Effect of Antiresorptive Therapy on Osteoblastic and Osteoclastic Activity in Postmenopausal Osteoporosis Women.

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Abstract

The awareness of osteoporosis has grown worldwide 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 Indian 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 and will be clinically useful in the management of post-menopausal osteoporosis women (PMO) as well as for assessing the effect of antiresorptive therapy. 

Aim: 1) To measure bone formation and resorption markers such as serum alkaline phosphatase and tartrate resistant acid phosphatase at the base line level in postmenopausal osteoporosis women & control. 2) These biochemical parameters were determined 3 months post antiresorptive therapy (alendronate + calcium + calcitriol) in postmenopausal osteoporosis patients. 

Study Design: Prospective Setting: Postmenopausal osteoporosis patients from civil hospital Sangli and Miraj. Participants: 60 clinically diagnosed postmenopausal osteoporosis patients and 60 normal subjects (postmenopausal nonosteoporosis women) were recruited as control. Results: Serum alkaline phosphatase and tartrate resistant acid phosphatase was significantly increased (P<0.001) in PMO as compared to controls and post therapy these levels were decreased significantly (P<0.001) in PMO. Conclusion: Biochemical markers of bone turnover provide information that can aid in predicting risk of future
bone loss and osteoporotic fracture. These markers can also be used to monitor antiresorptive therapy in the PMO patients.

**Keywords:** Alkaline phosphatase (ALP), Postmenopausal Osteoporosis (PMO), Tartrate resistant acid phosphatase (TRACP).

**INTRODUCTION**

Osteoporosis is second only to cardiovascular disease as a leading health care problem, according to the World Health Organization [1]. Increased mortality rate associated with fracture may be the worst consequence. The loss of independence and lowered quality of life of patients living with the disease for years might be the greatest burden of osteoporosis. Earlier diagnosis and prevention of fractures should decrease the medical, social and economic burdens of this disease.

Osteoporosis is a progressive systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [2]. World Health Organization (WHO) defines osteoporosis as bone density (BD) that is 2.5 Standard Deviation (SD) or more below the young adult mean value (T-score < -2.5). Bone density decreases with age as fracture risk rises rapidly. Given the increased aging on the population, osteoporosis & fractures are expected to continue to increase. Every SD of decrease in BMD increases fracture risk two to three fold [3].

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 [4]. In general, the process of bone formation and resorption are “coupled”, so that there is no net change in the bone mass. Throughout childhood 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, resulting in too little bone, or may lead to osteoporosis [5].

The hallmark of menopause is a reduction in skeletal mass caused by an imbalance between bone resorption and formation due to loss of ovarian function. Hence, loss of ovarian function is the most important factor in the development of postmenopausal osteoporosis [6]. Increase in life expectancy is another concept of formation of osteoporosis. The risk of nutritional disturbances, in particular principal element and vitamin deficiencies is high in postmenopausal women with osteoporosis [7].

The biochemical marker of bone formation which may be clinically useful, include serum alkaline phosphatase. An elevated level of serum alkaline phosphatase activity
reflects increased activity of the osteoblasts [8]. We have also studied bone resorption marker i.e. tartrate resistant acid phosphatase. Elevated levels of tartrate resistant acid phosphatase activity directly reflect the increased activity of osteoclasts [9].

The study was designed to offer considerable hope for management of osteoporosis and for monitoring response to antiresorptive therapy.

**MATERIALS AND METHODS**

Present study was conducted in the Department of Biochemistry, Government Medical College Miraj and P.V.P. General Hospital Sangli.

We performed a case control study of 60 osteoporotic postmenopausal women in the age group 45-60 years. Patients were selected who had clinical features suggestive of reduced bone mass viz- backache or generalized weakness or any fracture and radiological evidence of osteoporosis at one or more sites & lowered BMD. The study group was given alendronate 70 mg/week, tablet containing calcium citrate 1200 mg (elemental calcium- 253) and calcitriol 0.25µg was taken as once a day. Patients were instructed to take bisphosphonate on an empty stomach with a glass of plain water. Avoid lying down, stay fully upright (sitting, standing or walking) and other food, beverages or medication to be avoided for at least 30 min for better absorption and to avoid side effects(esophagitis).

Control group included 60 postmenopausal non osteoporotic women with normal bone density in the age group 45-60 years.

Patients taking HRT and anticonvulsants, having a chronic debilitating illness (cancer, AIDS), renal diseases, liver diseases and secondary type of osteoporosis were excluded from this study.

The Institutional Ethical Committee approved the study and Informed Consent was obtained from each participant in the study.

In the present study blood samples were collected under aseptic condition from control group and from osteoporotic postmenopausal women at baseline level. In the follow up study blood samples of osteoporotic women were collected after 3 months antiresorptive therapy. Serum was separated and analyzed for alkaline phosphatase by kinetic method [10] and tartrate resistant acid phosphatase by King and Armstrong method [11].

