Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 19s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Role of Calcium and Alkaline Phosphatase in Bone growth and its impact on Osteoporosis

Dr. Anju B. Uppin[1], Dr. B. R. Tubaki[2], Dr. Kiran Patil[3]

[1]PhD Scholar, KAHER, Karnataka,India.

[2]Professor and HOD, Department of Kaya Chikitsa(General Medicine), KLE Shri BMKAM, Karnataka, India.

[3]Professor, Department of Orthopaedics, JNMC, Karnataka, India.

*** Corresponding Author**

Dr. B. R. Tubaki

Cite this paper as: Dr. Anju B. Uppin, Dr. B. R. Tubaki, Dr. Kiran Patil, Dr. B. R. Tubaki, (2025) Role of Calcium and Alkaline Phosphatase in Bone growth and its impact on Osteoporosis. *Journal of Neonatal Surgery*, 14 (19s), 421-429.

ABSTRACT

Aim: The objective of this study is to determine bone mineral density (BMD) and the biochemical markers with variation in healthy, osteopenic and osteoporotic individuals. It reviews the part of alkaline phosphatase in assessment of bone metabolism and osteoporosis progression. The research also looks into the interaction of the calcium levels and estrogen deficiency in relation to bone health.

Methods: A total of three groups (healthy individuals, osteopenia and osteoporosis) were studied in a cross-sectional manner. Dual energy X-ray absorptiometry (DEXA) was used to measure BMD; and also, the serum samples analyzed for biochemical markers of calcium levels. The statistical comparison to identify the significant within the groups and correlation between biomarkers and the severity of osteoporosis were performed.

Results: Osteopenic and osteoporotic individuals' BMD is significantly lower than that in healthy group. With ALP levels higher also, osteoporotic participants showed increased bone turnover. There was only minor variation of calcium level except osteopenic and osteoporotic individuals showed a significant difference. The research further proves that estrogen deficiency greatly contributes to bone loss and the risk of fractures.

Conclusion: The finding of this study supports the importance of early detection and treatment of osteoporosis. BMD and biochemical markers simultaneously are used in combination for diagnosing (and monitoring) of bone health. Calcium supplementation, probiotics, as well as targeted molecular therapies based on a molecular analysis of luminal HC p5S fractions are recommended. With the success of chondroprotective nanotechnology, more work on novel interventions nanotechnology-based supplements and gene targeted treatments for osteoporosis prevention and treatment outcomes needs to happen.

Keywords: *Osteoporosis, Bone, Calcium, Osteopenic, Serum, ALP, BMD, Dexa*

1. INTRODUCTION

Osteoporosis is a skeletal disorder, progressive loss of bone mass and increased fragility of bones, more common in elderly population [1,2]. Osteoporosis is a disease affected by numerous factors, including hormonal changes, mineral disturbances, metabolic derangements which affect bone remodeling [1]. Calcium and ALP (a key bone growth and metabolism marker) are the most important markers in the assessment and management of osteoporosis [4,7].

Bone Disease	Ca^{++}	Phosphate	Alkaline Phosphatase
Osteoporosis	Normal	Normal	Normal
Osteomalacia	↓	↓	↑
Paget's	Normal	Normal	↑↑
Myeloma	↑	↑,Normal	Normal
Bone Metastasis	↑	↑,Normal	↑
1^{o} Hyperparathyroidism	↑	↓,Normal	Normal, ↑
Hypoparathyroidism	↓	↑	Normal
Renal Failure	↓	↑	Normal, ↑

Figure 1 Calcium and ALP levels in Bone Diseases (Medical Laboratories, 2023)

