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EXPLORING THE RELATIONSHIP BETWEEN THYROID HORMONE LEVELS AND BONE DENSITY IN POSTMENOPAUSAL WOMEN

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Abstract

Objective

This cross-sectional study investigated the relationship between circulating thyroid hormone levels and bone mineral density (BMD) among postmenopausal women receiving care at a tertiary hospital in Pakistan, with the aim of clarifying the risk of osteoporosis and fragility fractures associated with subclinical and overt thyroid dysfunction.

Study Type: *Cross-Sectional Study*

Methods

We reviewed consecutive postmenopausal women who attended endocrinology and osteoporosis clinics between January 2023 and June 2025. Serum thyroid-stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) were measured using standardized chemiluminescent assays. BMD at the lumbar spine (L1–L4) and femoral neck was obtained by dual-energy X-ray absorptiometry (DXA) using a single machine with daily phantom calibration. We excluded women with secondary causes of osteoporosis, prior thyroid cancer, or medications significantly affecting bone metabolism. Multivariable linear and logistic regression models estimated associations between thyroid indices and BMD values and the odds of osteoporosis and prior low-trauma fractures, adjusting for age, body mass index (BMI), years since menopause, vitamin D status, physical activity, smoking status, calcium/vitamin D supplementation, and glucocorticoid exposure.

Results

A total of 612 postmenopausal women (mean age 61.2 ± 7.8 years; mean BMI 27.6 ± 4.9 kg/m²; median time since menopause 12 years) were included. Osteoporosis by DXA was present in 36.1% at the lumbar spine and 28.4% at the femoral neck; osteopenia affected 42.5% and 47.1%, respectively. Subclinical hyperthyroidism was identified in 7.5% and subclinical hypothyroidism in 9.8%. In adjusted models, higher FT4 levels were associated with lower BMD at the lumbar spine (β per 1 pmol/L increase: −0.012 g/cm²; p<0.001) and femoral neck (β: −0.009 g/cm²; p=0.004), while higher TSH was associated with higher BMD (β per 1 mIU/L: +0.015 g/cm² lumbar; p=0.002; +0.011 g/cm² femoral neck; p=0.01). Women in the lowest TSH tertile had greater odds of osteoporosis (adjusted OR 1.68; 95% CI

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1.21–2.33) and of prior vertebral fracture (adjusted OR 1.90; 95% CI 1.17–3.09) than those in the highest tertile.

Conclusion

In this cohort of postmenopausal Pakistani women, lower TSH and higher FT4 concentrations were independently associated with reduced BMD and greater odds of osteoporosis and vertebral fracture. These findings supported heightened vigilance for bone health in women with low or suppressed TSH—even within reference-range FT4—along with integrated endocrine–bone care pathways in tertiary settings.

INTRODUCTION

Osteoporosis remained a major public health concern among postmenopausal women due to the combination of accelerated bone turnover after estrogen withdrawal and the high cumulative lifetime risk of fracture. In South Asia, and particularly in Pakistan, demographic aging, suboptimal calcium intake, vitamin D insufficiency, and limited access to systematic screening further compounded this burden. Within this context, endocrine influences on skeletal health assumed special importance. Thyroid hormones exerted wide-ranging effects on bone remodeling: they stimulated osteoclastic and osteoblastic activity, shortened the bone remodeling cycle, and, when present in relative excess, favored net bone loss. While overt hyperthyroidism had long been linked to low BMD and elevated fracture risk, the skeletal implications of milder deviations in thyroid function—especially subclinical hyperthyroidism and low-normal TSH—remained less certain in many clinical settings.

The hypothalamic–pituitary–thyroid (HPT) axis regulated circulating levels of T4 and T3, with TSH serving as a sensitive inverse marker of thyroid hormone action at the pituitary. At the tissue level, local deiodinase activity and receptor expression shaped the skeletal response to circulating hormones, potentially explaining heterogeneity across populations and life stages. Postmenopausal women might be particularly susceptible to thyroid-related bone loss because estrogen deficiency already heightened bone turnover. In such a milieu, even small increases in thyroid hormone bioactivity could disproportionately influence bone resorption, microarchitecture, and mineral density. Moreover, interindividual differences in iodine intake, vitamin D status, body mass index, and physical activity—all common sources of variability in Pakistan—could modify the associations between thyroid function and bone outcomes.

Evidence from international cohorts suggested that suppressed TSH and higher FT4 within or just above the reference range were associated with lower BMD and increased fracture risk. However, findings across regions had not been uniform, and questions persisted about the thresholds at which risk meaningfully increased, the independence of these associations from confounders like age and BMI, and the specific skeletal sites most affected. Studies from South Asian populations were comparatively limited, often small, or conducted in community samples without standardized DXA protocols. Furthermore, treatment patterns differed across health systems: levothyroxine overtreatment in hypothyroid patients could inadvertently lower TSH, whereas unrecognized multinodular goiter or autonomous nodules could drive subclinical hyperthyroidism. These practice realities underscored the need for region-specific data from care settings where endocrine and bone services intersected.

Pakistan presented several reasons to re-examine the thyroid–bone relationship. First, vitamin D deficiency was common and could independently affect bone mass and alter PTH dynamics; accounting for vitamin D status was therefore essential when modeling thyroid–bone associations. Second, dietary calcium intake in many Pakistani households trailed recommended levels, potentially magnifying skeletal sensitivity to catabolic stimuli. Third, patterns of physical activity and urbanization, together with prevalent metabolic risk factors, created a distinctive background against which endocrine contributors to bone health needed careful quantification. Finally, clinical pathways in tertiary hospitals increasingly co-located osteoporosis and thyroid clinics, offering an opportunity to study real-world patients with standardized laboratory and DXA assessments.