The results were expressed as means ± SD. Statistical analysis was done by using “Z test” and “Paired T test”.
RESULTS AND DISCUSSION

Biochemical parameters relevant to bone metabolism can give an idea as to the rate of bone formation and bone resorption. We have assessed osteoblastic activity by measuring serum alkaline phosphatase which is most commonly used index marker of bone formation.

Alkaline phosphatase activity was found to be significantly elevated in PMO when compared to controls (P<0.001). High levels of serum alkaline phosphatase activity encountered in osteoporosis might be a result of the osteoblastic cells; which try to rebuild bone that is being resorbed by the uncontrolled activity of osteoclasts. Our results indicate that bone regeneration is taking place or is being attempted and alkaline phosphatase probably participates in the initiation of bone mineralization [12, 13, and 14]. Decreased ability to produced calcitriol from vitamin D may be another reason for elevated alkaline phosphatase activity in the postmenopausal women with osteoporosis [15 & 16]. It may lower calcium and phosphorus absorption from intestine and calcium uptake by osteoblasts, which ultimately affects the mineralization of bone. Thus osteoid will be formed but poorly calcified, hence for mineralization of bone, osteoblastic activity may be increased. Our findings were also supported by the study of Indumati V.et al [17], Usoro CAO et al [18] and Verit FF et al [19].

After receiving antiresorptive therapy alkaline phosphatase activity comes down to near normal level. This therapy can increase intestinal absorption of calcium and phosphorus with a consequently higher influx of calcium ions at the bone level. This can decrease bone turnover and decelerate bone loss. Thus our study suggests that the antiresorptive therapy is useful to control rate of bone turnover and thereby, better management of PMO. Our findings were also supported by the study of Ones K et al [20]. Reid IR et al [21].

Measurement of alkaline phosphatase activity is simple, easy, routine biochemical test and can be used to assess the bone turnover. This marker can be measured in any clinical laboratory & can be utilized by the clinicians for better management of osteoporosis, even in semi-urban areas.

Significant increase in the activity of tartrate resistant acid phosphatase was found in PMO when compared to controls (P < 0.001) and decrease significantly observed 3 months post therapy. TRACP activity directly reflects the activity of osteoclasts. Hence, from our results it is evident that there is significant increase in osteoclastic activity, leading to greater resorption of bone.

Specific cytokines such as IL-1, IL-6 and TNF α (inhibits apoptosis and extends the life span of osteoclasts); granulocyte macrophage colony stimulating factors (GM-CSF) may be responsible for this. These cytokines may enhance bone resorption by increasing the recruitment, differentiation and activation of osteoclast cells. Decreased
IL-Ira concentration (interleukin1 receptor antagonist) may lead to enhanced osteoclast sensitivity to IL-1 in osteoporosis. The production of IGF-B and OPG-L factors that mediate osteoclast apoptosis may also be reduced in PMO. In this way the osteoclast number and activity may be increased in osteoporosis. Indeed, such an elevation in osteoclastic activity is shown in our study by increase in TRACP activity in PMO. Our findings were also supported by the study of Verit FF et al [19], Halleen JM et al [22], Price CP et al [23] and Garnero P et al [24].

The therapy contains a potent nitrogen containing drug i.e. alendronate which inhibits farnesyl diphosphate synthase, a critical enzyme in the cholesterol mevalonic acid pathway that is also required for protein prenylation. When the activity of this enzyme is blocked, the cytoskeleton integrity and intracellular functioning of the osteoclasts is disrupted and apoptosis ensues. In this way the therapy decreases the osteoclastic activity and its growth. Decrease in TRACP activity post therapy reflects renormalization of the bone resorption, by reducing the osteoclastic activity. Our findings were also supported by the study of Valimaki MJ et al [25], Matyszko J [26].

In conclusion, biochemical markers of bone reflect acute changes in bone turnover rate. Bone turnover decreases in PMO women receiving antiresorptive therapy and this may be demonstrated by the decrease in the levels of marker. Alterations in the concentration of these markers can be very well utilized to monitor the effectiveness of therapy. Therefore, bone markers should be used in the management of this disease and for monitoring response to antiresorptive therapy.

**Table No.1:** Biochemical markers of bone turnover in control group and PMO women pre and post therapy.

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Biochemical markers</th>
<th>Postmenopausal non osteoporosis women (Controls) n=60 Mean ± SD</th>
<th>Postmenopausal osteoporosis women Baseline n=60 Mean ± SD</th>
<th>Postmenopausal osteoporosis women Post therapy n=60 Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alkaline phosphatase (IU/L)</td>
<td>79.07 ± 13.123</td>
<td>112.272± 28.36*</td>
<td>90.509 ± 16.72*</td>
</tr>
<tr>
<td>2</td>
<td>Tartrate resistant acid phosphatase (TRACP) KA units</td>
<td>1.226 ± 0.357</td>
<td>3.521 ± 0.61*</td>
<td>1.986 ± 0.390*</td>
</tr>
</tbody>
</table>

* P<0.001- Highly significant (Z test & Paired T test)
REFERENCES


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