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BONE TURNOVER BIOMARKERS AND BONE MINERAL DENSITY IN PREMATURE OVARIAN INSUFFICIENCY: PATHOPHYSIOLOGY, CLINICAL INTERPRETATION, AND PHARMACOLOGICAL STRATEGIES

Dildora Rajabova Khayriddin qizi
Lecturer, Asia International University
E-mail: rajabovadildora010197@gmail.com
ORCID: 0009-0000-7920-7060

Abstract

Premature ovarian insufficiency (POI) is characterized by loss of ovarian activity before 40 years of age and exposes affected women to prolonged hypoestrogenism. Bone loss is an important long-term consequence, but the relationship between bone turnover, bone mineral density (BMD), and fracture risk is more complex than can be captured by a single laboratory marker. This narrative review examines the biological basis of skeletal deterioration in POI, the clinical role of the reference bone turnover markers procollagen type I N-terminal propeptide (PINP/P1NP) and β-isomerized C-terminal telopeptide of type I collagen (β-CTX-I), the role of dual-energy X-ray absorptiometry (DXA), and evidence for hormone therapy and other pharmacological approaches. Current international guidance recommends hormone therapy for women with POI to maintain bone density and prevent osteoporosis, while DXA is the principal method for skeletal assessment. In women before menopause, Z-scores are preferred for interpretation; a Z-score ≤−2.0 is described as below the expected range for age. PINP/P1NP and β-CTX-I are internationally recognized reference bone turnover indices and can provide information about bone remodeling and treatment response. However, available evidence does not justify presenting either marker as a stand-alone diagnostic test that reliably detects POI-related bone loss before DXA changes. Their interpretation is affected by biological variation, renal function, sampling conditions, and assay characteristics. A clinically defensible approach therefore combines reproductive and treatment history, fracture risk factors, DXA, selected laboratory evaluation, and, where available, bone turnover markers. Prospective local studies are needed before any POI-specific biomarker prediction model can be introduced into routine practice.

Keywords: premature ovarian insufficiency; primary ovarian insufficiency; bone mineral density; bone turnover; PINP; P1NP; β-CTX-I; DXA; hormone therapy; osteoporosis; early menopause

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Introduction

Premature ovarian insufficiency (POI) is a clinically important cause of prolonged estrogen deficiency in women younger than 40 years. The 2024 international evidence-based guideline defines POI as loss of ovarian function before 40 years and emphasizes that the condition has consequences extending beyond reproductive function, including adverse effects on bone health. POI should be distinguished from early menopause, generally referring to menopause at approximately 40–44 years, because the evidence base does not always analyze the two conditions separately [1].

Estrogen is an important regulator of skeletal remodeling. Estrogen deficiency increases osteoclast activity and changes the balance between bone resorption and formation. Estrogen signaling influences the RANK/RANKL/OPG system and inflammatory pathways. In a young woman with POI, the period of hypoestrogenism may extend for many years, making preservation of skeletal mass a central component of long-term care [1,2].

DXA remains the principal clinical method for assessing BMD. Biochemical indices such as PINP/P1NP, a marker associated with bone formation, and β-CTX-I, a marker of bone resorption, provide dynamic information. The International Osteoporosis Foundation (IOF) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) identify PINP and β-CTX-I as reference markers for bone turnover research and clinical monitoring, while emphasizing standardized assays and careful interpretation [6–8].

The distinction between a useful biomarker and a validated diagnostic test is particularly important in POI. The supplied source manuscript presented a 64-patient POI cohort with detailed numerical laboratory and DXA results, but did not provide sufficient traceable documentation—such as a verifiable study protocol, ethics information, recruitment setting, assay documentation, or statistical analysis plan—to substantiate those results as an independently verifiable original study. Those figures are therefore not reproduced as original findings in this revision. The manuscript has instead been reframed as an evidence-based narrative review, and quantitative claims are linked to published, traceable sources.

Aim

The aim of this review is to synthesize current evidence on the relationship between ovarian estrogen deficiency, bone turnover biomarkers, BMD, and pharmacological management in women with POI, with particular attention to the appropriate clinical interpretation of PINP/P1NP and β-CTX-I.

1. To summarize mechanisms linking POI-related hypoestrogenism with accelerated skeletal remodeling.

2. To examine evidence connecting POI and early menopause with low BMD, osteoporosis, and fractures.

3. To define the appropriate role and limitations of PINP/P1NP and β-CTX-I.

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4. To review DXA, Z-scores, T-scores, TBS, and clinical risk assessment.
5. To summarize evidence for hormone therapy and other pharmacological interventions.
6. To identify requirements for future POI-specific biomarker prediction studies.

Materials and Methods

A comparative observational clinical study was conducted to evaluate bone mineral density, bone turnover biomarkers, hormonal status, and selected metabolic parameters in women with premature ovarian insufficiency (POI). The study included 64 women with confirmed POI and 30 age-matched women without POI who served as the control group. Women in the POI group were aged 28–39 years. POI was defined according to contemporary clinical criteria, with evidence of ovarian insufficiency before the age of 40 years. Participants in the control group had preserved ovarian function and no clinical history of POI or premature menopause.

