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ORIGINAL ARTICLE

Thyroid and Bone Remodeling Markers in Premenopausal and Postmenopausal Women: A Multivariate Machine Learning Approach

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ABSTRACT

Introduction: Menopause induces significant hormonal shifts that may impact thyroid function and bone metabolism. This study aimed to compare thyroid profile (FT3, FT4, and TSH) and bone remodeling (serum calcium, phosphorus, and ALP) markers between premenopausal and postmenopausal women and to examine their predictive ability via multivariate and machine learning methods.

Method: This cross-sectional study was performed among 178 women (89 premenopausal, 89 postmenopausal) attending Manmohan Memorial Teaching Hospital (MMTH), Kathmandu, Nepal. Serum levels of FT3, FT4, TSH, calcium, phosphorus, and ALP were estimated using standard methods. Statistical analyses were carried out by using Mann–Whitney U tests, Spearman correlations, MANOVA, PCA, ANCOVA, and classification models such as logistic regression, LDA, SVM, and random forest.

Result: Postmenopausal women had markedly higher TSH and ALP levels, wereas lower serum calcium and phosphorus levels. MANOVA revealed a significant multivariate effect of menopausal status (Wilks'λ= 0.6818, p <0.001). Furthermore, the data were analyzed via machine learning models such as PCA, logistic regression and random forest. PCA revealed partial group separation. Among the different classification models, random forest performed better, with 81% accuracy, whereas LDA and logistic regression attained 78% accuracy. ALP and serum calcium were the most discriminative features. ANCOVA revealed that age, rather than menopausal status, significantly predicted calcium levels. A partial correlation confirmed a positive association between FT4 and calcium independent of age.

Conclusion: Menopausal status significantly affects the levels of thyroid and bone remodeling markers. ALP and calcium serve as strong discriminators of the menopausal state. Integrating endocrine and bone biomarkers with multivariate and machine learning models improves diagnostic insight into menopause-related physiological changes.

Key words: **Menopause; Thyroid function; Bone remodeling; Serum calcium; Alkaline phosphatase; Multivariate analysis; Machine learning**

INTRODUCTION

Menopause is a natural phenomenon characterized by permanent cessation of the menstrual cycle due to depletion of ovarian follicles and reduced estradiol and progesterone production, which are characterized by elevated FSH and LH levels[1]. In general, the menopausal transition is the period between menopause and the commencement of erratic monthly cycles, which are typically accompanied by certain menopausal symptoms[2]. The activity of ovarian follicular and reproductive life is stopped at this time. Chronological and ovarian aging are two simultaneous mechanisms that affect the length and speed of the menopausal transition[1]. The symptoms of thyroid dysfunction and menopause may coincide, causing difficulties in detecting thyroid disorders in postmenopausal women[3].

Thyroid hormones (THs) play a vital and age-dependent role in bone physiology by regulating both formation and resorption through genomic and nongenomic actions, primarily via TRα in skeletal tissue[4,5]. During the growth phase in childhood and adolescence, they promote ossification and skeletal maturation. In adulthood, excess thyroid hormone increases bone resorption and loss, and deficiency slows bone turnover and reduces bone quality. Disorders such as hyperthyroidism and hypothyroidism lead to bone-related problems, such as altered bone mass, delayed maturation, or increased fracture risk[4]. These effects are influenced by growth hormones, insulin-like growth factor (IGF-1), sex hormones, and vitamin D, highlighting the importance of thyroid function for bone health[4,5]. In postmenopausal women, age-related endocrine changes, including natural decreases in estrogen and alterations in thyroid function, disrupt this balance, increasing susceptibility to osteoporosis and fracture risk. The frequency of hypothyroidism increases with age, and hypothyroidism often remains undiagnosed because symptoms overlap with those of menopause, slowing bone modeling and impairing the quality of bone. However, a study by Bassett *et al.* in 2016 among patients with subclinical hypothyroidism revealed no consistent association with fracture risk, highlighting the greater skeletal impact of low TSH levels even within the subclinical range6. Alternatively, hyperthyroidism, including the subclinical type, can accelerate bone resorption, reduce bone mineral

density (BMD), and markedly increase the risk of vertebral and hip fractures[7]. Moreover, long-term high-dose thyroxine therapy, especially in thyroid cancer management requiring TSH suppression, can further compromise skeletal integrity[5]. Hence, routine thyroid screening and personalized treatment approaches are essential for preserving bone health in postmenopausal women[8].