Calcium is an important mineral used to form, maintain and remodel bone. It is a basic part of hydroxyapatite crystals, which are structural strength to bones. Low calcium levels change balance between bone resorption and formation, increasing the fragility of the bone. The hormones that regulate the calcium metabolism, parathyroid hormone (PTH), both affect bone turnover and mineralization [7]. Calcium supplementation has been a widely used drug for osteoporosis management, although to no avail in preventing fracture in many studies some such as no evidence of driving correlation between calcium levels in BMD in osteoporotic individuals [1, 2]. ALP is a bone formation and mineralization biomarker. It is manufactured by the osteoblasts and it catalyzes the hydrolysis of phosphate esters, thereby promoting the deposition of calcium and phosphorus into the bone matrix [4]. ALP has important role in skeletal development and turnover, and high ALP is a sign of increased osteoblastic activity [11]. Although ALP levels and osteoporosis have been studied in the past, there have been conflicting results pertaining to the relationship between ALP and BMD [1,2]. Nevertheless, ALP is a useful diagnostic and prognostic marker in bone metabolic disorders [12].

2. MATERIALS AND METHODS

Study Design

BMD and serum calcium levels were studied in three groups: Healthy, Osteopenia, Osteoporosis, of which this study was a comparative cross-sectional study. Assessment of BMD was done by using dual-energy X-ray absorptiometry (DEXA) and serum calcium levels were determined by standard biochemical assays.

Study Population

Three groups consisting of participants with a DEXA score were created:

- **Healthy group**: T-score ≥ -1.0
- **Osteopenia group**: T-score between -1.0 and -2.5
- **Osteoporosis group**: T-score ≤ -2.5

Inclusion Criteria: DEXA scan done in adults in the age of above 50 years, informed consent.

Exclusion Criteria: People with chronic diseases of bone metabolism (such as chronic kidney disease and hyperparathyroidism)

Data Collection and Analysis

- Assessment of the BMD was done through DEXA scan at the femoral neck.
- Serum calcium levels were measured by means of standard laboratory methods.
- **Statistical Analysis**:
    - BMD and serum calcium values from different groups were compared utilizing Kruskal Wallis ANOVA.
    - The Mann-Whitney U test was conducted on pairwise comparisons.
    - The level of $p < 0.05$ was considered statistically significant.

3. RESULTS

This part comprises comparative study of bone mineral density (BMD) and serum calcium levels measured in three categories i.e. Healthy, Osteopenia and Osteoporosis. Kruskal-Wallis ANOVA and Mann Whitney U tests on the results were statistically evaluated and revealed significant difference of DEXA values between groups ($p < 0.05$) whereas serum calcium levels were significant different only between Osteopenia and Osteoporosis groups.

Table 1: Comparison of three groups (Healthy group, Osteopenia group and Osteoporosis group) with Dexa values by Kruskal Wallis ANOVA

Groups	Mean	Median	Std.Dev.	95% CI for mean	
				Lower	Upper
Healthy group	0.81	0.70	0.52	0.70	0.92
Osteopenia group	-1.59	-1.60	0.49	-1.70	-1.49
Osteoporosis group	-1.90	-2.90	11.00	-4.21	0.40
H-value	225.6000				
P-value	0.0001*				
Pair wise comparisons by Mann-Whitney U test					
Healthy group vs Osteopenia group	P=0.0001*				
Healthy group vs Osteoporosis group	P=0.0001*				
Osteopenia group vs Osteoporosis group	P=0.0001*				

*p<0.05

A significant difference was observed between three groups (Healthy group, Osteopenia group and Osteoporosis group) with Dexa values (H=225.6000, p=0.0001) at 5% level of significance. It means that, the Dexa values are different in three groups.

Further, to know the pair wise comparisons, the Mann-Whitney U test was applied and results are presented in the above table. it clearly, shows the following:

- A significant difference was seen between healthy group and Osteopenia group with Dexa values (p=0.0001) at 5% level of significance. It means that, the Dexa values are significantly higher in healthy group as compared to Osteopenia group.
- A significant difference was seen between healthy group and Osteoporosis group with Dexa values (p=0.0001) at 5% level of significance. It means that, the Dexa values are significantly higher in healthy group as compared to Osteoporosis group.
- A significant difference was seen between Osteopenia Group and Osteoporosis group with Dexa values (p=0.0001) at 5% level of significance. It means that, the Dexa values are significantly higher in Osteopenia group as compared to Osteoporosis group.

