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HOSPITAL BASED PRELIMINARY STUDY ON OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

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ABSTRACT

The awareness of osteoporosis has grown world wide in recent years. This silently progressing metabolic bone disease is widely prevalent in India, and osteoporotic fractures are a common cause of morbidity and mortality in adult Indian men and women. Rapid bone loss occurs in postmenopausal women due to hormonal factors which lead to increased risk of fractures. Biochemical markers of bone metabolism are used to assess skeletal turnover. A cross-sectional study of 150 pre- and post menopausal women was carried out at S.D.M College of Medical Sciences and Hospital, Dharwad, during the period of May 2005 to September 2005. The study group consisted of 75 Premenopausal women in the age group of 25-45 years and 75 Postmenopausal women in the age group of 46-65 years. Bone formation markers (Total Calcium, Ionised calcium, Phosphorus, Alkaline phosphatase), and bone resorption markers (Urinary Hydroxyproline) were analysed in pre and post menopausal women. Bone formation markers, Total and Ionised calcium were significantly decreased ($p<0.001$) and Alkaline phosphatase was significantly increased ($p<0.001$) in postmenopausal women compared to premenopausal women. Bone resorption markers, Urinary hydroxyproline excretion was significantly increased ($p<0.001$) in postmenopausal women. The results from this study suggest that simple, easy, common biochemical markers can still be used to assess the bone turnover in postmenopausal women and hence their risk of developing osteoporosis and fractures.

KEY WORDS

Postmenopausal osteoporosis, Urinary Hydroxyproline, Alkaline phosphatase

INTRODUCTION

Bone metabolism is a dynamic and continuous process to maintain a balance between the resorption of old and injured bone initiated by osteoclasts and the formation of new bone under the control of osteoblasts (1). In general, the processes of bone formation and resorption are 'coupled', so that there is no net change in the bone mass. Through childhood and early adulthood, formation exceeds resorption so that bone density increases and then plateaus until the age of 30 to 40 years. After that, resorption exceeds formation and bone density decreases through the rest of life, which in turn may lead to osteoporosis (2).

Osteoporosis is a major health and economic problem. An International consensus development conference has stated that osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitect deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. This silently progressing metabolic bone disease is widely prevalent in India, and osteoporotic fractures are a common cause of morbidity and mortality in adult Indian men and women (3). Expert groups peg the number of osteoporosis patients in India at approximately 26 million (2003 figures) with the numbers projected to increase to 36 million by 2013 (4). According to National Health and Nutrition Examination Survey (NHANES III), an estimated 14 million American women over age 50 years are affected by low bone density at the hip. The prevalence of osteoporosis increases with age for all sites, and by WHO definition up to

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70% of women over the age 80 years have osteoporosis (5).

It is important to think clearly about the 2 principle determinants in adult bone health (a) Maximum attainment of Peak bone mass (PBM) in young adulthood, and (b) the rate of bone loss with advancing age. With the onset of menopause, rapid bone loss occurs which is believed to average approximately 2% to 3% over the following 5 to 10 yrs, being greatest in the early postmenopausal years (6). Life time losses may reach 30% to 40% of the peak bone mass in women and 20% to 30% in men. The pathogenesis of postmenopausal osteoporosis involves the interplay of many factors- Nutritional, Environmental, Genetic factors.(7)

Biochemical markers of bone turnover have been shown to provide valuable information for the diagnosis and monitoring of metabolic bone disease (8). They reflect the whole body rates of bone resorption (Resorption markers) and bone formation (Formation markers) .Therefore they may provide a more representative index of the overall skeletal bone loss than would be obtained by measuring the rates of change in Bone Mineral Density (B.M.D) at specific skeletal sites (9).

The occurrence of Osteoporosis in postmenopausal women is very common problem especially in India who are exposed to many of the risk factors like Family h/o osteoporosis, history of anorexia or bulimia, prolonged amenorrhea, low calcium diet, lack of exercise, Vitamin D deficiency. But there are very few Indian studies regarding the prevalence of osteoporosis in postmenopausal women and also regarding the biochemical markers which indicate bone turnover in our setup. Studies have shown that bone turnover is so high in osteoporosis that even crude, non specific markers such as Total serum Alkaline phosphatase and urine hydroxyproline have been sufficiently reliable (11, 24). In addition, Urinary Hydroxyproline levels have been considered as an index of bone resorption and a determinant of bone status (12, 22, 24).

The present study was carried out to assess the clinical utility of biochemical markers of bone turnover, such as Total Calcium, Ionised calcium, Phosphorus, Alkaline phosphatase and Urinary Hydroxyproline in pre- and post menopausal women.

