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# CORRELATION OF SERUM CALCIUM, PHOSPHATE, AND PARATHYROID HORMONE LEVELS IN OSTEOPOROSIS: A BIOCHEMICAL STUDY

*Original Research*

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## ABSTRACT

**Background:** Osteoporosis is a metabolic disease of the bones, which is accompanied by a loss of bone mineral density and high risks of fractures. The most important bone remodeling regulators include calcium, phosphate and parathyroid hormone (PTH), and their imbalance contributes to the pathophysiology of the disease. the purpose of the study was to determine the relationship between serum calcium, phosphate, and pth in patients diagnosed with the osteoporosis.

**Methods:** The cross-sectional study was carried out on 60 patients diagnosed with osteoporosis according to the criteria of the dual-energy X-ray absorptiometry (DEXA) scan (T-score ≤ -2.5) in the Department of diagnostic pathology between January 2023 and December 2023 at the University of Faisalabad TUF and PU Lahore. Age, sex and body mass index (BMI) were used as demographic variables. Venous blood samples in the fasting state were collected and assayed of the total serum calcium, phosphate and intact PTH was done using standardized automated biochemical assays. Bivariate relationships between variables were evaluated by means of Pearson correlation. Simple linear regression to assess the predictive value of serum calcium and phosphate on PTH levels was used. The SPSS version 26.0 was used to analyze data.

**Results:** The mean age of the participants was 62.7 ± 8.6 years and 68 percent of them were female. The mean serum calcium was 8.4 ± 0.6 mg/dL, phosphate 3.2 ± 0.5 mg/dL, and PTH 78.5 ± 25.3 pg/mL. The correlation between serum calcium and PTH revealed that a significant negative correlation existed between the two variables ($r = -0.49$, $p = 0.01$), whereas the correlation between phosphate and PTH was negative but not significant ($r = -0.31$, $p = 0.06$). Linear regression analysis revealed that serum calcium was a significant predictor of PTH levels ($\beta = –5.1$, $p = 0.002$, $R^2 = 0.24$), meaning that about 24% of the PTH variance could be attributed to calcium. Phosphate was not found to be a predictor of PTH in the regression model ($\beta = –2.8$, $p = 0.08$).

**Conclusion:** This study indicated that there is a considerable biochemical correlation between serum calcium and parathyroid hormone levels in osteoporotic patients, indicating there are compensatory changes in hormones to the disturbed calcium homeostasis. Observation of these indicators can improve the quality of diagnosis and guide the use of treatment in the management of osteoporosis.

**Keywords:** Osteoporosis, Calcium, Phosphate, Parathyroid Hormone, Bone Metabolism, Biochemical Markers.

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## INTRODUCTION

Osteoporosis is a common metabolic bone disorder which is marked by a loss in bone mass and destruction of bone tissue microarchitecture which results in the increased bone fragility and susceptibility to bone fracture (1,2). It is a significant health issue especially to the aged and postmenopausal women and it impacts on millions of people across the globe. The osteoporosis pathogenesis is a complex issue with the lack of bone formation and resorption balance (3). Among the many biological determinants of bone remodeling, calcium, phosphate, and parathyroid hormone (PTH) are some of the key determinants of maintaining skeletal integrity (4,5).

The major mineral components of the skeleton are calcium and phosphate, and their concentrations in serum are closely maintained by hormonal homeostasis in which PTH, vitamin D, and calcitonin are involved (6,7). One of the main regulators of calcium and phosphate metabolism is parathyroid hormone that is secreted by the parathyroid glands. It raises the level of serum calcium through stimulating bone resorption, renal calcium reabsorption and vitamin D activation which in turn raises intestinal calcium absorption (8,9). At the same time, PTH inhibits reabsorption of phosphate by the kidneys and causes phosphaturia. Thus, changes in the calcium or phosphate concentration can provoke alteration in the release of PTH, which could have direct consequences on the bone health (10).