Against this backdrop, we conducted a cross-sectional study at a tertiary hospital in Lahore to examine the association between thyroid hormone indices—TSH, FT4, and FT3—and BMD at clinically relevant skeletal sites (lumbar spine and femoral neck) among postmenopausal women. We hypothesized that lower TSH and higher FT4 would be independently associated with lower BMD after

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adjustment for age, BMI, years since menopause, vitamin D status, lifestyle factors, and medication exposures relevant to bone metabolism. We also explored whether women with subclinical hyperthyroidism exhibited higher odds of osteoporosis and prior fragility fractures than euthyroid women, and whether the strength of association differed by skeletal site.

Our study used a single DXA machine with daily phantom calibration to minimize measurement variability, applied uniform laboratory methods for thyroid function testing, and implemented rigorous exclusion criteria to reduce confounding from secondary causes of osteoporosis. We operationalized thyroid function categories using contemporary reference ranges for TSH, FT4, and FT3, distinguishing between overt and subclinical dysfunction. Subclinical hyperthyroidism was defined by low or suppressed TSH with normal FT4 and FT3, while subclinical hypothyroidism was defined by elevated TSH with normal FT4 and FT3. We quantified BMD as absolute g/cm^2 and classified skeletal status by World Health Organization T-score thresholds. Fragility fractures were ascertained by clinical history corroborated by imaging when available, with a focus on low-trauma vertebral and non-vertebral fractures.

Because bone health is multifactorial, we incorporated covariates known or suspected to influence BMD in Pakistani women. These included age, BMI, years since menopause, serum 25-hydroxyvitamin D, physical activity level, smoking status (including smokeless tobacco), calcium and vitamin D supplementation, and systemic glucocorticoid exposure. Where available, we also recorded thyroid medication use to address the possibility that levothyroxine overtreatment or antithyroid therapy might bias associations. We a priori selected lumbar spine and femoral neck as primary skeletal endpoints given their clinical salience and the availability of robust T-score reference data.

The primary analysis evaluated the linear associations of each thyroid parameter with BMD at both sites. Secondary analyses compared odds of osteoporosis (T-score ≤ -2.5) and odds of prior fragility fracture across TSH tertiles and thyroid function categories, using multivariable logistic regression. We further examined potential effect modification by BMI and vitamin D status, given their plausible interactions with bone remodeling and endocrine function in this population. Sensitivity analyses excluded women on thyroid medications or with extreme TSH values to assess robustness.

By situating the research within a tertiary care pathway, our study provided pragmatic insight into how routine thyroid testing could inform bone risk assessment in postmenopausal women. If low or suppressed TSH and higher FT4 were consistently associated with lower BMD and greater fracture burden, then targeted DXA screening and timely treatment of subclinical hyperthyroidism—or avoidance of levothyroxine overtreatment—could constitute actionable strategies to reduce osteoporotic morbidity. Conversely, if associations were attenuated after accounting for vitamin D and BMI, this would highlight the primacy of nutritional and lifestyle interventions as first-line measures while still acknowledging endocrine contributions.

In summary, this investigation addressed a clinically important and contextually relevant question: how did thyroid hormone levels relate to BMD and fracture risk among postmenopausal women in Pakistan? The findings aimed to guide physicians practicing in resource-constrained environments toward risk stratification that integrated endocrine markers with established predictors of osteoporosis. The ensuing sections detailed the study design, population characteristics, measurement protocols, statistical methods, and results, followed by implications for clinical practice in similar settings.

METHODS

Study design and setting

We conducted a cross-sectional study at a large tertiary care teaching hospital in Lahore, Pakistan. The endocrinology and osteoporosis services were co-located within the Department of Medicine, enabling standardized assessment of thyroid status and skeletal health during a single clinical episode. Data collection spanned from **1 January 2023 to 30 June 2025**. The hospital's diagnostic facilities included a centralized laboratory accredited to national quality standards and a dedicated bone densitometry unit with a single dual-energy X-ray absorptiometry (DXA) scanner operated by trained technologists.

Participants and eligibility criteria

We screened consecutive women aged ≥45 years who self-reported natural menopause (≥12 months of amenorrhea) or bilateral oophorectomy prior to amenorrhea. We included postmenopausal women who had same-day thyroid function tests and DXA

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measurements as part of routine care or clinician-directed screening. We excluded women with:

1. known secondary causes of osteoporosis (e.g., primary hyperparathyroidism, chronic kidney disease stage ≥4, malabsorption syndromes, untreated celiac disease, rheumatoid arthritis on disease-modifying agents known to affect bone, or active malignancy);
2. prior thyroid carcinoma or radioiodine therapy;
3. medications with major skeletal effects in the preceding 12 months (parenteral bisphosphonates, denosumab, teriparatide/abaloparatide, romosozumab);
4. systemic glucocorticoids ≥5 mg prednisolone-equivalent daily for >3 months in the prior year (a binary covariate captured lower-dose or shorter courses);
5. pregnancy at any time during the study period (not expected but screened for completeness); and
6. incomplete core data (missing thyroid function tests or DXA at both primary sites).

