International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 2(3): May-June 2012

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Life Sciences **Original Article……!!!**

Received: 04-05-2012; Revised; Accepted: 15-06-2012

EFFECT OF ANTIRESORPTIVE THERAPY ON BONE METABOLISM IN POSTMENOPAUSAL OSTEOPOROSIS

Jagtap Vanita R.*, Ganu Jayshree V.

Department of Biochemistry, Government Medical College, Miraj, Maharashtra, India

Keywords:

Postmenopausal osteoporosis (PMO), Bone Formation Marker, Bone Resoption Marker, Alkaline Phosphatase (ALP), Tartrate Resistance Acid Phosphatase (TRACP), Bone Mineral Density (BMD)

For Correspondence:

Dr. Vanita R. Jagtap

Department of Biochemistry, Government Medical College, Miraj, Maharashtra, India

E-mail:

ms.vanita_jagtap@rediffmail.com

ABSTRACT

Background: - 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. **Study Design:** prospective **Setting:** postmenopausal osteoporosis patients from Civil Hospital Sangli and Miraj. **Aim and Objectives** of this study are 1) to assess osteoblastic and osteoclastic activity by determining alkaline phosphatase and tartrate resistance acid phosphatase in postmenopausal osteoporosis women and postmenopausal non osteoporosis women. 2) The follow up study to evaluate the impact of specific antiresorptive therapy (alendronate + calcium + vitamin D) on bone metabolism in postmenopausal osteoporosis by assaying alkaline phosphatase and tartrate resistance acid phosphatase. **Material and Methods: -** 60 postmenopausal women with osteoporosis in the age group 45-60 years and 60 healthy postmenopausal women (normal bone mineral density) in the same age group were included as a control in the study. Activity of serum alkaline phosphatase and tartrate resistance acid phosphatase were measured in postmenopausal women with osteoporosis and without osteoporosis. In the follow up study these enzyme activities were determined 3 months post antiresorptive therapy (alendronate + calcium + vitamin D) in postmenopausal osteoporosis patients. **Results: -** Activity of serum alkaline phosphatase and tartrate resistance acid phosphatase were significantly increased ($P<0.001$) in postmenopausal osteoporosis women at baseline level as compared to control group. These enzyme activities were decreased significantly ($P<0.001$) post therapy in PMO patients. **Conclusion: -** Measurement of these enzyme activities is simple, easy, routine biochemical assays and can be used to assess the bone turnover. This marker can be measured in any clinical laboratory and can be utilized by the clinician for better management of osteoporosis, even in semi urban areas. Bone turnover decreases in osteoporotic patients after receiving antiresorptive therapy and this may be demonstrated by decrease in the levels of marker (enzymes). Alteration 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.

INTRODUCTION

Osteoporosis is a disease that may have a tremendous impact on the lives of many postmenopausal women. Osteoporosis and it's potentially devastating sequelae of fracture are increasing as the population ages and assessment of skeletal health is an important component of a women's routine care.[1] "It is a progressive systemic skeletal disorder characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture".[2]

Osteoporosis is second only to cardiovascular disease as a leading health care problem according to the World Health Organization[3]. It currently affects approximately one in three women and one in five men over age 50. India seems to have the highest prevalence of osteoporosis and osteopenia. With growing awareness of osteoporosis and its impact on life span especially in India, special attention is being paid to early detection, management and treatment of postmenopausal osteoporosis in women [4, 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]. The pathogenesis of postmenopausal osteoporosis involves the interplay of many factors such as aging, hormonal, nutritional, environmental, and genetic and life style factors etc. [7] In the developed countries a number of research projects are undertaken for the study of bone biomarkers, because of the current interest in osteoporosis. Similarly, in Western Maharashtra, there is a need for establishment of more rapid assays and for improvement in technical methods for measurement of these markers with a high priority in the management of osteoporosis. Assessment of BMD is the standard criterion for diagnosis and evaluation of osteoporosis in Western Maharashtra. BMD provide a static picture of skeleton, whereas the biochemical markers of bone turnover can provide dynamic status of bone remodeling. Typically, the biochemical markers of bone formation include alkaline phosphatase which may be clinically useful, as an index marker of bone formation. Alkaline phosphatase activity reflects the activity of osteoblast.[8] Tartrate resistant acid phosphatase activity directly reflects the osteoclastic activity and it is considered as clinical index of bone resorption [9]. We thought that study of this bone formation and resorption marker will throw light for better understanding the pathophysiology of disease, in addition to its aid in management of the

osteoporotic patients receiving antiresorptive therapy. With this view, we planned to determine the activity of alkaline phosphatase and tartrate resistant acid phosphatase in postmenopausal osteoporotic patient. The impact of antiresorptive therapy was evaluated by assaying the biochemical parameters pre and post therapy in PMO.