The complexity between the renal function and mineral metabolism is the focus of osteoporosis pathophysiology (11). Studies established that renal cellular signalling pathway, including epidermal growth factor receptor (EGFR) ubiquitination, is involved in the maintenance of kidney integrity and functionality, which indirectly regulate calcium and phosphate homeostasis (12). Renal tubulointerstitial fibrosis and dysfunction may result in dysregulation of electrolyte balance of the kidney which ultimately involves the bone mineral density due to disrupted PTH and vitamin D metabolism (13).

Menopausal estrogen deficiency is a proven cause of osteoporosis. A group of researchers found that it is through the expression of Derlin-1 and activation of AMP-activated protein kinase (AMPK) that estrogen negatively regulates the renal epithelial sodium channels, which are likely to regulate renal sodium, calcium, and phosphate (14). This is in line with clinical findings that loss of estrogen in the postmenopausal period predisposes to disturbances in bone mineral metabolism and bone loss acceleration. Hormonal interaction between renal sodium channel and bone health is a new topic that should be explored further (15).

The calcium-binding proteins, including S100A16, have also been associated with the reorganization of the cytoskeleton in the renal cells, which indicates the intricate processes behind the systemic regulation of mineral balance reabsorption by the renal cells (16). Similarly, it was reported that contribution of cofilin and its coupling with 14-3-3 isoforms in maintaining epithelial sodium channels, which demonstrates the importance of fine-tuning interactions between proteins to have an impact on the renal electrolyte transport and indirectly affect levels of calcium and phosphate in the bloodstream (17).

Another aspect of the kidney in the excretion of electrolytes and homeostasis is supported by researchers, who reported the correlation of urinary electrolyte excretion and clinical outcome parameters in patients with chronic kidney diseases (18). Reduced kidney function is one of the risk factors of secondary hyperparathyroidism and mineral bone diseases as renal health is very vital in the management of osteoporosis (19,20). The clinical disturbances in calcium homeostasis, including hypocalcemia found in patients with jaundice in the neonatal setting, give an idea of how the systemic conditions influence calcium metabolism (21). The knowledge of such perturbations serves to explain the biochemical milieu which predisposes people towards bone fragility (22).

New studies also carry the indication that other elements other than classical mineral metabolism affect the remodeling of bones (23). The pathophysiology of nerve growth factor (NGF) in inflammation and tissue remodelling, indicated that the inflammatory mediators could indirectly control bone turnover (24). This is in agreement with the facts that systemic inflammation is a factor in the progression of osteoporosis. Non-invasive methods of diagnosis, including salivary biomarker profiling, are under consideration as capable of depicting systemic biochemical modifications concerning bone metabolism (25). The tools may be used to improve early diagnosis and monitoring of osteoporosis through evaluating calcium and phosphate balance markers (26).

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Neurotrophins, which play a role in multi-organ pathophysiology, and can put another dimension of complexity in osteoporosis etiology are neuro-immune contacts and systemic inflammatory pathways (27,28). Also, micronutrient status such as zinc is important in the formation and remodeling of bones (29). It was emphasized that the impact of a low zinc level on short-chain fatty acid synthesis by intestinal microbiota that, consequently, could be relevant to the systemic inflammation and bone quality (30). This implies that the gut-bone axis is a new variable in the research on osteoporosis.

With regards to osteoporosis, the increased or decreased calcium-phosphate homeostasis and changes to the PTH levels can contribute to bone loss progression (31). The interrelationship between these biochemical markers in osteoporotic persons is however, not fully understood. Investigating their correlations may bring a better understanding of the disease pathophysiology and help to apply their therapies more personally. This study aims to examine the relationship between calcium and phosphate levels of the serum and the parathyroid hormone in individuals diagnosed with osteoporosis. The ability to establish these biochemical association can possibly not only assist in better diagnosis but also aid in the monitoring of disease progression, and the best approach to treating diseases in clinical practice.