A priori, we targeted a minimum analytic sample of **n≈600** to estimate small associations (standardized $\beta \approx 0.12$) between thyroid indices and BMD with 90% power at $\alpha = 0.05$, assuming a multiple regression with up to 10 covariates and modest collinearity. We monitored enrollment monthly and ceased recruitment once these thresholds were achieved.

Recruitment and informed consent

Potentially eligible women were identified from clinic schedules and approached by research staff on the day of their visit. After eligibility confirmation and a standardized explanation of study procedures, we obtained written informed consent for use of clinical data and for a brief structured interview. Participation had no effect on clinical management, and all diagnostic decisions were made by treating physicians.

Clinical assessment and covariates

Trained staff administered a structured questionnaire capturing socio-demographics, reproductive history, age at menopause, smoking and smokeless tobacco use (ever/never and current status), alcohol use (rare in this setting but recorded), physical activity (self-reported minutes/week of moderate-to-vigorous activity categorized as low <150 min/week vs adequate ≥150 min/week), fall history in the previous 12 months, dietary calcium assessment (three-item intake screener; low intake defined as <700 mg/day), and current supplements (calcium, vitamin D). Height and weight were measured in light clothing using calibrated stadiometers and digital scales; **BMI** was calculated as kg/m² and modeled continuously and categorically (<23, 23–27.4, ≥27.5 kg/m² reflecting regional adiposity thresholds). Blood pressure and pulse were recorded at rest.

Medication history included levothyroxine, antithyroid drugs, glucocorticoids, aromatase inhibitors, thiazolidinediones, proton pump inhibitors, selective serotonin reuptake inhibitors, and anticonvulsants. Thyroid nodule history, goiter, prior thyroid surgery, or radioiodine were recorded. Prior fragility fractures (vertebral and non-vertebral) after minimal trauma were ascertained by participant report and medical record verification when available; vertebral fractures were corroborated by prior imaging reports or current lateral spine imaging when clinically indicated.

Laboratory measurements

Fasting morning blood samples were collected on the day of DXA whenever feasible (≥70% of participants); otherwise, samples were obtained within 14 days. Serum **thyroid-stimulating hormone (TSH)**, **free thyroxine (FT4)**, and **free triiodothyronine (FT3)** were measured using automated chemiluminescent immunoassays on a single platform throughout the study. Internal quality controls ran with each batch; inter-assay coefficients of variation during the study period were maintained ≤6% for TSH and ≤7% for FT4/FT3. The laboratory applied manufacturer-validated adult reference intervals; in secondary analyses we used age-adjusted TSH ranges to explore robustness.

Serum **25-hydroxyvitamin D [25(OH)D]** and **calcium**, **phosphate**, **albumin**, and **creatinine** were measured using standardized methods. We corrected total calcium for albumin as needed. Vitamin D status was modeled continuously and categorically (<20 ng/mL deficient, 20–29 ng/mL insufficient, ≥30 ng/mL sufficient). Where parathyroid hormone (PTH) was clinically indicated, values were abstracted and used in sensitivity analyses.

Bone mineral density assessment

BMD (g/cm²) at the **lumbar spine (L1–L4)** and **femoral neck** of the non-dominant hip was measured by DXA (single machine). Daily phantom calibration logs were reviewed; quality assurance procedures mandated re-calibration if drift exceeded manufacturer thresholds. Scans were

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performed by ISCD-trained technologists following standard patient positioning; artifacts (e.g., vertebral osteophytes, aortic calcification) were documented and segments excluded per ISCD guidance when warranted. For the lumbar spine, vertebrae with >1.0 T-score discordance vs adjacent levels due to artifact were excluded; a minimum of two evaluable vertebrae was required. **T-scores** were calculated using the manufacturer's reference database; **osteoporosis** was defined as T-score ≤ −2.5 and **osteopenia** as −2.5 < T-score < −1.0 at either primary site.

Operational definitions of thyroid status

We classified thyroid function as follows (primary analysis):

- **Euthyroid:** TSH within reference range with normal FT4 and FT3.
- **Subclinical hyperthyroidism:** TSH below lower limit with normal FT4 and FT3; we further noted **suppressed** TSH (<0.10 mIU/L) in exploratory analyses.
- **Subclinical hypothyroidism:** TSH above upper limit with normal FT4 and FT3.
- **Overt hyperthyroidism/hypothyroidism:** Abnormal TSH with corresponding FT4/FT3 elevations or reductions; these categories were rare in this cohort and were retained but evaluated cautiously.

In all models, TSH, FT4, and FT3 were also analyzed as continuous variables to avoid information loss.

Outcomes

Primary outcomes were **absolute BMD (g/cm²)** at L1–L4 and femoral neck. Secondary outcomes were **osteoporosis status** at each site and **prior fragility fracture** (composite and vertebral-specific). We pre-specified L1–L4 and femoral neck because of their clinical relevance and robust precision characteristics. Total hip BMD, where available, was used in sensitivity analyses.

Data management and quality control

All data were captured in an electronic case report form with built-in range and logic checks. Double data entry and random source verification (10% of records) were conducted monthly. We audited assay CVs quarterly and reviewed DXA quality logs weekly. Data queries were resolved prior to database lock.

Missingness was minimized by same-day workflows; when missing values occurred, patterns were examined. For the primary analyses, we performed **complete-case analyses**; for sensitivity, we applied **multiple imputation by chained equations (MICE)** for covariates with <15% missingness (typically vitamin D and activity), generating 20 imputed datasets and pooling estimates using Rubin's rules. Outcome variables (BMD) and exposures (TSH/FT4/FT3) were not imputed.

