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STUDY OF BIOCHEMICAL PREDICTORS OF BONE LOSS AND BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN

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ABSTRACT

Measurement of bone remodelling biomarkers combined with assessing bone mineral density (BMD) helps in identification of postmenopausal women at increased risk of recurrent fractures and in monitoring therapeutic efficacy.

Objective: To assess BMD using ultrasound based regional bone densitometry and to determine the levels of serum markers of bone turnover in postmenopausal women.

Methods: Bone density was studied at heel and subjects were classified as normal, osteopenic, or osteoporotic according to WHO criteria based on bone mineral density (BMD) T scores and biochemical parameters predicting bone loss were measured in serum of postmenopausal women with and without osteoporosis.

Results: Serum calcium and phosphorus values did not reveal any statistically significant difference between case and control groups and also among normal, osteopenic and osteoporotics TRAP levels were more significant than BALP in case and control groups. Vitamin D showed lower mean values in cases than in controls**.**

Conclusions: Combined use of BMD and biochemical markers is more effective than use of single factor. Bone resorption marker (TRAP) is better indicators of bone remodeling. Vitamin D levels are important in maintenance of bone mineral density but its levels are not specific for osteoporosis.

INTRODUCTION

Millions of people all over the world are affected by osteoporosis which is called the "silent disease" and the number is expected to increase as the population ages. Majority of the affected individuals do not receive appropriate treatment. Early diagnosis with cost effective and reliable methods helps appropriate management of osteoporosis. Though, dual X-ray absorptiometry is the most commonly used and validated method for bone densitometry in clinical practice, due its high cost and risk of exposure to radiation its utility is restricted. As a consequence, combination of biochemical bone turnover markers and ultrasound-based densitometry involves no radiation exposure represent a cheap solution for identification of the case of osteoporosis. World Health Organization (WHO) describes, osteoporosis as "a systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture" (Burlet *et al*., 2008). As also observed by studies (Cooper *et al*., 1997), osteoporotic fractures are the leading cause of morbidity and mortality which reduces the quality of life and is responsible for sharp increase in healthcare costs. The socio-economic demand for the management of osteoporotic patients will also increase in the next years (Kanis *et al*., 2002). Hence a preventive approach to the this problem in postmenopausal women with the aim to stop its progression (Estell *et al*., 1998) should be encouraged. According to available data from Indian studies, osteoportic fractures occur 10-20 years earlier in Indian men and women than their Caucasian counterpart (Gupta, 1996). Early diagnosis is essential for timely treatment of patients who are at risk for osteoporotic fractures. Approximately 40 in 100 women experience one or more fractures after the age of 50 years. Osteoporotic fractures not only add financial burden but also affect the lifestyle of an individual. Study of biochemical bone markers in correlation with bone mineral density gives us an idea for further evaluation and in assessing the risk for

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fractures. Imaging of osteoporosis not only gives us the diagnostic information but can also be used for prognosis (WHO, 1994)

MATERIALS AND METHODS

This was a case control study done on postmenopausal women comprising, 32 cases of osteoporosis with history of osteoporotic fracture/fractures and 32 age matched healthy postmenopausal women. Individuals with hepatic disorders, hyperthyroidism, hyperparathyroidism and renal failure were excluded. About 10ml of venous blood was collected without using tourniquet from all the individuals belonging to both the groups. Following parameters were measured.

- Calcium by O-Cresolpthalein complex method
- Phosphorus by Fiske and Subbarow method
- Tartrate resistant acid phosphatase (TRAP) by modified king's method
- Bone specific Alkaline phosphatase (BALP) by heat inactivation method as mentioned by D.W. Moss *et al* 1975
- 25(OH) Vitamin D by Radio Immuno Assay (^{125}I RIA kit)

Bone density was studied by Ultrasound Method at heel (Achilles express, software version 4.1x). Bonemass was classified as normal, osteopenic, or osteoporotic according to World Health Organization criteria based on bone mineral density (BMD) T scores.