## METHODOLOGY

This cross-sectional study was conducted to assess the relationship between the level of serum calcium, phosphate, and parathyroid hormone (PTH) in patients diagnosed with osteoporosis in order to gain deeper insight into the biochemical dynamics that cause the disease. The study was carried out at the Department of diagnostic pathology between January 2023 and December 2023 at the University of Faisalabad TUF and PU Lahore (Ref: 2024/OP-2043B). The inclusion criteria comprised of patients age 40 years and above, and with a known diagnosis of osteoporosis based on dual-energy X-ray absorptiometry (DEXA) scan findings, a T-score of $\leq -2.5$ according to the World Health Organization (WHO) criteria. Patients who had known metabolic bone diseases (other than osteoporosis), chronic kidney disease, parathyroid disease, malignancy, or used any drugs that affect calcium or bone metabolism (e.g bisphosphonates, corticosteroids, vitamin D or calcium supplements within the past 3 months) were not included in the study. A total of 60 patients that met the inclusion and exclusion criteria and went through all of the assessments were included in the final analysis. OpenEpi version 3.0 was used to determine the sample size.

A consecutive sampling technique was adopted by outpatient clinics. Demographic information such as age, sex, and body mass index (BMI) was taken out in each participant. Sterile collection tubes containing fasting venous blood were analyzed by standardized automated biochemical assays of the total serum calcium, phosphate and intact PTH in the hospital laboratory.

The analysis of the data was done with the help of IBM SPSS 26.0 Windows version. In order to evaluate the linear relationship between serum calcium, phosphate and PTH levels, Pearson's correlation coefficient was determined. Also, simple linear regression was used to determine the predictive value of calcium and phosphate upon the level of PTH. The p-value of less than 0.05 was regarded as statistically significant.

### Results

There were 60 patients in the study who had osteoporosis diagnosed on the basis of DEXA scan findings. The average age of the respondents was 62.7 **± 8.6 years** and most of the participants were female (**68%**, *n = 41*). The average BMI among the study population was **23.9 ± 3.4 kg/m²**. Mean T-score of the participants was **–2.9 ± 0.4** which identified moderate to severe osteoporosis.

The following were the average serum concentrations obtained through biochemical analysis: Calcium: 8.4 ± 0.6 mg/dL, Phosphate: 3.2 ± 0.5 mg/dL, Parathyroid Hormone (PTH): 78.5 25.3 pg/mL

The demographic as well as the biochemical features of the study participants were summarized in Table 1.

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**Table 1: Demographic and Biochemical Characteristics of Study Participants**

| Parameter | Value (Mean ± SD / n [%]) | Test Used | Test Value | P-Value |
|---|---|---|---|---|
| Age (years) | 62.7 ± 8.6 | T-test | t = 1.21 | p = 0.231 |
| Gender (Female) | 41 (68%) | Chi-square | $\chi^2 = 6.42$ | p = 0.011* |
| BMI (kg/m²) | 23.9 ± 3.4 | T-test | t = –0.88 | p = 0.382 |
| T-score (DEXA) | –2.9 ± 0.4 | T-test | t = –4.35 | p < 0.001* |
| Serum Calcium (mg/dL) | 8.4 ± 0.6 | T-test | t = –2.95 | p = 0.005* |
| Serum Phosphate (mg/dL) | 3.2 ± 0.5 | T-test | t = –1.44 | p = 0.154 |
| Serum PTH (pg/mL) | 78.5 ± 25.3 | T-test | t = 3.18 | p = 0.002* |

***SD = Standard Deviation, n = number of participants, p < 0.05 considered statistically significant**

### Correlation Analysis

The Pearson correlation analysis was used to demonstrate that serum calcium and PTH had an inverse significant correlation (r = -0.49, p < 0.01), indicating that low calcium levels were correlated with high PTH. There was also a negative correlation between phosphate and PTH (r = -0.31) although it was not found to be statistically significant (p = 0.06). Serum calcium and phosphate levels did not show any significant correlation (r = +0.12, p = 0.35). The correlation coefficients are shown in Table 2.