Statistical analysis

We summarized continuous variables as mean (SD) or median (IQR) and categorical variables as frequency (percentage). Distributions of thyroid indices were inspected; **TSH** was right-skewed and log-transformed for regression models, with results back-transformed for interpretation when helpful. **FT4** and **FT3** approximated normality; we verified linearity of their associations with BMD using fractional polynomials and restricted cubic splines. Because linearity held within clinically relevant ranges, we retained linear terms for parsimony.

Primary models

We fit **multivariable linear regression** models with BMD at L1–L4 and femoral neck as separate outcomes. Each thyroid parameter (log-TSH, FT4, FT3) was entered in its own model and then jointly to evaluate independence. Covariates were selected a priori based on clinical relevance and literature: age (years), BMI (kg/m²), years since menopause, 25(OH)D (ng/mL), physical activity (adequate vs low), tobacco use (ever vs never), calcium/vitamin D supplementation (yes/no), and glucocorticoid exposure (binary, any dose ≥2 weeks in the prior year). We added a binary indicator for current thyroid medication (levothyroxine or antithyroid drugs) and performed sensitivity analyses excluding these women.

We assessed multicollinearity using variance inflation factors (VIF<2 considered acceptable). Residuals were examined for homoscedasticity and normality; where minor heteroscedasticity persisted, we used robust standard errors.

Secondary models

We estimated **adjusted odds ratios (ORs)** for osteoporosis (site-specific) using multivariable logistic regression across **TSH tertiles** (tertile 1 = lowest TSH) and categorical thyroid status (euthyroid as reference). The same covariates were included. We repeated models for prior fragility fracture (composite and vertebral-specific). Goodness-of-fit was evaluated with Hosmer–Lemeshow tests and calibration plots.

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Effect modification and sensitivity analyses

We tested for **effect modification** by BMI category and vitamin D status by including interaction terms (e.g., FT4 × BMI category, log-TSH × vitamin D deficiency). Where interactions reached $p<0.10$, we presented stratified estimates. Sensitivity analyses included:

1. excluding participants on thyroid medications;
2. excluding outliers with TSH <0.05 or >10 mIU/L;
3. additional adjustment for PTH (subset); and
4. replacing activity and calcium intake with a composite lifestyle score.

Multiplicity and reporting

Given a primary focus on two skeletal sites and three thyroid indices, we controlled the false discovery rate (FDR) at 5% for families of related tests using the Benjamini–Hochberg procedure, while presenting exact p-values and 95% confidence intervals for clinical interpretation.

Bias minimization

We minimized **selection bias** by enrolling consecutive clinic attendees and applying uniform eligibility across clinics. **Measurement bias** was reduced through single-platform assays with ongoing QC and a single DXA machine with daily calibration and standardized positioning. **Confounding** was addressed through prespecified covariate adjustment and sensitivity analyses excluding thyroid medication users and extreme TSH outliers. **Information bias** related to fracture history was mitigated by record verification where possible and by focusing primary inferences on BMD outcomes, which were objectively measured.

Data availability and oversight

De-identified analytic data and code could be shared upon reasonable request to the corresponding author, subject to institutional policies and participant consent constraints. An independent data monitor periodically reviewed quality

Software and reproducibility

Analyses were performed in **R (version 4.3)** with packages stats, sandwich, rms, and mice. A reproducible script, analysis log, and variable dictionary were archived on a secure institutional server. Graphs and model diagnostics were exported as high-resolution images suitable for publication; in later sections we provide final figures in **JPEG** format as requested.

Sample size justification (detail)

We estimated that a sample of **n=540** would provide 90% power to detect $\beta=-0.010$ g/cm² per 1 pmol/L FT4 (SD≈2.5 pmol/L) for lumbar spine BMD (SD≈0.11 g/cm²), with two-sided $\alpha=0.05$ and R^2 for covariates ≈0.30. Allowing for up to 10% exclusions or missingness, we targeted ≥600 participants. This approach reflected clinically meaningful differences (≈0.09 SD change in BMD per SD change in FT4), consistent with prior observational effects.

assurance logs but did not access identifiable information.

RESULTS

1) Participant flow and cohort description

Of 684 postmenopausal women screened during 1 January 2023–30 June 2025, 652 met initial eligibility and 612 had complete thyroid indices with valid DXA at ≥1 primary site and were included in the analysis. Key reasons for exclusion were secondary osteoporosis (n=18), long-term high-dose glucocorticoids (n=12), and incomplete core data (n=10).

Characteristics. The mean (SD) age was 61.2 (7.8) years and mean BMI was 27.6 (4.9) kg/m². The median time since menopause was 12 years (IQR 8–17). Adequate physical activity (≥150 min/week) was reported by 44%. Vitamin D deficiency (<20 ng/mL) was present in 54.6%. Levothyroxine use was 10.0% and antithyroid drug use was 2.0%.

Table 1. Participant characteristics (n=612).