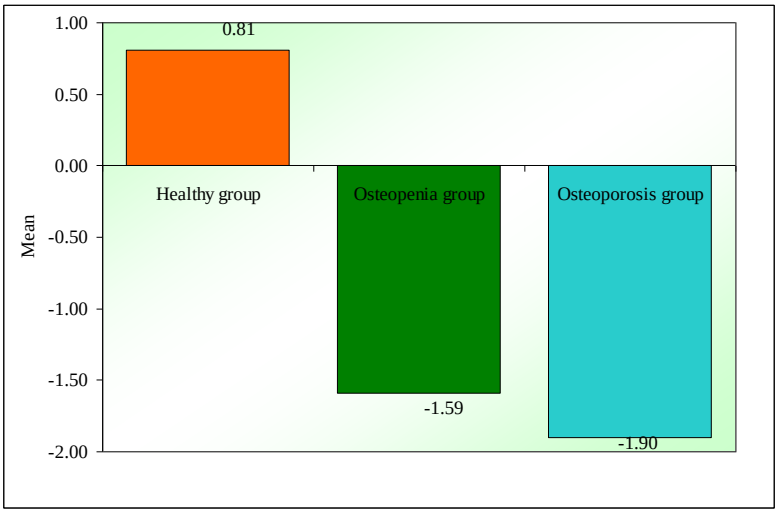

Figure 2 Comparison of three groups (Healthy group, Osteopenia group and Osteoporosis group) with Dexa values

Table 2: Comparison of three groups (Healthy group, Osteopenia group and Osteoporosis group) with Serum calcium values by Kruskal Wallis ANOVA

Groups	Mean	Median	Std.Dev.	95% CI for mean	
				Lower	Upper
Healthy group	9.56	9.60	0.77	9.40	9.72
Osteopenia group	9.74	9.70	0.43	9.65	9.83
Osteoporosis group	9.50	9.60	0.67	9.35	9.64
H-value	8.4170				
P-value	0.0150*				
Pair wise comparisons by Mann-Whitney U test					
Healthy group vs Osteopenia group	P=0.0795				
Healthy group vs Osteoporosis group	P=0.3132				
Osteopenia group vs Osteoporosis group	P=0.0038*				

*p<0.05

A significant difference was observed between three groups (Healthy group, Osteopenia group and Osteoporosis group) with Serum calcium values (H=8.4170, p=0.0150) at 5% level of significance. It means that, the Serum calcium values are different in three groups.

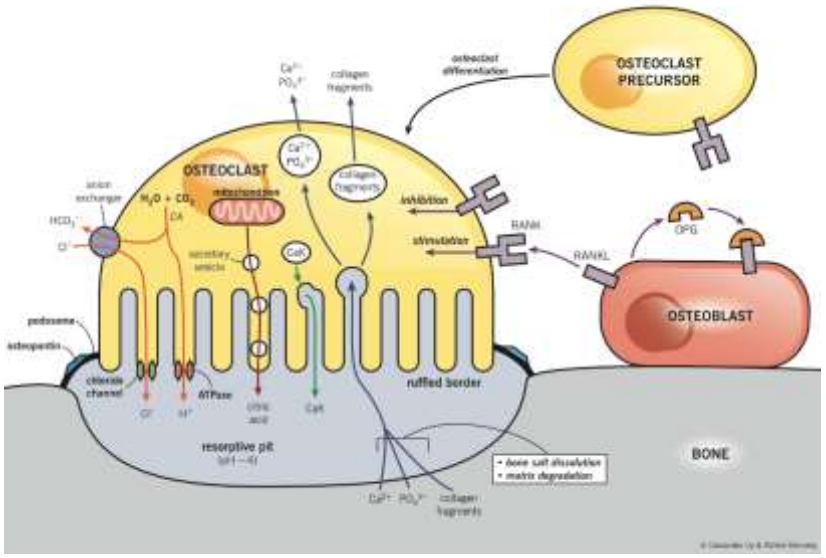

Figure 3 Calcium homeostasis (McMaster, 2020)

Further, to know the pair wise comparisons, the Mann-Whitney U test was applied and results are presented in the above table. it clearly, shows the following:

- No significant difference was seen between healthy group and Osteopenia group with Serum calcium values (p=0.0795) at 5% level of significance. It means that, the Serum calcium values are similar in healthy group and Osteopenia group.
- No significant difference was seen between healthy group and Osteoporosis group with Serum calcium values (p=0.0795) at 5% level of significance. It means that, the Serum calcium values are similar in healthy group and Osteoporosis group.
- A significant difference was seen between Osteopenia Group and Osteoporosis group were compared with Serum calcium values (p=0.0038) at 5% level of significance. It means that, the Serum calcium values are significantly

higher in Osteopenia group as compared to Osteoporosis group.

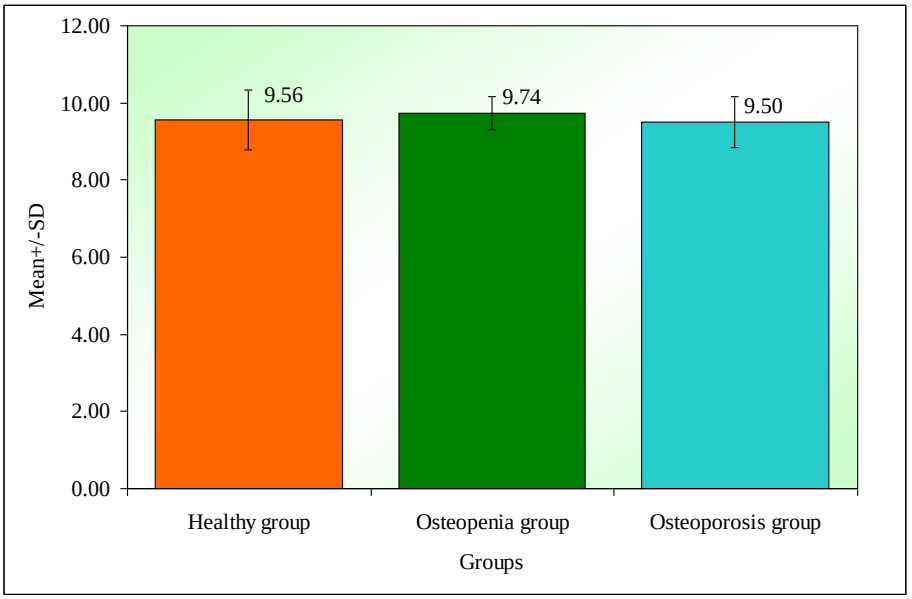

Figure 4 Comparison of three groups (Healthy group, Osteopenia group and Osteoporosis group) with Serum calcium values

Table 3: Comparison of three groups (Healthy group, Osteopenia group and Osteoporosis group) with Serum alkaline phosphatase values by one way ANOVA

Groups	Mean	Median	Std.Dev.	95% CI for mean	
				Lower	Upper
Healthy group	96.54	93.00	30.89	90.08	103.01
Osteopenia group	97.18	91.50	29.31	91.04	103.32
Osteoporosis group	99.21	92.50	32.75	92.35	106.07
F-value	0.1814				
P-value	0.8342				
Pair wise comparisons by Tukeys multiple posthoc procedures					
Healthy group vs Osteopenia group	p=0.9895				
Healthy group vs Osteoporosis group	p=0.8325				
Osteopenia group vs Osteoporosis group	p=0.8994				

*p<0.05

Figure: Comparison of three groups (Healthy group, Osteopenia group and Osteoporosis group) with Serum alkaline phosphatase values