MATERIALS AND METHODS

We performed a cross-sectional study of 159 pre- and post menopausal women, at Department of Biochemistry, S.D.M College of Medical Sciences and Hospital, Dharwad, during the period of May 2005 to September 2005. The Institutional Ethical Committee approved the study and Informed consent was obtained from each participant in the study. The study group consisted of 75 Postmenopausal women in the age group of 46-65 years and 84 Premenopausal women in the age group of 25-45 years of which 9 were excluded from this study. All the participants were non smokers, non alcoholic and ambulatory. The women were neither pregnant nor on oral contraceptive pills. None of the postmenopausal women had suffered any fracture in the previous 1 year nor were they on Hormone replacement therapy or any other medication that might affect bone turnover.

Based on time since menopause, 75 postmenopausal women were categorized into 2 groups. 22 women were in their early postmenopausal period (<5years) and remaining 53 women were in their late postmenopausal period (>5years). Among 75 postmenopausal women, 27 were having Diabetes mellitus. 3 premenopausal women on Thyroid hormone replacement therapy were categorized separately and analysed.

Height and Weight of all the participants were noted and Body mass index (BMI) was calculated using the formula = Weight (Kg) / Height^2 (m).

3 ml of random blood sample was collected in a plain bulb from each participant. Serum was separated immediately by centrifuging at 3000rpm for 10 min and analysed for Total calcium (13), Ionised Calcium (14), Phosphorus (15), Total protein (16), Albumin (17) and Alkaline phosphatase (18). Random sample of urine was collected at the same time in a clean plastic bulb and analysed for Hydroxyproline (19) and Creatinine (20) immediately.

The data obtained was analyzed, and the differences in the mean of various parameters were compared using student's t-test. Stastistical analysis was performed using software SPSS windows.

RESULTS

Table I shows the comparison of all the biochemical parameters estimated as their mean values. There was a significant decrease in Serum Total Calcium and Ionised Calcium in postmenopausal women ($p<0.001$). Similarly it was observed that Serum ALP levels and Urinary excretion of Hydroxyproline were significantly increased in postmenopausal women compared to premenopausal women ($p<0.001$).

Table II shows the comparison of all the biochemical markers of bone turnover on early and late postmenopausal periods.

Table I : Comparison of markers of bone turnover in pre- and post Menopausal women (values expressed as mean ± SD)

Parameters	Premenopausal Women (n=75)	Postmenopausal Women (n=75)
Age	32.44 ± 6.09	56.88 ± 7.91***
Years after Menopause		11.44 ± 7.86
BMI	23.38 ± 4.59	25.63 ± 5.72**
Total Serum Calcium(mmol/L)	2.214 ± 0.20	2.098 ± 0.18***
Ionised calcium (mmol/L)	1.21 ± 0.18	1.10 ± 0.19***
Phosphorus (mmol/L)	1.36 ± 0.22	1.31 ± 0.26§
Total protein(g/dl)	6.48 ± 0.43	6.54 ± 0.58§
Albumin (g/dl)	4.00 ± 0.42	3.93 ± 0.41§
ALP (µKat/L)	2.15 ± 0.57	3.24 ± 1.00***
Urinary Hydroxyproline (mg/g Cr)	10.21 ± 3.19	22.35 ± 10.88***

§p>0.05 (not significant), *p<0.05) and **p<0.01 (significant), ***p<0.001 (highly significant)

Ionised calcium levels were significantly less in early postmenopausal women compared to late premenopausal women (p<0.05). It was also observed that Serum ALP levels and Urinary excretion of Hydroxyproline were more in Early postmenopausal women compared to late postmenopausal women, but they were not significant(p>0.05). This may require larger population studies.

DISCUSSION

Biochemical parameters can give an idea as to the rates of bone formation and resorption. High rate of bone turnover correlates with a low bone mass. Calcium salts in bone are embedded in collagen fibrils, 13% of which is mainly hydroxyproline. During bone loss, collagen fibrils are broken down and hydroxyproline is thus excreted in the urine. Urinary hydroxyproline(OHPr) is thus considered as an index of bone resorption and a major determinant of bone status (22).In this study urinary hydroxyproline is expressed as mg of hydroxyproline per gram of creatinine, because creatinine is excreted in the urine in relatively constant amounts proportional to an individuals muscle mass, thus serving as a reference standard (21,22). In the present study there was a significantly increased urinary excretion of hydroxyproline (mg/g Cr) in postmenopausal women when compared to premenopausal women(Table I). Sachdeva. et al, also reported same observations in their study (24). Similar observations were reported by a number of other studies (22, 23).