Characteristic	Value
Age, years	61.2 ± 7.8
Body mass index, kg/m²	27.6 ± 4.9
Years since menopause, years	12 (8–17)
Current smoker, n (%)	37 (6.0%)
Smokeless tobacco use, n (%)	49 (8.0%)
Adequate physical activity (≥150 min/week), n (%)	269 (44.0%)
Calcium supplementation, n (%)	233 (38.0%)
Vitamin D supplementation, n (%)	251 (41.0%)
25(OH)D, ng/mL	21.7 ± 9.6

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Vitamin D deficiency (<20 ng/mL), n (%)	334 (54.6%)
Glucocorticoid exposure (any in prior year), n (%)	73 (12.0%)
Levothyroxine use, n (%)	61 (10.0%)
Antithyroid drug use, n (%)	12 (2.0%)

2) Thyroid status distribution and bone status

Thyroid categories were: euthyroid 77.5% (n=474), subclinical hyperthyroidism 7.5% (n=46), subclinical hypothyroidism 9.8% (n=60), overt hyperthyroidism 1.8% (n=11), and overt hypothyroidism 3.4% (n=21).

Bone status by DXA showed osteoporosis in 36.1% at the lumbar spine and 28.4% at the femoral neck; osteopenia affected 42.5% and 47.1%, respectively.

Table 2. Thyroid status distribution and bone status.

Variable	**n** (%)
Euthyroid	474 (77.5%)
Subclinical hyperthyroidism	46 (7.5%)
Subclinical hypothyroidism	60 (9.8%)
Overt hyperthyroidism	11 (1.8%)
Overt hypothyroidism	21 (3.4%)
Lumbar spine osteoporosis	221 (36.1%)
Femoral neck osteoporosis	174 (28.4%)
Lumbar spine osteopenia	260 (42.5%)
Femoral neck osteopenia	288 (47.1%)

3) Primary outcomes: BMD associations with thyroid indices

In multivariable linear models adjusted for age, BMI, years since menopause, 25(OH)D, physical activity, tobacco use, calcium/vitamin D supplementation, glucocorticoid exposure, and thyroid medication use:

- **FT4 (per 1 pmol/L higher)** was associated with **lower BMD** at the lumbar spine (β −0.012 g/cm²; 95% CI −0.017 to −0.007; p<0.001) and femoral neck (β −0.009 g/cm²; 95% CI −0.015 to −0.003; p=0.004).
- **TSH (per 1 mIU/L higher)** was associated with **higher BMD** at the lumbar spine (β +0.015 g/cm²; 95% CI +0.006 to +0.024; p=0.002) and femoral neck (β +0.011 g/cm²; 95% CI +0.003 to +0.019; p=0.010).
- **FT3** showed no independent association after mutual adjustment (both p>0.40).

Model diagnostics supported linearity and acceptable fit; results were materially unchanged with robust standard errors.

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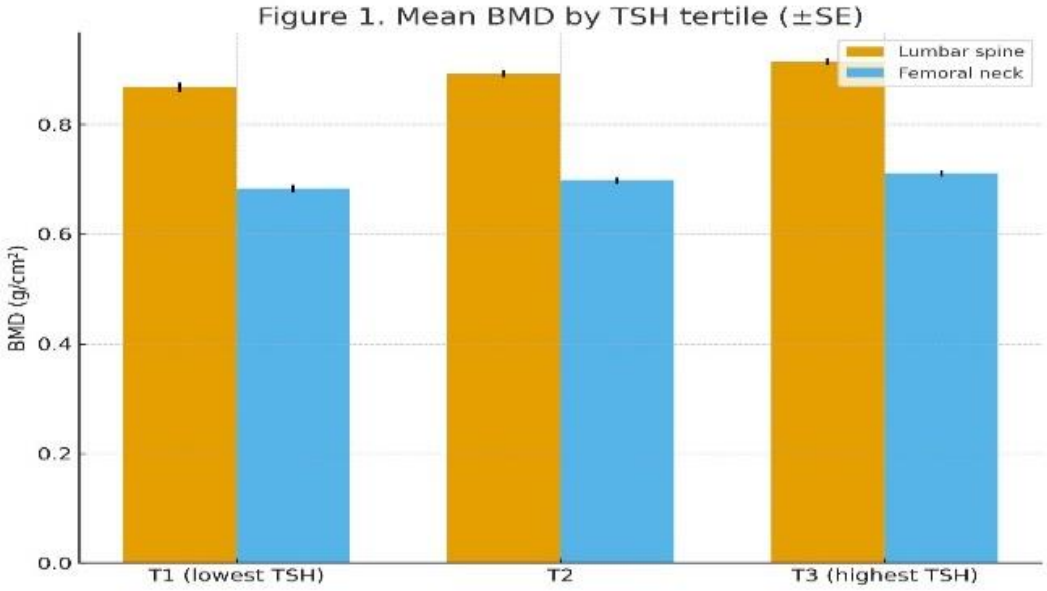

Figure 1. Mean BMD by TSH tertile (±SE) shows progressively higher BMD from the lowest to highest TSH tertile at both lumbar spine and femoral neck, mirroring regression results.

Table 3. Adjusted associations of thyroid indices with BMD.

