# Bone Turnover Markers in Menopausal Women: A Comparative Study

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## Abstract

**Introduction:** Menopause, characterized by the permanent cessation of menstrual cycles due to declining ovarian function, is diagnosed retrospectively after 12 months of amenorrhea. Postmenopausal women are at an increased risk of osteoporosis, a condition marked by reduced bone density and higher fracture risk. This study aims to assess markers of bone formation—serum total alkaline phosphatase (ALP) and bone-specific alkaline phosphatase (BSAP)—in postmenopausal women compared to premenopausal women. Additionally, urinary hydroxyproline, a marker of bone resorption, was measured and compared between the two groups.

**Methods:** This case-control study included 20 healthy postmenopausal women (cases) and 26 healthy premenopausal women (controls). Following informed consent, blood samples were collected after an overnight fast to measure serum calcium, phosphorus, estradiol, total ALP, BSAP, and urinary hydroxyproline levels.

**Results:** Postmenopausal women exhibited significantly higher serum total ALP, BSAP, and urinary hydroxyproline levels compared to premenopausal women ($P < 0.001$). Estradiol levels were significantly lower ($P < 0.001$), while serum phosphorus was higher in postmenopausal women ($P = 0.017$). Serum calcium levels showed no significant difference between the two groups ($P = 0.911$).

**Conclusions:** The findings indicate that estrogen decline during menopause accelerates bone remodeling, as demonstrated by altered bone turnover markers, highlighting the increased risk of osteoporosis in postmenopausal women.



## INTRODUCTION

Menopause typically occurs between the ages of 49 and 52, with the average age being 51.[1] The transition from regular menstrual cycles to their permanent cessation is not abrupt but rather involves a series of hormonal and clinical changes due to declining ovarian function. This transitional phase begins long before the onset of menopause itself.[2] The hormonal shifts during this period play a pivotal role in the development of various diseases.[3]

After menopause, the ovaries produce less estrogen, leading to an estrogen-deficient state. This deficiency can increase osteoclastic activity, disrupting the balance between bone formation and resorption. When resorption surpasses formation, osteoporosis develops. Osteoporosis is a systemic condition characterized by low bone density and an increased risk of fractures, especially in postmenopausal women. Bone turnover markers, which increase gradually with age, show significantly higher values in postmenopausal women with osteoporosis.[4] Studies have shown that menopause can cause a 37 - 52% increase in bone formation markers and a 79 - 97% increase in bone resorption markers. The more pronounced rise in resorption markers is considered a risk factor for osteoporosis in postmenopausal women.[5] Estrogen deficiency in menopause contributes to osteoporosis by promoting bone resorption, which releases calcium into the extracellular space. This process suppresses parathyroid hormone (PTH) secretion, calcitriol synthesis, and calcium absorption in the intestines. Consequently, assessing bone turnover markers can be valuable for evaluating the risk of osteoporosis and predicting future bone mineral density (BMD) in postmenopausal women.[6]

Research has focused on evaluating the levels of bone turnover markers in postmenopausal women. Studies have shown that reduced BMD is strongly associated with advanced age, particularly during the menopausal phase.[7] Menopause brings about significant physiological and biochemical changes that affect bone mineral metabolism, heightening the risk of osteoporosis. This condition is defined by decreased bone mass and microarchitectural deterioration of the skeleton, leading to increased bone fragility and a higher risk of fractures.[8] Osteoporosis prevalence is notably high among elderly postmenopausal women, with some reports indicating a 10% or greater reduction in BMD during the menopausal transition, significantly raising fracture risk.[9,10] This case control study has been planned to study the level of serum total alkaline phosphatase (ALP) and bone-specific alkaline phosphatase (BSAP)—in postmenopausal women and premenopausal women.

## METHODS

This case control study was conducted following informed consent from participants. It included 20 healthy postmenopausal women (cases) who had experienced a cessation of menstruation for at least one year, and 26 healthy premenopausal women (controls) with regular menstrual cycles. The participants were selected from the staff, their relatives, and external individuals attending the staff health clinic and the Obstetrics and Gynaecology outpatient department. Ethical approval for this case control study was obtained from the Institutional Ethics Committee of Sri Venkateswara Institute of Medical Sciences with approval number [SVIMS/989/2020].