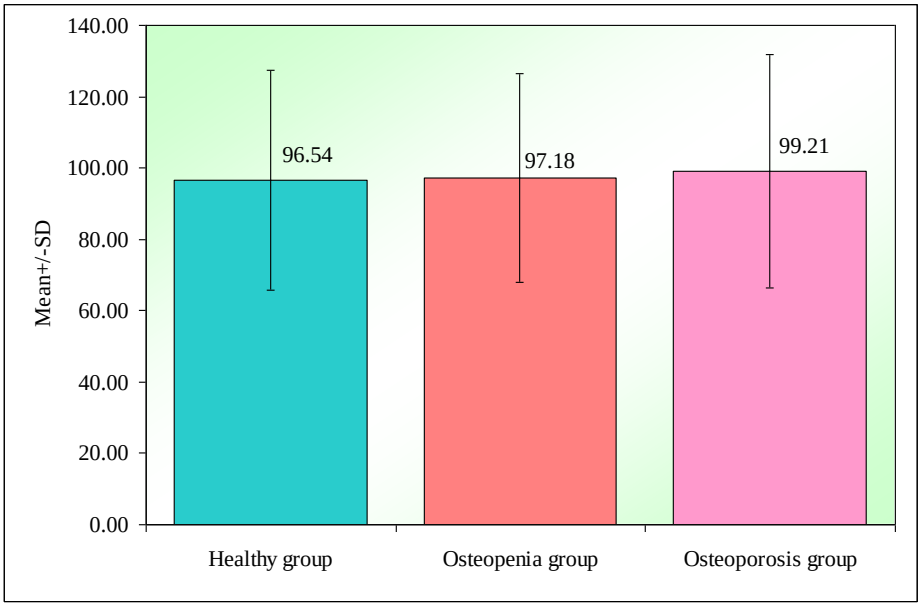

Figure 5 Comparison of three groups (Healthy group, Osteopenia group and Osteoporosis group) with Serum alkaline phosphatase

4. DISCUSSION

The results of the study, reveal that there is a great difference amongst the three groups in Dexa values (H=225.6000, p=0.0001). The bone mineral density (BMD) was the highest in healthy individuals, then in osteopenia groups and the lowest in osteoporosis groups. In large scale NHANES analyses, elevated ALP has been shown to be a risk biomarker for osteoporosis and lower BMD [5][6][9]. Higher ALP levels in osteoporosis patients also add to the role of bone metabolism in the disease progression [10]. Findings have also been made that estrogen deficiency accelerates bone turnover and increases fracture risk, as BMD in osteoporosis patients has also significantly dropped [13]. It has been shown that nutritional supplementation, calcium fluoride nanoparticles or probiotics mitigate BMD loss in an intervention. It emphasizes on early intervention strategies [15][16][19].

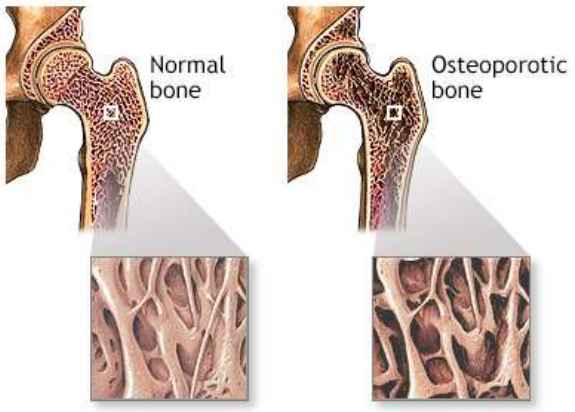

Figure 6 BMD levels in normal bone v. Osteoporotic Bone (Mount Sinai, 2023)

Different brands of commercial drug tests give different results, but less so than in Dexa values (H=8.4170, p=0.0150), and serum calcium levels were variable among groups. No significant difference was seen between the healthy and osteopenia groups (p=0.0795) or healthy and osteoporosis groups (p=0.3132) thus calcium homeostasis may not be the sole indicator of osteoporosis. An important difference between the osteopenia and the osteoporosis groups (p=0.0038) is however to calculated calcium regulation in osteoporosis. Examples of studies that matched with this include showing an association of osteoporosis with altered calcium metabolism and bone turnover markers [8][15]. Not only that, calcium gluconate, combined with calcitriol, have been shown to improve BMD, suggesting that improving calcium absorption is key for managing osteoporosis [17]. Likewise, supplementary nanopowder eggshell improves bone biomarkers and calcium levels

in osteoporotic models, which may suggest some therapeutic applications [18].