Bone metabolism is often assessed via the use of serum calcium, inorganic phosphorus, and alkaline phosphatase (ALP), which serve as primary biomarkers. In postmenopausal women, a significant decline in serum calcium levels alongside elevated ALP suggests increased bone turnover and impaired mineral homeostasis[9]. The process of ossification requires ALP, an essential enzyme that facilitates the hydrolysis of organic phosphate esters and promotes mineral deposition by enhancing calcium–phosphate complex formation[10]. In contrast, the deposition of inorganic phosphorus and elevated ALP levels positively correlate with the number of years since menopause, reflecting progressive skeletal remodeling and possible demineralization. Notably, a significant inverse correlation between serum calcium and ALP indicates an imbalance in bone resorption and formation, which contributes to the risk of osteoporosis in aging women[11].

Although studies have suggested that menopause and thyroid dysfunction play independent roles in bone health, few interdisciplinary studies have investigated how thyroid and bone markers interact across the menopausal transition. In particular, serum levels of free triiodothyronine (FT3), free thyroxine (FT4) and thyroid-stimulating hormone (TSH) may offer insights into hormonal regulation, whereas biochemical markers such as calcium, phosphorus, and alkaline phosphatase (ALP) provide quantitative indicators of bone metabolism.

Hence, exploring the dynamic relationships among these markers can improve proactive detection of vulnerable individuals and support the development of prophylactic frameworks. This study aims to evaluate and juxtapose thyroid and bone remodeling markers between premenopausal and postmenopausal women and to scrutinize their multivariate predictive modeling via both conventional statistical methods and modern machine learning approaches.

METHODS

Study Design and Participants

A cross-sectional study was conducted at Manmohan Memorial Teaching Hospital among healthy premenopausal and postmenopausal women. A total of 178 women visiting the hospital were recruited, of whom 89 were premenopausal and 89 were postmenopausal. Informed consent was obtained from all the patients prior to sample collection. Menopausal status was defined clinically on the basis of menstrual history: premenopausal women had regular menstrual cycles, whereas postmenopausal women had experienced amenorrhea for at least 12 consecutive months. Healthy women between the ages of 18 and 85 years were included, whereas patients with known endocrine disorders, chronic conditions affecting bone health (chronic kidney disease, malabsorption disorders), and systemic diseases such as hypertension and diabetes were excluded from the study.

Biochemical measurements

Venous blood was collected in the morning after overnight fasting (8–10 hours). The serum calcium and phosphorus levels were measured via standard colorimetric methods, and alkaline phosphatase (ALP) levels were determined enzymatically (Biosystem S.A., Barcelona, Spain). Serum free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) concentrations were measured via a fully automated chemiluminescence immunoassay analyzer (MAGLUMI X3, Snibe Diagnostics, Shenzhen, China). Both the intra- and interassay coefficients of variation were within the analytical performance limit (<10%), and test performance was carried out in compliance with the manufacturer's instructions.

Statistical analysis

Data analysis was performed via Python 3.10.12 within the Google Colaboratory (Colab) environment, which is a cloud-based interactive platform that enables statistical computing, data visualization, and machine learning implementation. The Shapiro–Wilk test was used to assess the normality of the distribution, and for nonnormally distributed data, medians with interquartile ranges (IQRs) were calculated. Nonparametric comparisons between groups were performed via the Mann–Whitney U test, and effect sizes were calculated via Cohen's d. Moreover, Spearman correlation analysis, MANOVA, and PCA were used among different biochemical markers to identify associations, visualize the clustering pattern, and determine the multivariate impact on menopausal status. For evaluation of biomarker predictive potential, classification models such as logistic regression, LDA, SVM, and random forest were used, whereas ANCOVA and partial correlation analyses were used to determine the influence of age on calcium and FT4 levels; significance was set at $p < 0.05$.

RESULTS

The study included a total of 178 women, of whom 89 were categorized into premenopausal and postmenopausal groups on the basis of menstrual status, with median ages of 34 years (IQR: 27-39) and 54 years (IQR: 50-60), respectively.