| Parameter | Method | Instrument |
|---|---|---|
| Serum calcium (mg / dL) | Arsenazo III dye binding method | Beckman coulter AU 480 auto analyzer (California,USA) |
| Serum phosphorous (mg / dL) | UV ammonium molybdate method | |
| Serum alkaline phosphatase activity (IU / L) | Kinetic method | |
| Serum estradiol (pg / mL) | Chemiluminescence method | Beckman coulter AU 480 auto analyzer (California,USA) |
| Serum bone specific alkaline phosphatase (IU / L) | Heat inactivation method | Perkin Elmer Lambda 25UV Vis spectrophotometer |
| Urine hydroxy proline(mg / 24 hrs) | Modified Neuman and Logan method | |

The control group consisted of women who were in the reproductive age group and had regular menstrual cycles. Women with history of fractures in the past year, use of hormone replacement therapy, medications that affect bone metabolism, liver or kidney diseases, chronic inflammatory conditions, thyroid and parathyroid disorders, and malignancies were excluded. Blood samples (5 ml) were collected after an overnight fast using sodium citrate and plain vacutainers under aseptic conditions. The remaining 3 ml of blood was allowed to clot for 30 minutes, then centrifuged at 5000 RPM for 10 minutes to measure serum calcium, phosphorus, estradiol, bone-specific alkaline phosphatase, and urinary hydroxyproline levels. The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Data are presented as mean ± standard deviation or median (interquartile range, IQR), depending on the distribution. Group comparisons were made using the Mann-Whitney U test. The association between variables was evaluated using Spearman's rank correlation. A P value of $< 0.05$ was considered statistically significant. Statistical analysis was conducted using Microsoft Excel and SPSS for Windows, version 16.0.

## RESULTS

Biochemical markers were measured in both premenopausal and postmenopausal women.

Postmenopausal women were significantly older than premenopausal women (P < 0.001), with no significant difference in BMI between the two groups (P = 0.584). As shown in the figures below, serum ALP activity, BSALP activity, and urinary hydroxyproline levels were significantly higher in postmenopausal women compared to premenopausal women (P < 0.001). Serum estradiol levels were significantly lower in postmenopausal women (P < 0.001). Serum phosphorus was significantly higher in postmenopausal women (P = 0.017), while calcium levels showed no significant difference between the two groups (P = 0.911), as shown in Table 1.

The correlation analysis results between estradiol and the studied markers are presented in Table 2. Serum estradiol levels showed significant negative correlation with age (r = -0.629; P < 0.001); however, no correlation was observed between estradiol and BMI in Figure 5. Scatter plots showing relationship of estradiol with ALP activities are shown in Figure 6. Serum estradiol levels are inversely correlated with activities of both total and bone specific ALP. Scatter plot showed significant inverse correlation between serum estradiaol with urinary hydroxyproline as shown in Figure 7. Similarly, the relationship of correlation between serum estradiol and serum calcium and phosphorus has been depicted in Figure 8. Scatter plots showing relationship of estradiol with calcium and phosphorous are shown in Figure 8. There was inverse relationship between serum estradiol levels and phosphorous levels but no significant correlation was found between calcium and estradiol levels.

**Table 1:** Biochemical markers studied in pre- and post-menopausal women

| Parameter | Pre-meno-pause (N = 26) | Post-meno-pause (N = 20) | P value |
|---|---|---|---|
| Age (years) | 34.69 ± 7.64 | 55.5 ± 7.51 | < 0.001 |
| BMI (Kg / m²) | 25.90 ± 5.20 | 25.00 ± 4.36 | 0.584 |
| Total ALP activity (IU / L) | 69.65 ± 15.21 | 95.59 ± 13.28 | < 0.001 |
| BSALP (IU / L) | 11.99 ± 4.75 | 27.21 ± 6.01 | < 0.001 |
| Urine hydroxy proline (mg / 24 hrs) | 19.12 ± 3.84 | 31.36 ± 9.27 | < 0.001 |
| Estradiol (pg / mL) | 76.50 (47.25-120.00) | 14.50 (7.25-29.50) | < 0.001 |
| Calcium (mg / dL) | 9.80 ± 0.47 | 9.80 ± 0.43 | 0.911 |
| Phosphorous (mg / dL) | 3.17 ± 0.47 | 3.48 ± 0.36 | 0.017 |