The findings also stress the relevance of the inflammatory markers as well as the oxidative stress in osteoporosis. As previously demonstrated by other researchers, osteoporotic fracture patients demonstrate elevated inflammatory markers such as CRP and D dimer, that decrease over time following the operation as bone healing progresses [3]. Due to the antioxidative agents, probucol has been shown to promote osteogenic differentiation and to alleviate osteoporosis by decreasing oxidative stress [14]. Besides, studies on Wif1 confirm its function in promoting osteoblast mineralization and bone formation to add to molecular mechanisms in osteoporosis treatment [20].

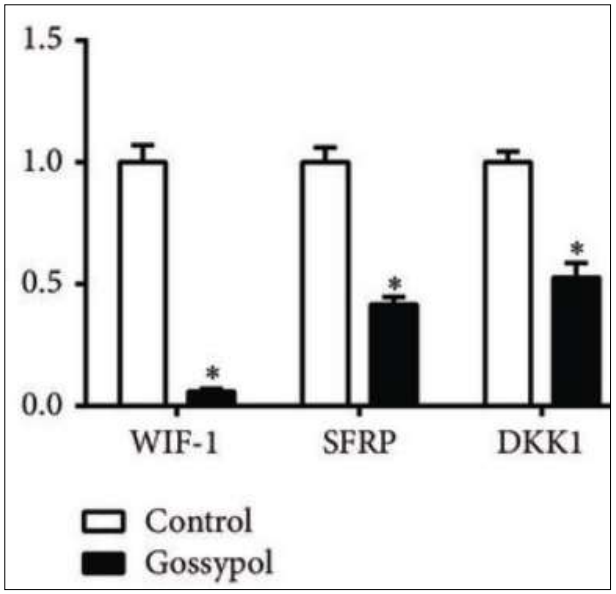

Figure 7 Gossypol treatment using Wif1 of osteoporosis (ResearchGate, 2019)

Taking these findings into account, it is important to detect and treat osteoporosis early. The findings of the negative correlation between ALP and BMD suggests that the ALP is a potential predictor of future bone loss [9]. Additionally, combining calcium with probiotics, or specific, targeted molecular therapies is also a potential to improve bone density and also to reduce further osteoporosis progression [15][16][19][20]. These findings confirm the critical need of personalized treatments strategy both in nutrition, pharmacology and in molecular aspects to promote bone health and prevent fractures.

5. CONCLUSION

The observations made in this study highlight the critical involvement of bone metabolism in the course of the disease and dogmatize the broad differences in bone mineral density (BMD) between normal, osteopenic and osteoporotic people. These findings support that osteoporosis is also associated with decreased BMD, elevated total and BMD alkaline phosphatase. These biochemical markers of bone turnover and of potential disease progression are in the level expected in previous large studies of osteoporosis risk factors. The results also show that estrogen is important in preventing the bone loss since it has also been shown to slow bone resorption and decrease fractures. Therefore, it is essential to prevent complications related to osteoporosis with early identification of people at risk and adequate interventions.

The study also proves that the calcium levels alone is not always enough to diagnose osteoporosis as there were no significant differences in calcium levels between osteopenic and osteoporotic persons. This indicates that the homeostasis of calcium is disturbed in the advanced osteoporosis but is only minimally affected in earlier stages. Our findings highlight the importance of bone health evaluation that includes measurement of BMD in combination with the bone turnover markers, instead of serum calcium levels. It is also known that the inflammation and oxidative stress play a role in osteoporosis pathology and it was shown with the previous research that there is correlation between inflammatory markers and risk of fractures and delayed bone healing. Therefore, directed anti-inflammatory and antioxidant therapies may help to improve bone health and fracture recovery.

This research adds to the requirement of early detection and personalization in the strategy for the treatment of osteoporosis. However, calciumsupplementation, probiotics and interventions directed to molecular therapy of bone metabolism could be highly integrative. In future studies, new therapeutic approaches are needed that are based on the use of nanotechnology as supplements or gene targeted treatments to improve outcomes in osteoporosis prevention and treatment.

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