Biochemical differences between groups

Compared with premenopausal women, postmenopausal women presented distinct biochemical patterns (Table 1). These patients had higher levels of TSH (3.65 μIU/mL [IQR: 1.69–7.20] vs. 2.52 μIU/mL [IQR: 1.70–4.24], $p = 0.038$) and ALP (95 IU/L [IQR: 84–110] vs. 72 IU/L [IQR: 63–82], $p < 0.0001$). In contrast, Calcium and Phosphorus levels were lower in the postmenopausal group (Calcium: 8.70 mg/dL [IQR: 8.00–9.20] vs. 9.20 mg/dL [IQR: 8.90–9.70], $p < 0.0001$;

Phosphorus: 4.00 mg/dL [IQR: 3.60–4.30] vs. 4.20 mg/dL [IQR: 4.00–4.40], p = 0.0013). Effect size analysis revealed the largest difference for ALP (d = -1.08), followed by Calcium (d = 0.81) and Phosphorus (d = 0.52). No significant differences were found for FT3 or FT4 levels.

Table 1: Baseline characteristics and biochemical parameters of premenopausal and postmenopausal women

Marker	Pre-Median (IQR)	Post-Median (IQR)	Mann-Whitney U p-value	Cohen's d
FT3	3.52 (3.17-3.87)	3.38 (2.99-3.78)	0.173	0.34
FT4	12.10 (11.20-13.30)	12.90 (11.50-14.00)	0.123	-0.12
TSH	4.17 (1.70-4.24)	3.65 (1.69-7.20)	0.038*	-0.25
Calcium	9.32 (8.90-9.70)	8.70 (8.00-9.20)	<0.001*	0.81
Phosphorus	4.20 (4.00-4.40)	4.00 (3.60-4.30)	0.0013*	0.52
ALP	72.00 (63.00-82.00)	95.00 (84.00-110.00)	<0.001*	-1.08

* Mann-Whitney U test

Correlation patterns

Spearman correlation analysis revealed significant differences between the groups (Figures 1 and 2). In premenopausal women, only a moderate positive correlation was observed between serum calcium and phosphorus (ρ = 0.46). In contrast, postmenopausal women presented stronger patterns, including significant negative correlations of TSH with both FT3 (ρ= -0.54) and calcium (ρ= -0.62) and a moderate positive correlation between FT3 and calcium (ρ = 0.38). These changes indicate that thyroid–calcium interactions become more pronounced after menopause.

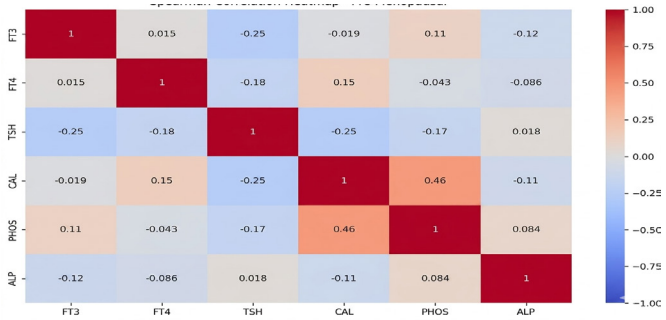

Figure 1: Spearman correlation matrix for premenopausal women showing a moderate positive association between calcium and phosphorus (ρ = 0.46)

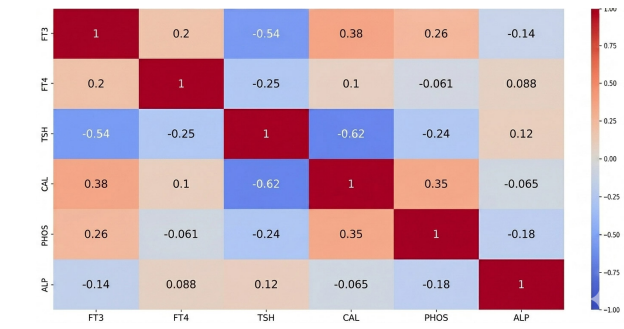

Figure 2: Spearman correlation matrix for postmenopausal women showing significant negative associations of TSH with FT3 (ρ = –0.54) and calcium (ρ = –0.62), and a positive correlation between FT3 and calcium (ρ = 0.38).