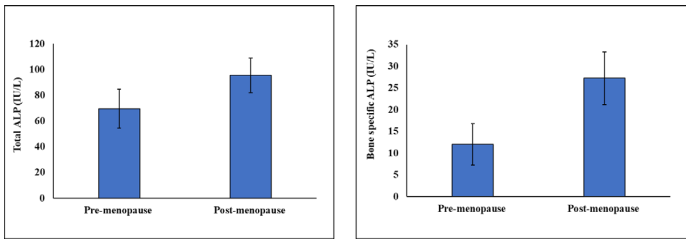


**Fig1:** Total and bone specific alkaline phosphatase activity of pre- and post-menopausal women

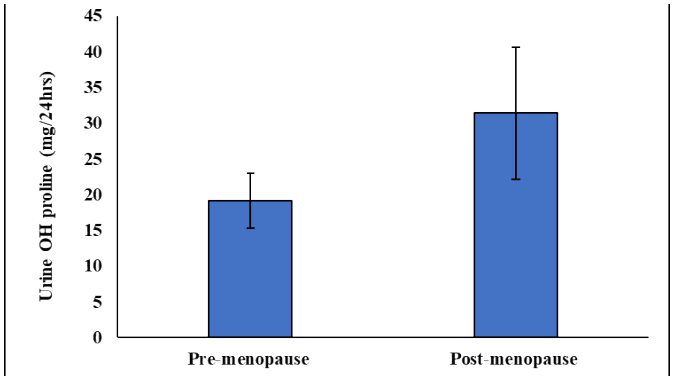


**Fig 2:** Mean urinary hydroxyproline levels of pre- and post-menopausal women

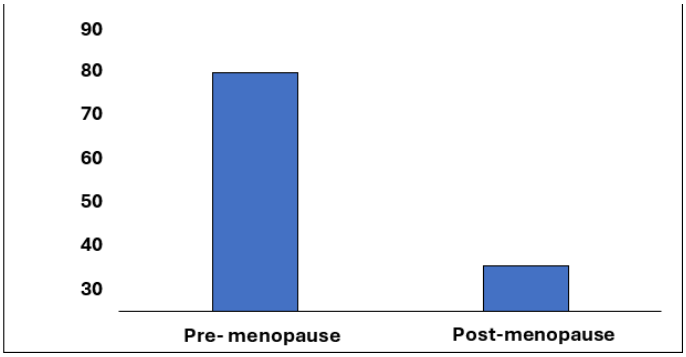


**Fig 3:** Mean serum estradiol levels of pre- and post-menopausal women

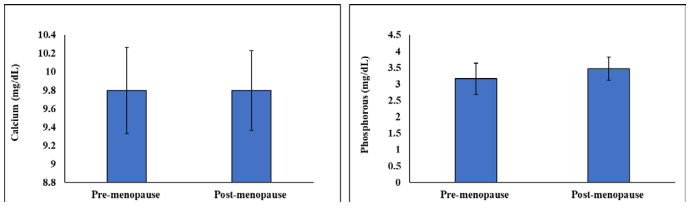


**Fig 4:** Mean calcium and phosphorous levels of pre- and post-menopausal women

**Table 2:** Correlation of serum estradiol with the markers studied

| Parameter | r | P value |
|---|---|---|
| Age | - 0.629 | < 0.001 |
| BMI | - 0.002 | 0.991 |
| Total ALP activity | - 0.559 | < 0.001 |
| BSALP activity | - 0.528 | < 0.001 |
| Urine hydroxy proline | - 0.580 | < 0.001 |
| Calcium | - 0.116 | 0.443 |
| Phosphorous | - 0.361 | 0.014 |