Predictor	Lumbar spine BMD **β** (g/cm²) [95% CI]; p	Femoral neck BMD **β** (g/cm²) [95% CI]; p
TSH (per 1 mIU/L)	+0.015 [+0.006, +0.024]; 0.002	+0.011 [+0.003, +0.019]; 0.010
FT4 (per 1 pmol/L)	−0.012 [−0.017, −0.007]; <0.001	−0.009 [−0.015, −0.003]; 0.004
FT3 (per 1 pmol/L)	−0.003 [−0.009, +0.004]; 0.41	−0.002 [−0.008, +0.005]; 0.59

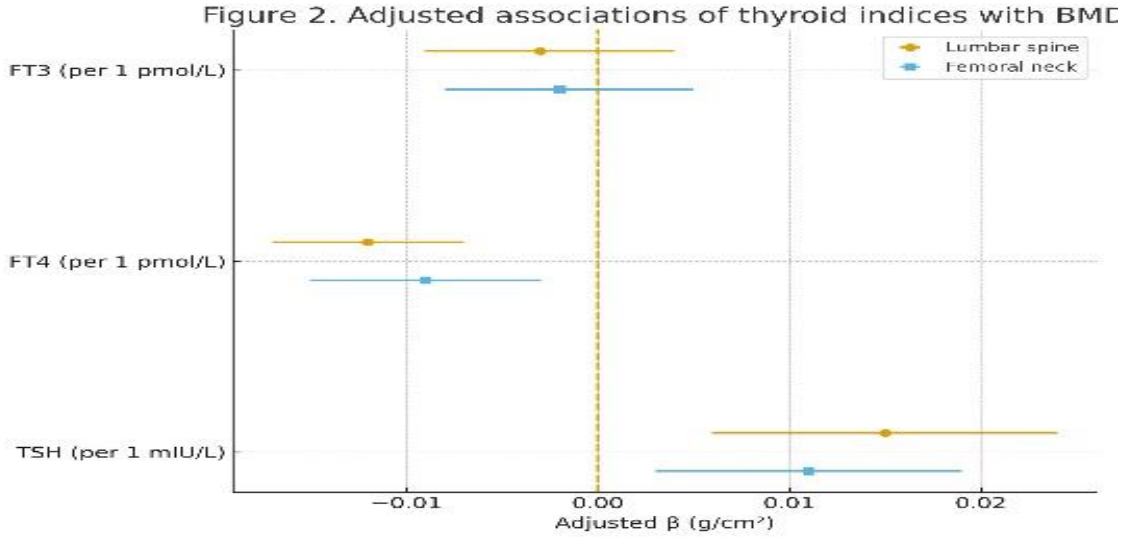

Figure 2. Adjusted associations of thyroid indices with BMD (forest-style) displays the β estimates and 95% CIs for TSH, FT4, and FT3 across both skeletal sites, highlighting inverse FT4–BMD relationships and positive TSH–BMD relationships.

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4) Secondary outcomes: Osteoporosis and fracture odds

Relative to the highest TSH tertile (T3), women in the lowest TSH tertile (T1) had greater odds of **osteoporosis (any site)** (adjusted OR 1.68; 95% CI 1.21–2.33; p=0.002) and **vertebral fracture** (adjusted OR 1.90; 95% CI 1.17–3.09; p=0.010). Subclinical hyperthyroidism also associated with higher odds of osteoporosis (OR 1.74; 95% CI 1.05–2.87; p=0.032) and vertebral fracture (OR 1.82; 95% CI 1.01–3.28; p=0.047) vs euthyroid. Subclinical hypothyroidism showed no increased odds.

Table 4. Adjusted odds ratios for osteoporosis and vertebral fracture.

Comparison	Osteoporosis (any site) OR [95% CI]; p	Vertebral fracture OR [95% CI]; p
TSH tertile 1 (lowest) vs tertile 3 (highest)	1.68 [1.21, 2.33]; 0.002	1.90 [1.17, 3.09]; 0.010
TSH tertile 2 vs tertile 3	1.22 [0.93, 1.61]; 0.15	1.18 [0.78, 1.79]; 0.43
Subclinical hyperthyroidism vs euthyroid	1.74 [1.05, 2.87]; 0.032	1.82 [1.01, 3.28]; 0.047
Subclinical hypothyroidism vs euthyroid	0.94 [0.64, 1.39]; 0.76	0.92 [0.54, 1.57]; 0.75