Multivariate and dimensionality reduction analyses

Table 2 shows that multivariate analysis of variance (MANOVA) revealed significant differences in the combined biomarker profile between the two groups (Wilks'λ = 0.682, F(6,171) = 13.30, p < 0.001). The findings were supported by other test statistics (Pillai's trace = 0.318; Hotelling–Lawley trace = 0.467; Roy's greatest root = 0.467), establishing the robustness of the findings. Principal component analysis (PCA) revealed that the first two components (PC1 vs PC2) explained 58% of the total variance, with partial but incomplete clustering by menopausal status (Figures 3-4).

Table 2: Multivariate test statistics from MANOVA examining the effect of menopausal status on six biochemical variables.

Test Statistic	Value	Num DF	Den DF	F Value	p-value
Wilks' Lambda	0.682	6	171	13.30	<0.001
Pillai's Trace	0.318	6	171	13.30	<0.001
Hotelling-Lawley Trace	0.467	6	171	13.30	<0.001
Roy's Greatest Root	0.467	6	171	13.30	<0.001

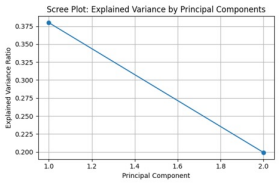

Figure 3: Scree plot of PCA components indicating variance contribution by each principal component.

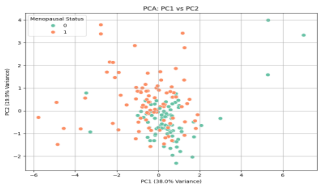

Figure 4: Principal Component Analysis (PCA) projection of biochemical data onto the first two principal components.

Predictive modeling

Binary logistic regression (Figure 5) achieved an accuracy of 78% and an area under the ROC curve (AUC) of 0.85, indicating strong discriminatory ability. The model demonstrated balanced classification performance (F1 score ≈ 0.78) for both groups. ALP (β = 1.37, OR = 3.95) appeared to be the strongest predictor of postmenopausal status, followed by FT4 (β = 0.32, OR = 1.37). Calcium had the strongest negative association (β = -1.02, OR = 0.36), with smaller negative effects from TSH, FT3, and phosphorus.

One-dimensional projection from the linear discriminant analysis (Figure 6) performed similarly, with an accuracy of 78%. ALP (+1.14) and FT4 (+0.36) contributed most positively to the postmenopausal classification, whereas calcium (-0.80) was the largest negative contributor, with smaller negative contributions from FT3 (-0.20), TSH (-0.11), and phosphorus (-0.15).

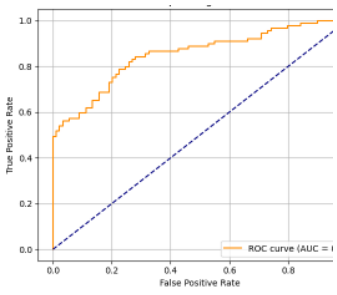

Figure 5: ROC curve for binary logistic regression predicting menopausal status

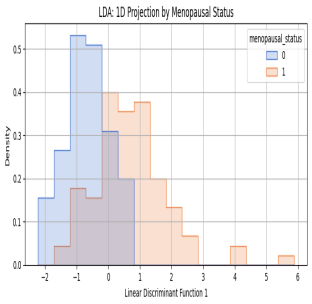

Figure 6: Linear Discriminant Analysis (LDA) 1D projection of biochemical features used to classify menopausal status

Age-adjusted associations

Partial correlation analysis revealed a significant positive association between serum FT4 and calcium after adjusting for age (r = 0.233, 95% CI: 0.09–0.37, p = 0.0018). The partial regression plot (Figure 7) revealed age-related variability and a steady trend in the regression line and confidence band. Furthermore, ANCOVA results (Figure 8) confirmed that menopausal status was not a significant predictor of calcium levels (p = 0.51), whereas age remained significant (p = 0.003).