MATERIAL AND METHODS

Present study was conducted in the Department of Biochemistry, Government Medical College Miraj and P.V.P.Government Hospital; Sangli. Study group included 60 postmenopausal women in the age group 45-60 years and diagnosed as primary osteoporosis by clinicians. Diagnosis was based on clinical features, any fracture and radiological evidence of osteoporosis at one or more sites and lower BMD. Control group included 60 postmenopausal non osteoporotic women with normal bone mineral density in the age group 45-60 years. Patients with secondary type of osteoporosis, liver disease, renal disease, metastatic bone disease, having a chronic debilitating illness (cancer, AIDS),

Patients taking hormone replacement therapy and anticonvulsants, were excluded from this study. The study group was given alendronate 70 mg / week and tablet containing calcium citrate 1200 mg (elemental calcium-253mg) 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 minutes for better absorption and to avoid side effects (esophagitis). The Institutional Ethical Committee approved the plan of study and informed consent was obtained from each participant in the study. Blood samples were collected from control group and from study group at baseline level under aseptic conditions. In the follow up study blood samples were collected from study group after 3 months therapy. Serum was separated and analyzed for measurement of 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

Alkaline phosphatase activity was found to be significantly elevated in PMO when compared to controls. ($P<0.001$, Table No.1) We have assessed osteoblastic activity by the measuring serum alkaline phosphatase which is most commonly used index marker of bone formation.

High levels of serum alkaline phosphatase activity encountered in osteoporosis might be a result of the action 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 are probably participates in the initiation of bone mineralization [12, 13&14]. Decreased ability to produce 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 Indumati V et al [17], Usoro CAO et al [18], and Verit F F 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 Ones K et al [20], Reid IR et al [21].

Measurement of alkaline phosphatase activity is simple, easy; routine biochemical marker 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 ($P<0.001$, Table no. 1) 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 (interleukin 1 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 Verit FF et al [19] Halleen JM et al [22], Price CP et al[23], Garnero P et al [24, 25].

Table No-1 shows that TRACP activity was decreased significantly from baseline to post therapy of 3 months in PMO (alendronate + calcium + vitamin D). 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 cytoskeletal 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 [26], Matyszko J et al [27]

CONCLUSION

In conclusion, biochemical markers of bone reflect acute changes in bone turnover rate. Elevated levels of serum alkaline phosphatase and tartrate resistance acid phosphatase were found in postmenopausal osteoporosis women at baseline level. 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. BMD provide a static picture of skeleton, whereas the biochemical markers of bone turnover can provide dynamic status of bone remodeling. Therefore, bone markers should be used in the management of this disease and for monitoring response to antiresorptive therapy.

TABLE NO. 1

Comparison of markers of bone formation and resorption in control group and PMO women pre and post therapy

Sr. No.	Biochemical markers	Postmenopausal Non osteoporosis women (Controls) n=60 Mean ± SD	Postmenopausal osteoporosis women Baseline n=60 Mean ± SD	Postmenopausal osteoporosis women Post therapy n=60 Mean ± SD
1	Alkaline phosphatase (IU/L)	79.07 ± 13.12	112.27 ± 28.36*	90.50 ± 16.72*
2	Tartrate resistant acid phosphatase (TRACP) KA units	1.22 ± 0.35	3.52 ± 0.61*	1.98 ± 0.39*

*Highly significant (z test and paired t test)