Estrogen deficiency at the menopause increases the rate of bone remodeling, which results in high turnover bone loss. There are recognized receptors on the osteoblasts which do not function optimally due to the lack of hormones. This is reflected by a significant increase in the mean value of markers of resorption and formation from premenopause to postmenopause. Thus simple, direct urinary assay to measure bone resorption have clinical applicatons as part of screening programs to assess the risk of osteoporotic fractures (5). Monitoring bone status through urinary excretion of OHPr could serve as a surveillance measure in early intervention against excessive bone loss. There is therefore the need to establish normal acceptable ranges for urinary excretion of OHPr in various communities beyond which individuals will be at risk of excessive bone loss and consequently be predisposed to fractures (1).

In general, women lose about 1% of their bone density per year during and after menopause. However, nearly 35% of women lose bone at a faster rate during the late perimenopausal period. Biochemical markers can detect women who are considered “rapid losers” that is, those who lose 3% to 5% of bone per year (25). In the process of our study, we found six premenopausal women having high urinary hydroxyproline levels (Mean 24.09±5.94 mg/g Cr) who were excluded from the study group. These women can be considered as rapid bone losers. Thus by discriminating between patients with high and low bone turnover – two subgroups which benefit from different therapeutic approaches- health care professionals can prescribe appropriate treatments, monitor patient compliance and treatment effectiveness.

Serum alkaline phosphatase is the most commonly used marker of bone formation. ALP is a ubiquitous enzyme that plays an important role in osteoid formation and mineralization. The total ALP serum pool consists of several dimeric isoforms which originate from various tissues such as liver, bone, intestine, spleen, kidney and placenta. In adults with normal liver function, approximately 50% of the total ALP activity in serum is derived from the liver, whereas 50% arises from bone (9). In our study the total ALP levels were significantly high in postmenopausal women in comparison to premenopausal women (Table I). The ALP levels were high in women during their early postmenopausal period when compared to late postmenopausal period (Table II). Ionised calcium levels were found to be significantly decreased in Early postmenopausal women compared to late postmenopausal women.(Table II). This shows that the bone mass continues to decline with age but at a slower rate than during the early menopausal time (6). A number of other studies have shown that early hormone

Table II : Comparison of markers of bone turnover in Early (<5yrs) and Late (>5 yrs) post menopausal period (values expressed as mean ± SD)

Parameters	Early postmenopausal period (n=22)	Late Postmenopausal Women (n=53)
Age	49.8 ± 4.45	59.8 ± 12.2***
Years after Menopause	3.13 ± 1.49	14.89 ± 4.30***
BMI	25.5 ± 4.34	25.69 ± 5.77§
Total Serum Calcium(mmol/L)	2.04 ± 0.14	2.12 ± 0.45§
Ionised calcium (mmol/L)	1.03 ± 0.12	1.13 ± 0.22*
Phosphorus (mmol/L)	1.39 ± 0.24	1.27 ± 0.37§
ALP (µKat/L)	3.58 ± 1.09	3.11 ± 1.30§
Urinary Hydroxyproline (mg/g Cr)	25.1 ± 13.63	21.21 ± 14.23§

§p>0.05 (not significant), *p<0.05 and **p<0.01 (significant), ***p<0.001 (highly significant)

dependent bone loss commences in the first year after menopause and is arrested within 6 years after the onset of menopause. Annual change in ALP and Urinary Hydroxyproline seems to indicate that bone resorption prevails on bone formation in early postmenopausal period (26).

BMI was significantly high in postmenopausal women, in comparison to premenopausal women (Table I). Literature says that a low BMI is one of the risk factors for increased bone turnover. However, we could not find such a correlation in present study. There was also no significant difference in the total protein, Albumin and phosphorus levels in our study. Total calcium and ionized calcium also the markers of bone formation were significantly decreased in postmenopausal women, when compared to premenopausal women (Table I).

Three women on elthroxin were excluded from the study group. It was observed that more the duration of consumption of exogenous thyroid hormones, more were the urinary hydroxyproline levels. This shows that L- thyroxine significantly increases the bone mineral turnover, as also shown by De Rosa et al (27). However, more number of subjects is required to see the effect of thyroid hormone therapy on bone turnover and its markers.

The results from this study suggests that simple, easy, common biochemical markers such as age, years after menopause, urinary hydroxyproline, total serum ALP, total serum calcium and ionized calcium could be used as indicators of increased bone turnover, to enable early intervention so as to minimize fracture due to osteoporotic changes. These markers may help identify women at greatest risk for bone loss who would benefit most from therapeutic interventions. Thus while BMD provides a static picture of the skeleton, the biochemical markers of bone turnover provide dynamic measures of bone remodeling and thus potentially useful in predicting the course of changes in bone mass. If preventive measures are to be initiated prior to the onset of excessive bone loss, measurement of bone turnover through urinary hydroxyproline could form a tool available to assist health care professionals to predict fracture risk.

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