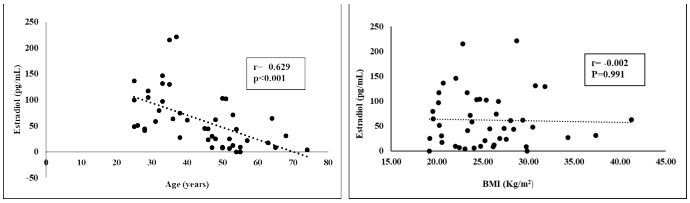


**Fig 5:** Correlation of estradiol with age and body mass index

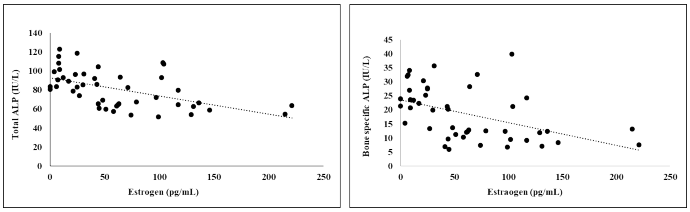


**Fig 6:** Correlation of estradiol levels with total ALP and bone specific ALP activities

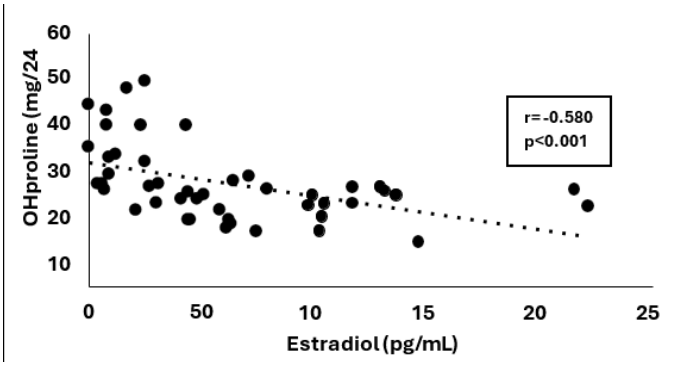


**Fig 7:** Correlation of estradiol with urinary hydroxyproline

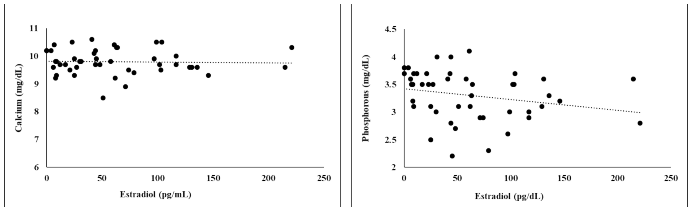


**Fig 8:** Correlation of estradiol with calcium and phosphorous

## DISCUSSION

As women age, ovarian function naturally declines, leading to changes in hormone levels, such as a decrease in estradiol and an increase in gonadotropic hormones. While menopause is a natural biological process, it is associated with various symptoms that can significantly impact the quality of life for postmenopausal women.

One common complication observed in postmenopausal women is osteoporosis, a condition characterized by a reduction in bone mass. This loss of bone density increases the risk of fractures, making it crucial to assess bone mass in this population. Although bone mineral density (BMD) can be measured using dual X-ray absorptiometry (DXA), BMD alone does not fully predict fracture risk.[11] In this regard, biochemical markers of bone turnover have been identified as reliable indicators for screening, diagnosing, and monitoring osteoporosis.[12]

Estrogen plays a crucial role in maintaining bone health through multiple mechanisms. It directly inhibits osteoclast activity and promotes osteoblast function, thereby maintaining the delicate balance between bone formation and resorption. Estrogen also enhances intestinal calcium absorption and reduces renal calcium excretion, contributing to calcium homeostasis. The hormone regulates the production of various cytokines and growth factors that influence bone metabolism, including reducing the production of bone-resorbing cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-alpha. When estrogen levels decline during menopause, this protective effect is lost, leading to accelerated bone turnover with resorption exceeding formation.

In the present study, serum activities of total ALP and bone specific ALP of postmenopausal women were found to be significantly higher when compared to those of premenopausal women (69.65 ± 15.21 and 95.59 ± 13.28 IU/L; P < 0.001 for total ALP and 11.99 ± 4.75 and 27.21 ± 6.01 IU / L; P < 0.001 for BSALP) (Table 1). Similar findings were reported in earlier studies show a higher alkaline phosphatase level in postmenopausal women when

compared to premenopausal women.

Rai et al observed that postmenopausal women had significantly higher levels of BSALSP when compared to premenopausal women. They have further reported that total ALP increased by 46%, while BSALP increased by 39% after the menopause.[13] Tariq et al found significantly higher serum ALP and BSALP in postmenopausal women with osteoporosis compared to those without osteoporosis. They further observed that the levels of these markers are higher in postmenopausal women with osteoporosis who are not on hormone replacement therapy (HRT) when compared to postmenopausal osteoporotic women who are being treated with HRT, thus suggesting the beneficial effect of HRT in reducing bone turnover rate.[14]

ALP is one of the widely measured markers in clinical practice. Total ALP activity includes the sum of the activities of various isoforms of ALP that are derived from liver, bone and intestine. The major isoenzymes of ALP are derived from liver and bone each of which contributes to almost 50% of the total effect of all the isoenzymes.[15] ALP plays an important role in osteoid formation and mineralization of bone through its hydrolyzing effect on inorganic pyrophosphate generating phosphate.[16] Although not a specific marker of bone metabolism, increased ALP activity has been reported in patients with bone disease. Similarly, BSALP is another enzyme that is involved in bone formation and mineralization. BSALP is a more specific bone marker and is used as an indicator of overall bone turnover.[17] The decreased estrogen level during menopause results in the loss of the beneficial effect of estrogen on bone causing an increased rate of bone turnover in these women.

