ADVANCING INTEGRATIVE DIAGNOSTIC MODELS FOR EARLY DIAGNOSIS AND PREDICTION OF OSTEOPOROSIS RISK IN WOMEN WITH PREMATURE AND EARLY MENOPAUSE

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ABSTRACT

This study presents an enhanced multi-factorial diagnostic and predictive model for osteoporosis and fragility fracture risk in women experiencing premature ovarian insufficiency (POI, <40 years) and early menopause (40–45 years). Conventional areal Bone Mineral Density (aBMD) measured by DXA often underestimates early structural degradation under conditions of acute estrogen deprivation. By synthesizing structural microarchitecture metrics (Trabecular Bone Score - TBS and pQCT parameters) with metabolic velocity biomarkers (β-CTX, P1NP, and Sclerostin), this research establishes a high-sensitivity diagnostic framework. The integration of dynamic metabolic markers with volumetric density enables the identification of rapid bone loss up to 12–18 months prior to detectable shifts in standard T-scores.

Keywords: *Premature menopause, early menopause, osteoporosis, Trabecular Bone Score (TBS), β-CTX, P1NP, Sclerostin, pQCT, FRAX.*

1. INTRODUCTION

1.1. Relevance of the Problem

Premature cessation of ovarian function—specifically premature ovarian insufficiency (POI, occurring before age 40) and early menopause (occurring between ages 40 and 45)—represents a complex medico-social challenge in gynecological and endocrinological practice. Population data indicate that approximately 1% of women suffer from premature ovarian insufficiency and nearly 5% experience early menopause. Estrogens act via specific hormone receptors (particularly ERα) as primary regulators maintaining bone remodeling balance by inducing osteoclast apoptosis and sustaining osteoblast vitality.

Upon the onset of estrogen deficiency, bone resorption within the remodeling cycle begins to significantly outpace bone synthesis. While annual postmenopausal bone loss

at natural age ranges between 1% and 2%, early and premature menopause induce rapid losses of 3% to 6% per year during the first 5 years post-diagnosis. This trajectory increases the risk of osteoporotic complications—particularly pathologic fractures of the vertebral column and femoral neck—by 3- to 4-fold in younger female cohorts.

1.2. Diagnostic Gap and Scientific Challenge

Dual-Energy X-ray Absorptiometry (DXA) measuring areal bone mineral density (aBMD, g/cm²) remains the clinical gold standard for skeletal evaluation. However, conventional aBMD diagnostic criteria exhibit notable methodological limitations when applied to young women with early or premature menopause:

- Two-Dimensional Distortion: DXA calculates overall mineral mass across a two-dimensional projection, failing to depict three-dimensional trabecular microarchitecture and bone tissue quality.
- Delayed Sensitivity: Radiographic changes in mineral density register on DXA software only after significant calcium loss has occurred (typically requiring 12–24 months), delaying preventive and therapeutic intervention.
- Morphological Misleading: Acute hypoestrogenism can cause severe trabecular microarchitectural disruption (loss of connectivity and thinning) while overall mineral quantity remains temporarily intact, leading to fragile structural fractures even at borderline T-scores (e.g., -1.5).

1.3. Objective of the Study

To establish an advanced methodology for early detection of osteoporosis and precise 10-year fracture risk prediction in women with premature and early menopause by integrating areal bone mineral density (aBMD), trabecular microarchitecture metrics (TBS, pQCT), and dynamic metabolic biomarkers (β-CTX, P1NP, Sclerostin).

2. MATERIALS AND METHODS

2.1. Study Design and Patient Cohorts

A prospective observational cross-sectional study was performed evaluating women with premature ovarian insufficiency (<40 years) and early menopause (40–45 years):

- Group 1 (Primary Group A): Premature menopause (<40 years), n = 45.
- Group 2 (Primary Group B): Early menopause (40–45 years), n = 50.
- Group 3 (Control Group): Healthy women with preserved ovarian function matched for age and body mass index (BMI), n = 35.

Inclusion Criteria: Amenorrhea lasting ≥ 6 months, serum FSH level >30 IU/L, estradiol (E_2) <20 pg/mL.

Exclusion Criteria: Primary hyperparathyroidism, chronic kidney disease (CKD stages 3–5), chronic glucocorticoid therapy, bone metastases, systemic connective tissue disorders.

2.2. Instrumental and Densitometric Methods

- Areal Bone Mineral Density (aBMD): Central DXA was performed at the lumbar spine (L_1-L_4) and proximal femur. Results were recorded as g/cm², T-scores, and Z-scores.
- Trabecular Bone Score (TBS): Evaluated from lumbar DXA acquisitions via dedicated software to assess spatial gray-level texture variations. TBS thresholds were stratified as: >1.310 — Normal microarchitecture; 1.230–1.310 — Partially degraded microarchitecture; <1.230 — Severely degraded microarchitecture.
- Peripheral Quantitative Computed Tomography (pQCT): Volumetric bone mineral density (vBMD, mg/cm³) and cortical thickness were measured at the distal radius.

2.3. Laboratory and Biochemical Assays

Venous blood samples were assayed via Enzyme-Linked Immunosorbent Assay (ELISA) for key biomarkers:

- β-CTX (Beta-C-terminal telopeptide): Primary dynamic marker of osteoclastic bone resorption.
- P1NP (Procollagen Type 1 N-terminal Propeptide): Quantitative marker of osteoblastic matrix formation.
- Sclerostin: Osteocyte-derived protein that inhibits osteoblast function by blocking Wnt/β-catenin signaling.
- Serum 25(OH)D and Parathyroid Hormone (PTH).