RESULTS

In our study the age of the subjects varied between 45-75 years. In the case group of 32 subjects the fractures noted were hip (40%), vertebra (36%), wrist (20%), arm (4%). Subjects were classified as normal, osteopenic, or osteoporotic based on their calcaneal mineral density according to World Health Organization. The descriptive results were expressed as mean and SD, p- value less than 0.05 were considered statistically significant. The mean values for the subjects belonging to both groups are given as in Figure 1 and Table 1 shows the statistical significance of the biochemical parameters among cases and controls

Table 1. Biochemical parameters among cases and controls expressed as Mean$^{+}_{/-}$ SD

PARAMETERS	CONTROLS (n=32) Mean$^{+}_{/-}$ SD	CASES (n=32) Mean$^{+}_{/-}$ SD	p-value
S.Calcium (mg%) *Ref. range;* 8.7-11	8.9$^{+}_{/-}$ 0.4	8.8$^{+}_{/-}$0.4	0.355
S.Phosphorus (mg%) *Ref. range;34-4.5*	3.4$^{+}_{/-}$0.3	3.7$^{+}_{/-}$0.2	0.001**
TRAP (KA units) *Ref. range;* 1.0-3.2	3.6$^{+}_{/-}$0.9	5.3$^{+}_{/-}$1.0	0.000**
BALP (U/L) *Ref. range;* 5.4-18.6	8.9$^{+}_{/-}$ 2.3	10.1$^{+}_{/-}$1.5	0.031*
25(OH)VitaminD(ng/ml) *Ref. range;* 9.0-37.6	21.36 $^{+}_{/-}$5.3	18.8$^{+}_{/-}$4.9	0.075

*p-value of <0.05 was considered statistically significant
**p-value of <0.005 was considered statistically highly significant

Table 2. Levels of biochemical parameters of the bone remodeling in osteopenic and osteoporotic postmenopausal women

PARAMETERS	OSTEOPENIC(-1 to -2.5)			OSTEOPOROTIC(<-2.5)		
	Controls	Cases	p-value	Controls	Cases	p-value
S.Calcium (mg%)	8.7 $^{+}_{/-}$0.4	8.9$^{+}_{/-}$ 0.44	0.444	8.8$^{+}_{/-}$ 0.5	8.7$^{+}_{/-}$ 0.5	0.570
S.Phosphorus (mg%)	3.4 $^{+}_{/-}$ 0.4	3.6$^{+}_{/-}$ 0.2	0.175	3.4 $^{+}_{/-}$ 0.3	3.7$^{+}_{/-}$ 0.2	0.037*
TRAP (KA units)	3.6$^{+}_{/-}$ 0.7	5.2$^{+}_{/-}$ 1.1	0.001**	4.3 $^{+}_{/-}$ 1.0	5.4 $^{+}_{/-}$ 0.9	0.023*
BALP (U/L)	8.5 $^{+}_{/-}$ 1.1	9.8$^{+}_{/-}$ 1.3	0.042*	10.5$^{+}_{/-}$ 3.4	10.4$^{+}_{/-}$ 1.6	0.930
25(OH) Vitamin D (ng/ml)	22.8$^{+}_{/-}$ 5.1	19.6$^{+}_{/-}$ 4.5	0.212	17.9 $^{+}_{/-}$ 4.3	18.1$^{+}_{/-}$5.2	0.916

*p-value of <0.05 was considered statistically significant
**p-value of <0.005 was considered statistically highly significant

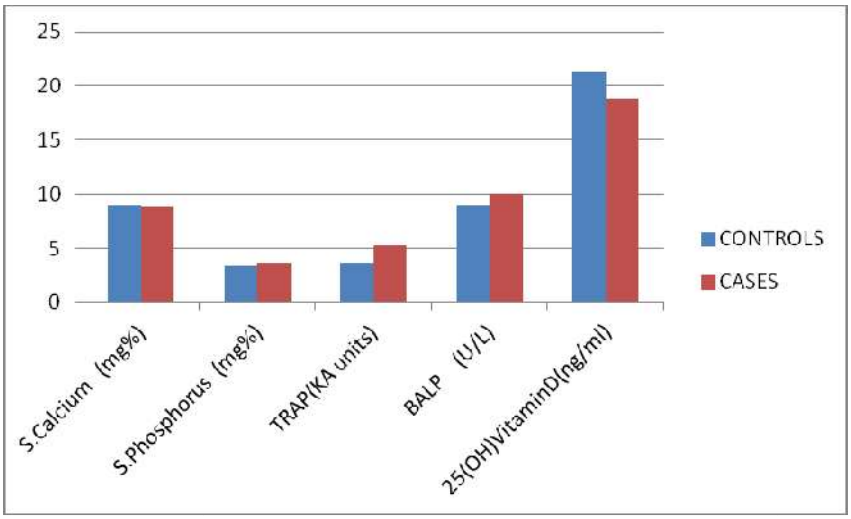
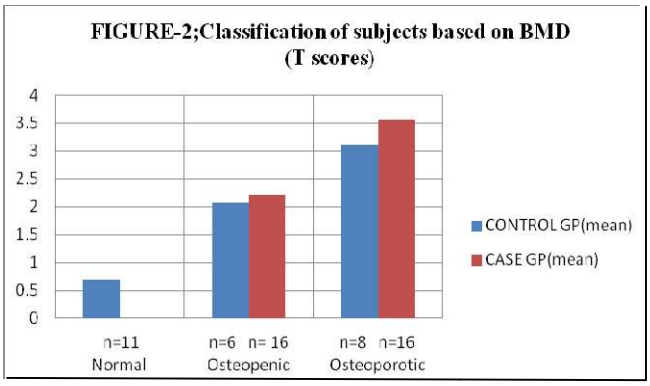