Hence, the increased ALP and BSALP observed in postmenopausal women in the present study could be a result of increased bone turnover in them occurring due to decreased estrogen levels. This was further supported by the observation of lower estradiol levels in postmenopausal women when compared to premenopausal women in the present study {76.50 (47.25-120.00) vs 14.50 (7.25- 29.50)} pg / mL in pre and post menopausal women respectively. ($P < 0.001$) (Table 1)

Urinary hydroxyproline is a well-established biochemical marker of bone resorption. During bone resorption, osteoclasts break down the collagen matrix, releasing hydroxyproline which is subsequently excreted in the urine. Since hydroxyproline cannot be reused for collagen synthesis and is not significantly metabolized, its urinary excretion directly reflects the rate of collagen degradation and, consequently, bone resorption. The elevated levels of urinary hydroxyproline observed in postmenopausal women in our study (19.12 ± 3.84 vs 31.36 ± 9.27 mg / 24 hrs in pre and post menopausal women, respectively ($P < 0.001$) indicate increased bone resorption, characteristic of the accelerated bone turnover seen after menopause.

Postmenopausal women in the present study were older than premenopausal women (34.69 ± 7.64 vs 55.5 ± 7.51 years) for pre and post menopausal women respectively ($P < 0.001$) and serum estradiol levels showed a significant negative correlation with age ($r = -0.629$; $P < 0.001$) (Table 2). Both groups had a similar BMI (25.90 ± 5.20 and 25.00 ± 4.36 kg / $m^2$ for pre and post menopausal women, respectively ($P = 0.584$) (Table-1).

The menopausal transition is associated with significant alterations in the hormonal levels, most notably a reduction in the estradiol levels which occurs almost by about 60% and the low estrogen level in menopausal women is considered as one of the important risk factors for osteoporosis in these women. Accordingly, when the relationship of estradiol with ALP and BSALP was analyzed, it was found that both total ALP and BSALP showed significant negative correlation with serum estradiol ($r = -0.559$; $P < 0.001$ for total ALP and $r = -0.528$; $P < 0.001$ for BSALP) (Table 2). Pardhe et al also observed decreased estradiol levels in postmenopausal women when compared to premenopausal women and the estradiol levels correlated negatively with ALP. No significant correlation was observed between estradiol and BMI in the present study ($r = -0.002$; $P = 0.991$) (Table 2). Serum calcium and phosphorous were measured as other biochemical markers of bone metabolism in the present study. It was found that phosphorous levels of postmenopausal women were significantly higher than premenopausal women (3.17 ± 0.47 and 3.48 ± 0.36 mg / dL) in pre and postmenopausal women respectively ($P = 0.017$).

However, serum calcium levels were similar between the two groups of women (9.80 ± 0.47 and 9.80 ± 0.43 mg / dL in pre and postmenopausal women respectively ($P = 0.911$) (Table 1). It should be noted that participants were not on calcium supplementation, and the similar calcium levels between groups likely reflect the body's homeostatic mechanisms that maintain serum calcium within normal ranges despite altered bone metabolism. Bosman et al[18] reported that calcium and phosphate levels did not show significant difference between pre and postmenopausal women in their studies. Prabha et al[19] observed significantly higher phosphorous levels and lower calcium levels in postmenopausal women than premenopausal women. The variation in the findings could be a result of difference in the study population and geographical variations.

Findings of correlation analysis in the present study revealed

significant negative correlation between phosphorous and estradiol (r = -0.361; P = 0.014) (Table 2). However, no significant correlation was observed between calcium and estradiol (r = -0.116; P = 0.443) (Table 2). Pardhe et al reported negative but non significant correlation between phosphorous and estradiol levels in postmenopausal women in their study while a positive correlation was found between calcium and estradiol.

The hormonal alterations in the menopausal state that are mainly characterized by decreased estrogen levels result in various metabolic changes including those of bone metabolism.[20] The resultant increase in bone turnover leads to an increased osteoclastic activity which ultimately results in the development of osteoporosis.[21,22] Measurement of markers of bone turnover that can be assayed using simple and inexpensive methods help in the detection of osteoporosis and taking up appropriate steps for the prevention of osteoporosis and risk of fractures in postmenopausal women.

## CONCLUSIONS

The decreased estrogen during menopause results in accelerated bone remodeling as reflected by altered levels of markers of bone turnover. These markers can be measured in serum and urine, are simple to analyses, are inexpensive and hence can be effectively used for the detection and monitoring of bone turnover in postmenopausal women. Early identification of osteoporotic changes helps in early intervention and management thereby preventing the risk of fractures as well as improving the quality of life of postmenopausal women.

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