneus and Serum BAP)

Variable	Group n=30	0 mth	6 mths	Mean % change	P value
BMD by ultrasound	Study	-2.423± 0.721	-2.33± 0.69	-3.8	> 0.05*
	Control	-2.483± 0.981	-2.62± 0.93	5.5	< 0.05**
BAP (U/L)	Study	35.25± 11.30	25.867± 12.21	26.6	< 0.05**
	Control	30.63± 6.80	32.833± 7.363	-7.2	< 0.05**

* Insignificant, ** Significant

In our study, a significant change in serum BAP (a fall of 26.6%) was seen following 6 months therapy with raloxifene whereas a significant increase in BAP was observed in the control group. (Table 1). However no significant differences were observed in the values of serum calcium and phosphorus. The above findings are in accordance with that of a randomized controlled trial conducted on healthy post menopausal women wherein It was observed that raloxifene reduced biochemical indices of bone turnover by 20-50%(13). In another European study, it was revealed that raloxifene decreased bone turnover as

assessment by biochemical markers of bone metabolism and decreases in urinary c-telopeptides were significantly lower at all time points in a 24 month period for the raloxifene group as compared with the placebo group. The favourable effect of raloxifene on bone turnover has been further confirmed by many other studies (14).

Raloxifene has been reported to have a favourable effect on lipid profile and reduces serum total cholesterol, LDL cholesterol, lipoprotein(a) and plasma fibrinogen, while increasing the HDL (sub-class HDL-2). In our study, raloxifen caused a significant decrease in total cholesterol, LDL and Triglycerides with significant rise in HDL levels after 6 months of therapy. No significant change in VLDL was noticed (Table 2). However, in the control group a significant increase was seen in serum cholesterol, triglycerides, LDL and a significant decrease was observed in HDL levels. In the MORE study (15,16), after 4 years of use of raloxifene there was a significant improvement in total cholesterol and triglyceride level and 40% decrease in cardiovascular and cerebrovascular disease outcome in established and high risk cases. In the RUTH trial (Raloxifene Use of The Heart), raloxifene (60/120 mg/dl) significantly lowered LDL-cholesterol, apolipoprotein-B, lipoprotein and fibrinogen and increased apolipoprotein A-1 as compared with placebo (17).

No significant adverse effects were detected with the use of raloxifene. All the women included in the study had good acceptability for the drug and there were no compliance issues. Osteoporosis in post menopausal women places a tremendous socioeconomic burden on the society. Raloxifene as an alternative to HRT appears encouraging. However lack of studies in Indian population make it imperative that large scale studies be carried out.

Table 2: Comparative effect of Raloxifene and Placebo on serum lipid profile

Variable	Group (n=30)	0 mth	6 mths	Mean % Change	P value
S.cholesterol (mg/dl)	Study	231.17± 60.63	191.50± 55.88	-17	< 0.05**
	Control	207.73± 52.56	221.50± 57.45	6.6	< 0.05**
S.triglycerides (mg/dl)	Study	160.10± 55.92	146.37± 52.61	-8.5	< 0.05**
	Control	146.73± 27.87	159.70± 33.22	8.8	< 0.05**
S.HDL (mg/dl)	Study	43.40± 10.69	52.33± 8.47	20.5	< 0.05**
	Control	50.27± 4.81	48.67± 6.42	-3.2	< 0.05**
S.LDL (mg/dl)	Study	155.23± 45.2	125.77± 42.35	18.9	< 0.05**
	Control	145.87± 31.63	154.03± 32.69	5.6	< 0.05**
S.VLDL (mg/dl)	Study	32.02± 11.18	29.27± 10.52	-8.5	> 0.05*
	Control	29.34± 5.57	31.94± 6.64	8.8	> 0.05*

* Insignificant, ** Significant

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