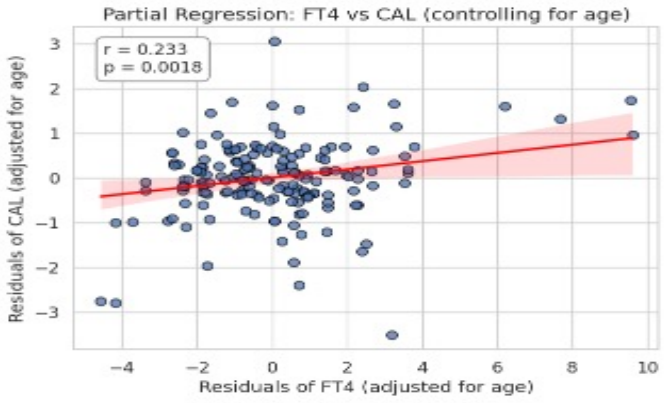

Figure 7: Partial regression plot showing a positive association between FT4 and calcium after adjusting for age (r = 0.233, p = 0.0018).

Machine learning performance

The random forest model outperformed with an accuracy of 81%, followed by the SVM model with slightly lower accuracy (75%). Among these features, alkaline phosphatase (ALP) was found to be a significant predictor, with a feature importance score of 0.32, followed by calcium (0.32). TSH and FT3 contributed moderately (0.15 and 0.14), whereas FT4 and phosphorus made the smallest contributions (Figure 9). The random forest model was found to be excellent in classifying ALP, calcium, and TSH as the top three predictors of menopausal status on the basis of feature importance.

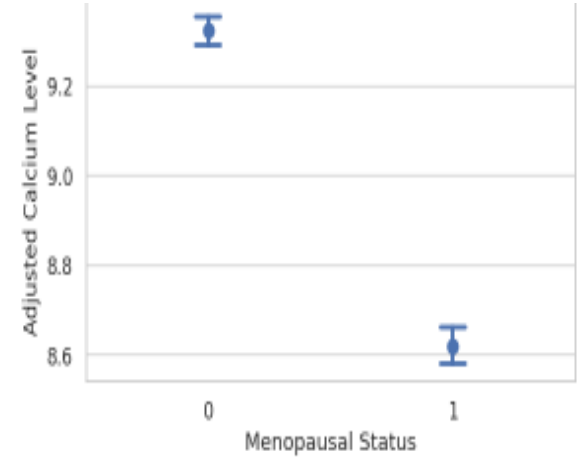

Figure 8: ANCOVA results showing that menopausal status was not a significant predictor of calcium (p = 0.51), while age had a significant effect (p = 0.003).

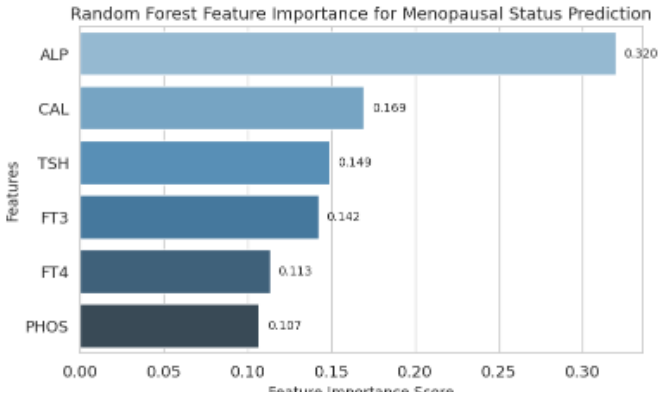

Figure 9: Feature importance plot for the Random Forest model, which achieved an accuracy of 81%. ALP (0.32), calcium (0.17), and TSH (0.15) were the top predictors, with FT3, FT4, and phosphorus contributing less.

DISCUSSION

This study examined substantial physiological changes associated with menopause, with a unique biochemical variable in postmenopausal women compared with premenopausal women. There was a significantly greater level of ALP and lower serum calcium and phosphorus in postmenopausal women than in premenopausal women, with ALP showing a greater effect size, indicating increased bone turnover, which might be due to estrogen deficiency. Additionally, a significant reduction in serum calcium and phosphorus suggested that altered mineral metabolism was associated with the menopausal transition. These findings align with those of studies by Bhadarge *et al.* and Dhungana *et al.*; however, the serum phosphorus level in postmenopausal women was greater than that reported in our study[12-13]. Similarly, a number of studies have reported an increase in phosphorus levels among postmenopausal women in comparison with premenopausal women, whereas the remaining parameters were in agreement with our study[14–16]. The development of estrogen insufficiency affects sodium phosphate transporter regulation, which diminishes phosphaturia, causing elevated phosphate levels[17-18]. Similarly, the levels of alkaline phosphatase and phosphorus were elevated among postmenopausal women with and without diabetes[19]. Moreover, TSH tends to increase with menopause compared with premenopausal women; however, there was no significant variation in FT3 and FT4 levels. These findings are consistent with those of studies by Chandrashekhar (2018), Konalu *et al.* (2019) and Nagarajaiah *et al.* (2021), who reported similar trends across diverse cohorts[20–22]. The increase in TSH in postmenopausal women is attributable to age-dependent changes in hypothalamic pituitary thyroid axis sensitivity, an increased incidence of autoimmune thyroiditis and changes in thyroid hormone metabolism due to estrogen deficiency[8].