REFERENCES

1. Brown S.A, Rosen C.J. Osteoporosis, Med Clin N Am, 2003; 87: 1039-1063.
2. Gupta A. Osteoporosis in India- nutritional hypothesis, Natl Med J INd, 1996; 9(6): 268-274.
3. Calcium, magnesium, silica and boron their combined roles in maintaining bone strength. According to a study published in the July, 2004; Issue of Archives of Internal Medicine. (www. google. com.)
4. Neetakumar, Tandon N, Goswami R, Dineshkumar, Singh A. Ethnic variation of host and risk factors in silent epidemic of osteoporosis, Orthopedics Today, 2004; VI (4): 240-244.
5. Agrawal S, Raghunandan C. Correlation of bone mineral density with biochemical markers in post menopausal women, Indian Journal of Clinical Biochemistry, 2009; 24(3): 262-265.
6. Stevenson J.C, Postmenopausal osteoporosis, British Medical Journal, 1982; 285: 585-587.
7. Delmas P.D. Biochemical markers of bone turnover for the clinical investigation of osteoporosis, Osteoporosis Int, 1993; 3(1):81-86.
8. Russell R.G.G, Caswell A.M, Hearn P.R, Sharrard R.M. Calcium in mineralized tissues and pathological calcification, British Medical Bulletin, 1986; 42(4):435-446.
9. Price C.P, Kirwan A, Vader C. Tartrate - resistant acid phosphatase as a marker of bone resorption, Clin Chem, 1995; 41, (5): 641- 643.
10. Tietz N.W, (Ed): Study group on alkaline phosphatase. A reference method for measurement of alkaline phosphatase activity in human serum, Clin. Chem, 1983; 29:751.
11. King E.J, Armstrong A.R. Canad. Med. Ass. J, 1934; 31: 376.
12. Need A.G. Bone resorption markers, Clinica Chemica Acta, 2006; 368:48-52.
13. Sarac F, Saygili F. Causes of high bone alkaline phosphatase, Biotechnology & Biotechnology, EQ. 2007; 21(2): 194-197.
14. Vandana K.L, Savitha B. Role of alkaline phosphatase in fibrogenesis or fibrolysis, Journal of Oral and Maxillofacial Pathology, 2004; 8 (2): 70-72.
15. Narang A.P.S, Batra S, Sabharwal S, Ahuja S.C. 1, 25 Dihydroxycholecalciferol levels in osteoporosis, Indian Journal of Clinical Biochemistry, 2004; 19(2): 111-113.
16. Satyanarayan U, Mineral metabolism, Textbook of Biochemistry, 2006; 3rd edn: 403- 424.
17. Indumati V, Patil V.S, Jailkhani R. Hospital based preliminary study of osteoporosis in postmenopausal women, Indian Journal of Clinical Biochemistry, 2007; 22 (2): 96-100.

18. Usoro C.A.O, Biochemical bone turnover markers in postmenopausal women in calabar municipality, Asian Journal of Biochemistry, 2007: 2(2):130-135.
19. Verit F.F, Yazgan P, Zer Y, Celik A. Diagnostic value of TRAP 5b activity in postmenopausal osteoporosis, Clinical Study Turkish-German Gynecological Association, 2006. (http://www.google.com.)
20. Ones K, Cagler N. Effects of combined treatment with alendronate and alfacalcidol on bone mineral density and bone turnover in postmenopausal osteoporosis: A two years, randomized, multiarm, controlled trial, The Inter Journal of Epidemiology, 2007; 4(4):1-9.
21. Reid I.R, Reid H.F, Bava U, Bolland M.J, Gamble G.D. Randomized controlled trial of calcium in healthy older women, The American Journal of Medicine, 2006; 119:777-785.
22. Halleen J.M, Cheng S, Janckila A.J, Vaananen H.K. Serum tartrate resistant acid phosphatase 5 b is a specific and sensitive marker of bone resorption, Clin Chem, 2001; 47(3): 597-600.
23. Price C.P, Thompson P.W. The role of biochemical tests, screening and monitoring of osteoporosis, Ann Clin. Biochem, 1995; 32:244-260.
24. Garnero P, Shin W.J, Gineyts E, Karpf D.B, Delmas P.D. Comparison of new biochemical markers of bone turnover in late postmenopausal osteoporotic women in response to alendronate treatment, J Clin Endocrinol Metab, 1994; 79(6): 1693-1700.
25. Cheung C.K, Panesar N.S, Haines C. Radio immunoassay of tartrate resistant acid phosphatase, Clin Chem, 1995; 41: 679-686.
26. Valimaki M.J, Tahtela R. Serum tartarate- resistant acid phosphatase 5B an amino terminal propeptide of type I procollagen for monitoring bisphosphonate therapy in postmenopausal osteoporosis, Clin Chem, 2005; 51:2382-2385.
27. Matyszko J, matyszko J.S, Pawlak K, Wotczynski S, Mysliwiec M. Tartrate resistant acid phosphatase 5b and its correlations with other markers of bone metabolism in kidney transplant recipients dialysed patients, Advances in Medical Science, 2006; 51: 69-72.