2.4. Statistical Analysis

Data were processed using SPSS 26.0 and R-Studio. Quantitative variables are expressed as mean ± standard deviation (M ± SD). Inter-group comparisons were evaluated using Student's t-test and the Mann-Whitney U test. Diagnostic sensitivity and specificity were analyzed via Receiver Operating Characteristic (ROC) curves and Area Under the Curve (AUC) calculations. Statistical significance was set at $p < 0.05$.

3. RESULTS

3.1. Densitometric and Microarchitectural Dynamics

Despite mean aBMD T-scores remaining above the osteoporotic threshold (<-2.5) in the majority of early menopause subjects, their Trabecular Bone Score (TBS) revealed severe microarchitectural degradation.

Parameter	Group 1 emature, n=45)	Group 2 (Early, 50)	Group 3 ntrol, n=35)	p-value
Age (years)	36.4 ± 2.8	42.8 ± 1.9	41.2 ± 3.1	>0.05

aBMD L1-L4 m^2)	0.884 ± 0.06	0.921 ± 0.05	1.085 ± 0.04	<0.001
aBMD T-score -L4)	-1.82 ± 0.4	-1.45 ± 0.5	+0.12 ± 0.3	<0.001
TBS (Trabecular re)	1.185 ± 0.04	1.224 ± 0.05	1.362 ± 0.03	<0.001
pQCT becular vBMD g/cm^3)	112.4 ± 12.3	128.6 ± 15.1	185.2 ± 11.4	<0.001

While Group 1 and Group 2 displayed mean T-scores in the osteopenic range (-1.45 to -1.82), their TBS values crossed into severe structural degradation (<1.230). This confirms that standard DXA can create a false sense of security, necessitating mandatory TBS assessment.

3.2. Dynamic Biochemical Biomarker Analysis

Accelerated bone resorption secondary to acute estrogen deficiency was clearly reflected in altered biomarker ratios.

β-CTX Levels: In women with premature menopause, β-CTX measured 0.78 ± 0.08 ng/mL, representing a 2.7-fold increase compared to the control group ($p < 0.001$).

P1NP to β-CTX Ratio: Uncoupled resorption relative to formation led to a marked shift in the β-CTX / P1NP index toward skeletal catabolism.

Sclerostin: Estrogen loss elevated osteocytic Sclerostin production (42.1 ± 4.2 pmol/L vs 22.4 ± 2.8 pmol/L, $p < 0.001$), suppressing endogenous bone regenerative capacity.

3.3. ROC Curve Analysis of the Integrated Model

- Standalone aBMD (DXA): AUC = 0.684 (Moderate sensitivity).
- aBMD + TBS: AUC = 0.812 (Good sensitivity).
- Integrated Model (aBMD + TBS + β-CTX + Sclerostin + Adjusted FRAX): AUC = 0.942 (High diagnostic accuracy: Sensitivity = 91.3%, Specificity = 88.6%).

4. DISCUSSION

4.1. Pathophysiological and Microarchitectural Synthesis

In premature and early menopause, the sudden and prolonged withdrawal of ovarian estrogens rapidly accelerates systemic bone turnover. Estrogen depletion disrupts the RANKL/OPG ratio, reducing Osteoprotegerin (OPG) expression while enhancing RANKL-mediated osteoclastogenesis and osteoclast survival.

As a consequence, osteoclasts dig deep resorption cavities (pits) across trabecular surfaces. While these cavities do not immediately alter two-dimensional mineral mass

(aBMD), they induce trabecular strut perforation and microarchitectural disconnectivity. This explains why TBS detects early skeletal vulnerability much earlier than standard DXA.

4.2. Staged Diagnostic and Predictive Algorithm

Based on empirical findings, a multi-stage diagnostic pathway is established for clinical implementation:

- Presentation with Premature (<40y) or Early (40–45y) Menopause
- STAGE 1: Metabolic Turnover Velocity Evaluation — Assay S-β-CTX, S-P1NP, and Serum Sclerostin; S-β-CTX >0.55 ng/mL identifies “Fast Bone Losers”.
- STAGE 2: Densitometry and Microarchitectural Assessment — Central DXA (aBMD) + Lumbar Spine TBS Software; pQCT (optional trabecular vBMD evaluation).
- STAGE 3: Integrated FRAX Risk Recalibration — Recalculate 10-year fracture probability using TBS adjustment; account for duration of hypoestrogenism.
- HIGH RISK CATEGORY: TBS <1.230 AND/OR S-β-CTX Elevated → Immediate HRT / Antiresorptive Therapy.
- LOW/MODERATE RISK: TBS ≥1.230 AND S-β-CTX Normal → Dynamic Monitoring.

4.3. Clinical and Practical Significance

This integrative framework provides clinicians with objective metrics to guide systemic hormone replacement therapy (HRT) or targeted osteoprotective regimens in young women with ovarian failure. Monitoring β-CTX and TBS dynamics allows therapeutic efficacy to be confirmed within 3 to 6 months rather than waiting up to 2 years for DXA density changes.

CONCLUSION

- Standard areal bone mineral density (aBMD) metrics fail to adequately capture early structural skeletal vulnerability in women with premature and early menopause. While T-scores in 73.3% of these patients indicated moderate osteopenia, their Trabecular Bone Score (TBS) demonstrated severe microarchitectural degradation (<1.230).
- Serum β-CTX and Sclerostin serve as highly sensitive dynamic biomarkers of rapid bone turnover in hypoestrogenic states. A β-CTX threshold exceeding 0.55 ng/mL predicts rapid bone loss 12 to 18 months prior to observable radiographic density drops on standard DXA.
- Combining densitometric (aBMD), microarchitectural (TBS), and biochemical (β-CTX, P1NP, Sclerostin) metrics into a unified predictive model with TBS-adjusted FRAX elevates diagnostic accuracy to AUC = 0.942, enabling early targeted intervention before irreversible skeletal damage occurs.

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