In our study, postmenopausal women presented significant negative associations of TSH with FT3 (ρ = -0.54) and calcium (ρ = -0.62), suggesting enhanced thyroid-calcium interactions after menopause. There were weak associations among biochemical markers in premenopausal women, with

a moderate correlation between calcium and phosphorus (ρ = 0.46). A recent case–control study reported a significant negative correlation between TSH and serum calcium levels (r ≈ -0.52 for total calcium and -0.48 for ionized calcium, p < 0.05) in postmenopausal women with hypothyroidism[23].

Multivariate analysis revealed a significant difference in overall biochemical parameters between premenopausal and postmenopausal women (Wilks' λ = 0.682, F (6, 171) = 13.30, p < 0.001), indicating that these markers are influenced by the menopausal transition. However, there was some overlap between the groups, which suggests individual variability, and only some of the biomarkers may be responsible for group differences according to principal component analysis (PCA). This finding was further supported by a logistic regression model that demonstrated good accuracy in classifying menopausal status, such as ALP and calcium, as the most influential predictors and highlighted their potential use in identifying postmenopausal physiological shifts. Additionally, after adjusting for age, partial correlation analysis revealed a significant positive association between FT4 and serum calcium levels, suggesting a potential link between thyroid function and calcium homeostasis independent of age-related effects.

Among the different machine models assessed, the random forest classifier obtained the highest predictive accuracy (81%) in classifying menopausal status on the basis of biochemical markers. Furthermore, the feature importance score indicated that ALP, serum calcium and TSH were the most influential features that described the importance of thyroid function and bone metabolism in differentiating menopausal stages. On the other hand, the support vector machine (SVM) showed lower performance, with an accuracy of 75%, and the findings indicate that the random forest classifier provided superior classification performance and interpretable insight into the most relevant indicators of menopausal status. Analysis of covariance (ANCOVA) revealed that menopausal status was not a significant predictor of calcium levels after adjusting for age (p = 0.507), whereas age remained a strong independent predictor (p = 0.003). A substantial positive correlation between FT4 and calcium was found via partial correlation (r = 0.23, p = 0.0018), indicating that thyroid function may have a direct effect on calcium regulation regardless of age.

The limitation of the study was that it was cross-sectional, which limits the causal inference between hormonal changes and bone health. Bone mineral density was not measured, and probable confounders such as vitamin D status, diet, and physical activity were not assessed. These factors should be included in future longitudinal research to better clarify the observed associations.

CONCLUSIONS

This study revealed that postmenopausal women exhibit a significant metabolic shift characterized by elevated levels of ALP and TSH, alongside reduced serum calcium and phosphorus. Further correlation analyses revealed a meaningful association between the levels of thyroid hormones, mainly FT4, and serum calcium, which suggests a possible regulatory link independent of age.

Multivariate and machine learning methods confirmed the strong ability of the random forest algorithm to classify major biomarkers with the highest accuracy, followed by logistic regression, linear discriminant analysis (LDA), and support vector machines (SVMs). Serum calcium and ALP were the most significant variables across all the models, confirming their pivotal role in bone remodeling among postmenopausal women. The menopause transition appears to modify the interrelation through modifications in thyroid bone dynamics, even though age was a significant predictor of calcium level according to ANCOVA.

In summary, this study revealed that menopausal status significantly influences routine biomarkers, such as ALP, calcium, and TSH, particularly thyroid and bone-related markers. It is therefore recommended that screening of routine biomarkers enables early detection and management of bone and thyroid dysfunction in postmenopausal women.

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CONFLICT OF INTEREST

The authors declare no competing interests

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