**Table 2: Pearson Correlation Between Biochemical Parameters**

| Variable Pair | Correlation Coefficient (r) | p-value |
|---|---|---|
| Calcium vs. PTH | –0.49 | p < 0.01* |
| Phosphate vs. PTH | –0.31 | p = 0.06 |
| Calcium vs. Phosphate | +0.12 | p = 0.35 |

***PTH = Parathyroid hormone, * = Significance at p-value <0.05***

### Linear Regression Analysis

To determine the predictive value of serum calcium and phosphate on the levels of PTH, simple linear regression analysis was applied. Serum calcium provided a significant negative predictor of PTH levels (**β = –5.1**, 95% CI: –8.3 to –1.9, *p* = 0.002), with a **$R^2$ value of 0.24**, which means that 24% of the variation in the PTH levels could be attributed to variations in serum calcium.

The level of serum phosphate did not strongly predict PTH (**β = –2.8**, 95% CI: –5.9 to +0.3, *p* = 0.08), even though a tendency to a negative relationship was observed. The summary of regression analysis is presented in Table 3.

**Table 3: Simple Linear Regression Predicting PTH Levels**

| Predictor Variable | β Coefficient (95% CI) | $R^2$ | p-value |
|---|---|---|---|
| Serum Calcium (mg/dL) | –5.1 (–8.3 to –1.9) | 0.24 | 0.002* |
| Serum Phosphate (mg/dL) | –2.8 (–5.9 to +0.3) | 0.09 | 0.08 |

**n =** ***Number of Participants,*** **β =** ***Beta Coefficient,*** **CI =** ***Confidence Interval,*** **$R^2$ =** ***Coefficient of Determination,*** **p-value =** ***Probability Value, * = Significance at p < 0.05***

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**Interpretation**

These findings highlight the imperative role of calcium homeostasis in the regulation of PTH secretion in osteoporotic patients. The average negative correlation and high predictive value indicate that even mild hypocalcemia can initiate a compensatory increase in PTH, which could be among the causes of bone resorption and additional bone loss. Even though the serum phosphate had a tendency of inverse correlation with the PTH, the predictive value was not significant in this cohort.

## DISCUSSION

This study explored the biochemical interaction between serum calcium, phosphate and parathyroid hormone (PTH) levels in patients with osteoporosis with the view of gaining more insight on the metabolic changes that cause bone loss. Our results showed that there is a strong negative correlation between PTH and serum calcium, hence, lower levels of calcium are linked to a high secretion of PTH. Conversely, the correlation between phosphate and PTH was negative though not statistically significant probably because of multifactorial regulation of phosphate metabolism. Moreover, the serum calcium was also found as an important predictor of the PTH levels indicating that changes in calcium homeostasis can be one of the most effective regulatory factors of the PTH secretion among osteoporotic people.

The described inverse correlation between serum calcium and PTH is consistent with the known physiological principles (32). Calcium plays a key role in balancing the release of PTH in a feedback loop with a process that involves calcium-sensing receptors in the parathyroid glands (33). A decrease in serum calcium causes an increase in secretion of PTH, to repair calcium homeostasis by enhancing bone resorption, augmenting calcium reabsorption in the kidneys, and amplifying intestinal calcium uptake through the activation of vitamin D (34). This is compensatory hormonal feedback necessary to keep extracellular calcium in a very small physiological range but may be very harmful to bone density when raised chronically (35). Our results indicate that slight hypocalcemia in osteoporosis can stimulate PTH secretion causing an increase in bone turnover and deterioration of skeletal strength.

Also, it should be note that PTH and bone remodeling activity are dynamically interconnected. PTH does not only regulate the homeostasis of calcium and phosphates, but it directly affects the work of osteoblasts and osteoclasts (36,37). Occasional rises in PTH are able to trigger bone formation, and constant high levels, such as those seen in most osteoporotic patients, primarily stimulate bone resorption (38). This twofold response implies that the pattern and duration of PTH elevation is of great importance in the determination of net skeletal effect of PTH (39). In patients with prevalent osteoporosis, where long-term high levels of PTH tend to be caused by a lack of calcium or vitamin D, the chronic resorptive process may result in cortical thinning and damage to the trabecular structure (40). These processes also help to emphasize that it is not only the absolute levels of PTH that are important to evaluate when determining the risk of fractures and the execution of therapeutic interventions (41,42).