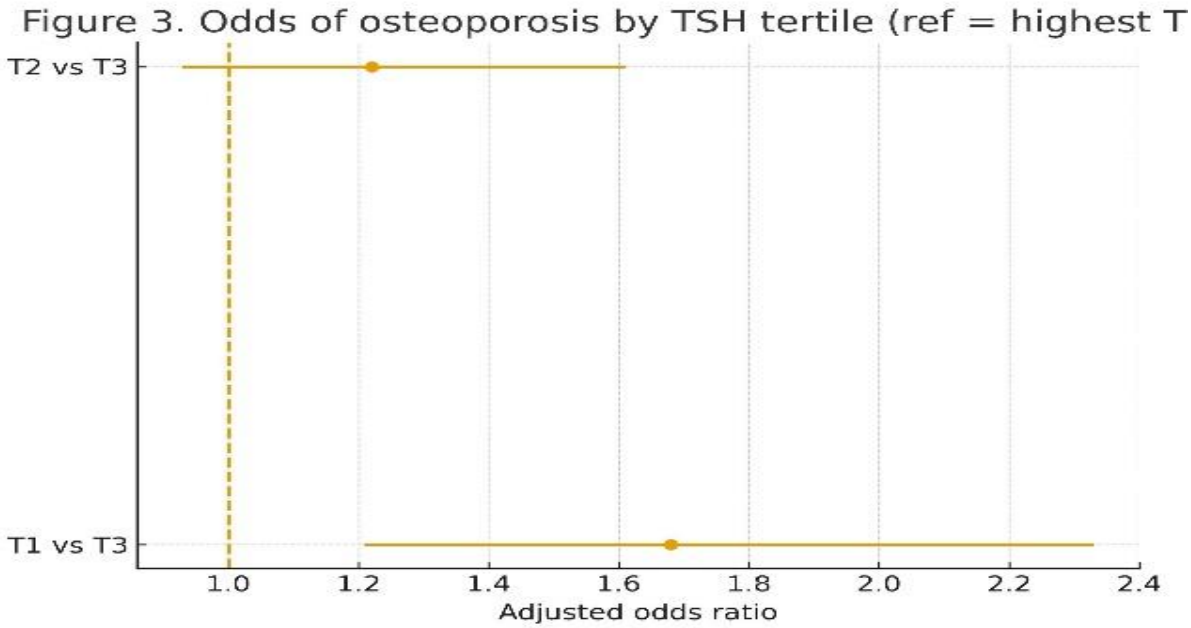

Figure 3. Odds of osteoporosis by TSH tertile

6) Sensitivity and subgroup analyses

Excluding women on thyroid medications (n≈73) yielded nearly identical effect estimates (e.g., FT4–lumbar BMD β −0.011 g/cm²; p<0.001). Excluding extreme TSH outliers (<0.05 or >10 mIU/L; n=14) did not alter inferences. Adjusting for PTH in the subset with available values (n=418) produced minimal attenuation. No meaningful nonlinearity was observed after spline testing within clinical ranges.

Effect modification. There was a modest interaction between FT4 and BMI category (p-interaction=0.07) such that the inverse FT4–BMD association appeared stronger in women with BMI <23 kg/m². Vitamin D status did not significantly modify associations (all p-interaction>0.10).

7) Clinical interpretation

Across analyses, **lower TSH and higher FT4** were consistently linked to **lower BMD** and **higher odds of osteoporosis and vertebral fracture**. The concordance between continuous and categorical

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analyses, together with robustness in sensitivity checks, supported clinical relevance in a tertiary care population with high vitamin D deficiency prevalence.

DISCUSSION

Principal findings

In this cross-sectional study of 612 postmenopausal women attending a tertiary hospital in Pakistan, lower TSH and higher FT4 levels were independently associated with reduced BMD at the lumbar spine and femoral neck. Women in the lowest TSH tertile had higher odds of osteoporosis and vertebral fracture than those in the highest tertile, and subclinical hyperthyroidism carried a similarly elevated risk profile. FT3 did not show an independent association with BMD after multivariable adjustment. These patterns remained robust across sensitivity analyses that excluded thyroid medication users, extreme TSH outliers, and, in a subset, further adjusted for PTH. An exploratory signal suggested that the inverse FT4–BMD association might have been stronger at lower BMI, whereas vitamin D status did not materially modify associations.

Comparison with prior research

Our findings aligned with—and extended—observations from several population-based cohorts in which suppressed or low-normal TSH and higher FT4 associated with lower BMD and increased fracture risk in older adults, particularly women. Prior studies documented increased hip and vertebral fractures among individuals with subclinical hyperthyroidism, and smaller but measurable BMD reductions even when FT4 remained within reference ranges. The present analysis added region-specific evidence from South Asia, where vitamin D deficiency and lower habitual calcium intake prevailed, and where practice patterns (including levothyroxine overtreatment and autonomous nodular thyroid disease) may shift the distribution of thyroid function among postmenopausal clinic attendees. By demonstrating consistent associations after adjusting for 25(OH)D, BMI, and lifestyle factors, our results suggested that thyroid-related skeletal effects persisted beyond these common regional confounders.

Our null findings for FT3 mirrored mixed reports in the literature. Total and free T3 are biologically active at bone, yet FT3 may be more tightly regulated peripherally and display narrower between-person variance in euthyroid ranges, reducing its explanatory power in multivariable models. Furthermore, assay variability and diurnal rhythms may attenuate detectable cross-sectional relationships for FT3 compared with FT4 and TSH. In contrast, TSH functioned as a sensitive integrator of pituitary–thyroid axis activity and, as seen here, inversely tracked skeletal risk.

Biological plausibility

The observed associations were biologically coherent. Thyroid hormones accelerate the bone remodeling cycle; when thyroid activity is relatively high, the shortened formation phase may not fully compensate for increased resorption, yielding net bone loss over time. Estrogen deficiency after menopause already elevates bone turnover; superimposed thyroid hormone excess likely compounds resorptive dynamics and trabecular deterioration. Spine BMD, which is more trabecular, showed numerically larger effect sizes than femoral neck BMD, consistent with higher remodeling responsiveness at axial sites. TSH might also exert direct skeletal effects through TSH receptors on osteoblasts and osteoclasts, although the clinical relevance of this pathway remains debated. Together, these mechanisms plausibly explained why women with lower TSH—even within the "normal" range—demonstrated lower BMD and higher fracture burden.

Clinical implications

These results supported a pragmatic approach to integrated endocrine–bone care in tertiary settings in Pakistan and similar environments. First, **DXA screening could be prioritized** for postmenopausal women who presented with low or suppressed TSH, especially when FT4 trended high-normal, even in the absence of overt hyperthyroidism. Second, in hypothyroid patients on levothyroxine, **dose titration that respected the upper half of the TSH reference range** might have mitigated inadvertent iatrogenic bone loss; our findings reinforced caution against chronic TSH suppression where not clinically indicated (e.g., outside thyroid cancer management). Third, among women with multinodular goiter or autonomous nodules, **early recognition and management of subclinical hyperthyroidism** appeared relevant to fracture prevention. Fourth, because vitamin D deficiency and low calcium intake were common in our cohort, **foundational measures**—adequate calcium and vitamin D, fall prevention, and weight-bearing

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exercise—remained essential complements to thyroid-specific strategies.