Figure 1. Comparison of biochemical parameters among cases and control

Based on the bone mineral density T scores, as studied by Ultrasound Method at heel (Achilles express, software version 4.1x) subjects from both the groups are classified as normal (>-1), osteopenic (-1 to-2.5), or osteoporotic (<-2.5) as shown in Figure 2. Levels of biochemical parameters of the bone remodeling in osteopenic and osteoporotic postmenopausal women are given in Table 2.



DISCUSSION

The usefulness of biochemical parameters of bone turnover and bone mineral density to estimate the risk of fractures in women are not well established. The combined use of BMD and bone markers helps for further evaluation and in assessing the risk for bone fractures. The evaluation of the cost effective bone markers in serum is easier and faster and can be measured in most of the laboratories thereby helping many people in monitoring their bone health. The skeleton is a dynamic adaptable mineral reserve bank in which the body stores its calcium and phosphorus in a metabolically stable and structurally useful way. When the assets of the skeletal bank fall below normal for body size, age, sex and race, osteoposis results. In our study ultrasound densitimetry was used to classify the subjects belonging to both the groups into normal, osteopenic, osteoporotic based on their calcaneal density. Serum 25(OH) vitamin D, calcium, phosphorus used as indicators of bone mineral status. Serum alkaline phosphatase bone isoform used as bone formative marker and tartrate resistant acid phosphatase as bone resorptive marker.

The corresponding serum calcium and phosphorus values did not reveal any statistically significant difference between case and control groups and also among normal, osteopenic and osteoporotics which is in accordance with study by Davidson *et al* 1979 who suggested that calcium values remain normal in osteoporotics. Calcium flux studies would give better information, but are technically difficult (Nelson B. Watts 1999). The serum levels of serum alkaline phosphatase bone isoform and tartrate resistant acid phosphatase levels showed significant difference in mean values when compared between cases and controls which is in accordance with study done by Delmas *et al*., 2000. The study showed that TRAP levels were more significant than BALP in case and control groups. This is consistent with the observation that the resorptive markers are more sensitive than formative markers as resorption process takes 7-10 days while formation requires 2-3 months (Garnero, 1996).Vitamin D showed lower mean values in cases than in controls. Inadequate serum vitamin D associated with increased bone turnover increases the fracture risk. In addition to its role in calcium homeostasis, studies suggest a direct effect of vitamin D on muscle strength. Pfeifer *et al*., 2001 suggested that low 25(OH) vitamin D leads to muscle weakness, musculoskeletal pain, increased body swaying which increases the risk of fall and leading to fall related fractures .Vitamin D levels are subject to variation in lifestyle and environmental characteristics. Many studies in elderly postmenopausal women show an association, independent of BMD, between the indices of bone turnover and osteoporotic fracture risk, although the results are discordant, particularly with regard to bone (Garnero, 2008). Studies suggest that ultrasound based densitometry frequently leads to hypodiagnosis. Markers increase in postmenopausal women. Combined approach, using BMD and biochemical markers of bone remodeling, improves the prediction of fracture risk in postmenopausal women, and this risk increases in those with low BMD and/or elevated markers of bone remodeling (Robbins *et al*., 2005)

Conclusion

- Bone resorptive marker like TRAP is better indicator of bone remodeling.
- Biochemical markers are better as therapeutic monitors than as diagnostic markers.
- Combined use of BMD and biochemical markers is more effective than use of single factor
- Vitamin D levels are important in maintenance of bone mineral density but its levels are not specific for osteoporosis.
- However there is need for more data to help the clinician decide which marker to be measured and when to be measured

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