Although closely connected to bone metabolism, phosphate homeostasis is regulated through a more complicated interaction between dietary intake and excretion by the kidney, fibroblast growth factor 23 (FGF23), and other hormonal factors than PTH alone (43,44). This multifactorial regulation and the relatively small phosphate range in our study may explain why the phosphate and PTH correlation were not statistically significant in this study. Besides, in osteoporosis, the phosphate balance is commonly kept under tight control by renal clearance, and the changes in phosphates may not be significant in osteoporosis with no severe renal dysfunction (45). Nonetheless, the negative association between phosphate and PTH is in line with the known phosphaturic effect of PTH, which is higher secretion of phosphate by increasing PTH to avert hyperphosphatemia and balance the mineral (46,47).

Our findings align with the previous studies that point to the pivotal position of calcium-PTH interactions in osteoporosis as well as associated metabolic bone diseases (48). High levels of PTH especially with secondary hyperparathyroidism caused by vitamin D deficiency or hypocalcemia have been associated with heightened bone resorption and risk of fracture (49). A number of studies have documented that the bone turnover indicators of PTH are better associated with calcium than phosphate, indicating that the role of calcium homeostasis in the pathophysiology of osteoporosis is important (50). These minerals and hormones interact with each other, which highlights the complexity of the metabolic regulation in osteoporosis and the necessity of biochemical monitoring (51).

Clinically, the noted results underscore the need to check the level of serum calcium and PTH in osteoporotic patients on a routine basis (52). The early diagnosis of the patients, who are at risk of secondary hyperparathyroidism and augmented bone loss, can be helpful in addressing the calcium deficiency and restoring the normal range of PTH release (53). Possibly effective therapeutic interventions include calcium and vitamin D supplementation, as well as lifestyle changes, which would help reduce bone resorption and enhance a

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clinical outcome (54). Also, the level of such biochemical indicators could help to determine the degree of effect of treatment and prescribe individual management strategies (55,56).

The limitations of the study should be considered. The cross-sectional design does not allow proving causality or determining temporal variations of biochemical parameters in the process of disease progression or treatment. Our findings might be limited by the limited sample size and the univariate center to generalize results. Additionally, the essential variables, including vitamin D levels, kidney, and diet, which have been reported to affect calcium, phosphate, and PTH metabolism, were not measured in the study. The longitudinal design, larger and divergent populations, and extensive evaluation of the associated biochemical parameters, including vitamin D, FGF23, and bone turnover markers, should be introduced in future studies.

Further research into the interaction of vitamin D, FGF23 and bone turnover and calcium, phosphate and PTH would help give a more comprehensive picture of osteoporosis pathophysiology (57). Also, the investigation of genetic and epigenetic control over mineral metabolism and hormonal conditions may become a potential step towards modifying therapeutic measures (58). Incorporation of environmental and lifestyle issues into the research paradigms such as diet and exercise will help us to create the culturally tailored management approaches (59,60).

## CONCLUSION:

Finally, the current work demonstrates the high biochemical dependence between serum calcium and PTH levels in patients with osteoporosis and suggests the importance of the compensatory hormonal responses to the calcium homeostasis impairments. The results justify the importance of frequent calcium/PTH monitoring in clinical practice to improve the management of osteoporosis. More knowledge of the interactions with minerals and hormones will guide the creation of individualized treatments that will help in minimizing bone loss and the risk of fractures.

### AUTHOR CONTRIBUTION

| Author | Contribution |
|---|---|
| Muhammad Akram* | Substantial Contribution to study design, analysis, acquisition of Data<br>Manuscript Writing<br>Has given Final Approval of the version to be published |
| Syed Ahmad Bilal Bukhari | Substantial Contribution to study design, acquisition and interpretation of Data<br>Critical Review and Manuscript Writing<br>Has given Final Approval of the version to be published |

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