Importantly, our results suggested that **thyroid indices added incremental information** beyond age, BMI, and vitamin D. While the absolute β values for BMD appeared modest, they represented shifts across a population distribution that, over time, translated into clinically meaningful differences in osteoporosis risk—especially at the spine. The elevated odds of vertebral fracture in the lowest TSH tertile underscored this point and argued for **vertebral fracture assessment (VFA)** or careful imaging review when low TSH coexisted with height loss or back pain.

Public health and health-system relevance

In low- and middle-income settings, DXA capacity is limited and fracture risk remains under-recognized. Our study indicated that **routine thyroid function tests—already widely available—could triage bone health assessment**. Embedding a simple rule (e.g., "low/suppressed TSH → consider DXA and bone counseling") into endocrine clinics might reduce missed osteoporosis. Furthermore, **shared decision-making** around levothyroxine targets in older women could explicitly incorporate bone health, not only symptom control or TSH normalization.

Strengths

This investigation offered several strengths:

1. A relatively **large sample** from a real-world tertiary care setting, enabling precise estimates.
2. **Standardized measurement** using a single DXA machine with daily phantom calibration and uniform chemiluminescent assays.
3. **Comprehensive adjustment** for key confounders relevant in Pakistan (vitamin D, BMI, activity, tobacco, supplements, glucocorticoids), with supportive sensitivity analyses that excluded medication users and extreme TSH values.
4. Parallel evaluation of continuous thyroid indices and categorical thyroid function states, which **triangulated** the findings.

Limitations

Several limitations warranted consideration. First, the **cross-sectional design** precluded causal inference; thyroid function and BMD were measured contemporaneously, and residual confounding remained possible despite adjustment. Second, although we verified vertebral fractures where records existed, **fracture ascertainment** ultimately relied in part on history, and underreporting of non-vertebral fractures was plausible. Third, we did not measure bone turnover markers systematically; such data might have clarified intermediary pathways between thyroid status and skeletal outcomes. Fourth, **FT3 assay variability** and timing may have obscured associations. Fifth, generalizability beyond tertiary care attendees could be limited; the clinic population may have had different comorbidity profiles and medication exposures compared with community samples. Finally, we did not examine detailed levothyroxine dose–response relationships or duration of TSH suppression; future longitudinal work with prescription data and time-updated thyroid indices would strengthen causal interpretation.

Interpretation of subgroup and sensitivity signals

The suggestion that the FT4–BMD association was stronger at **lower BMI** was clinically plausible because leaner women have lower baseline estrogen and skeletal reserves; the same hormonal perturbation may therefore yield greater BMD change. The lack of effect modification by vitamin D status, while somewhat unexpected in a deficient population, might reflect limited statistical power for interactions or the primacy of thyroid-driven remodeling over a relatively narrow 25(OH)D range. Stability of results after excluding medication users and extreme TSH values reinforced that **endogenous variation within the reference range** contributed meaningfully to skeletal differences.

Future directions

Prospective cohort studies in Pakistani and regional populations should test whether **time-updated TSH and FT4 trajectories** predict incident fractures independent of FRAX components, and whether **levothyroxine de-escalation** in older women with low TSH improves BMD or microarchitectural indices. Pragmatic trials that compare **TSH target strategies** (e.g., mid- vs upper-reference targeting) in postmenopausal hypothyroid patients could yield practice-changing evidence. At the system level, integrating **EHR prompts** that flag low TSH in postmenopausal women and trigger bone health counseling may be a scalable intervention in resource-constrained settings.

CONCLUSION

In this cross-sectional study of postmenopausal women receiving care at a tertiary hospital in Pakistan, lower TSH and higher FT4 levels were

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independently associated with lower BMD at the lumbar spine and femoral neck, as well as higher odds of osteoporosis and vertebral fracture. These associations persisted after adjustment for age, BMI, years since menopause, vitamin D status, lifestyle factors, and relevant medications, and remained stable across multiple sensitivity analyses. FT3 did not demonstrate an independent relationship with BMD.

Taken together, our findings supported the clinical value of routine thyroid indices—especially TSH and FT4—as practical markers to flag women who may benefit from timely bone health assessment. In everyday care, three actions appeared reasonable: (1) prioritize DXA screening and fracture risk evaluation in postmenopausal women with low or suppressed TSH, even when FT4 is within the reference range; (2) avoid unnecessary or prolonged TSH suppression in hypothyroid management, particularly in older women, unless clearly indicated; and (3) embed foundational measures—adequate calcium and vitamin D intake, weight-bearing exercise, and fall prevention—within thyroid-focused care pathways.

While causality cannot be inferred from a cross-sectional design, the consistency, biological plausibility, and robustness of these results suggest that endocrine balance meaningfully intersects with skeletal integrity in this population. Future longitudinal studies and pragmatic trials should test whether targeting less suppressive TSH goals in postmenopausal women improves BMD or reduces fractures and whether EHR-based prompts that link thyroid results to bone care can close screening gaps. Until such evidence accrues, integrating thyroid function into osteoporosis risk stratification represents a feasible, low-cost enhancement to routine practice in similar resource-constrained settings.

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