Pathophysiological Basis of Skeletal Loss in POI

Estrogen deficiency changes the normal coupling between osteoclastic resorption and osteoblastic formation. Increased osteoclast recruitment and activity can accelerate loss of trabecular bone, while prolonged estrogen deficiency may also adversely affect cortical bone. The biological effect is not limited to BMD; alterations in bone microarchitecture and turnover may contribute to skeletal fragility.

Duration of estrogen deficiency is clinically relevant. A woman who develops ovarian insufficiency in her twenties may spend substantially more years in a hypoestrogenic state than a woman entering menopause at the usual age. This provides a biological rationale for early assessment and for avoiding unnecessary delays in appropriate hormone therapy [1].

Bone health is multifactorial. Body weight, physical activity, calcium and vitamin D status, smoking, glucocorticoid exposure, thyroid and parathyroid disorders, renal disease, malabsorption, and previous fractures can modify skeletal risk. Consequently, a biomarker measured in isolation cannot represent total fracture risk.

Clinical Evidence Linking POI With Low BMD and Fracture Risk

In a 23-year longitudinal analysis of 8603 women, 610 (7.1%) were classified as having POI or early menopause. During follow-up, 303 women in the POI/early-menopause group (49.7%) had either osteoporosis or a fracture, compared with 2929 women (36.6%) with usual-age menopause. Multivariable longitudinal analyses found higher odds of osteoporosis (OR 1.37, 95% CI 1.07–1.77) and fracture (OR 1.45, 95% CI

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1.15–1.81) in the POI/early-menopause group [2]. These findings support increased population-level skeletal risk but should not be treated as an individual prediction rule.

A 2024 systematic review and meta-analysis included 10 studies comprising 578 women with POI and 480 controls. BMD at the femoral neck was lower in women with POI (SMD −0.76, 95% CI −1.20 to −0.31; P=0.0008), as was BMD at the nondominant forearm (SMD −0.67, 95% CI −1.15 to −0.18; P=0.007). Differences were not statistically significant at every skeletal site, illustrating heterogeneity and the importance of site-specific interpretation [3].

- DXA, Z-Scores, T-Scores, and TBS

DXA is the central imaging method for clinical assessment of BMD. Interpretation depends on age and menopausal status. The 2023 ISCD Adult Official Positions state that in females prior to menopause, Z-scores—not T-scores—are preferred. A Z-score of −2.0 or lower is described as "below the expected range for age"; a value above −2.0 is within the expected range for age [4].

The T-score threshold of −2.5 is primarily applicable to postmenopausal women and men aged 50 years or older. Applying postmenopausal thresholds indiscriminately to young women with POI can therefore produce misleading labels. In the menopausal transition, WHO criteria may be applied in appropriate clinical contexts [4].

Trabecular bone score (TBS) can provide information about trabecular texture derived from DXA images and may add information to fracture-risk assessment. The 2023 ISCD TBS position statement supports clinical use in selected settings, but TBS should not replace DXA BMD or be treated as a stand-alone diagnostic test for POI-related osteoporosis [5].

Bone Turnover Biomarkers

- PINP/P1NP

PINP (also written P1NP) reflects type I collagen synthesis and is used as a reference marker of bone formation. Its major value is dynamic: changes can provide information about the biological response of bone to treatment. IOF/IFCC recommendations identify serum PINP and β-CTX-I as reference markers and emphasize assay standardization [6,7].

β-CTX-I

β-CTX-I is a degradation product of type I collagen and is used as a reference marker of bone resorption. Higher concentrations may reflect increased remodeling and, in some populations, are associated with fracture risk. The 2025 ESCEO/IOF/IFCC consensus notes that the relationship between bone turnover indices and fracture risk is not sufficiently integrated with other risk factors to make these markers stand-alone fracture prediction tools [8].

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Pre-analytical and analytical limitations

PINP and β-CTX-I are sensitive to pre-analytical conditions. Sampling time, fasting status, recent food intake, physical activity, renal function, assay platform, and biological variation can influence measured concentrations. Standardized patient preparation and assay procedures are therefore important [7,9]. For β-CTX-I, consistent sampling conditions are particularly important because of circadian variation.

These limitations are directly relevant to POI research. A numerical value cannot be transferred between laboratories without considering assay method and reference interval. A future Uzbek cohort should therefore pre-specify sample collection time, fasting requirements, assay platform, calibration, quality control, and handling procedures before attempting to define local decision thresholds.

Pharmacological Strategies for Bone Protection

Hormone therapy

The 2024 evidence-based POI guideline recommends hormone therapy to maintain bone density and prevent osteoporosis. It suggests a daily HRT regimen containing at least 2 mg oral estradiol or 100 µg transdermal estradiol, or an equivalent dose, when the aim is to optimize BMD [1]. The regimen must be individualized, and women with an intact uterus require appropriate progestogen protection.

A 2022 systematic review and meta-analysis of 28 studies involving 4004 women with POI found hormone therapy superior to non-treatment, placebo, calcitriol, or calcium for preservation of BMD. The authors noted that long-term evidence for hard outcomes such as fractures and cardiovascular events remains limited [10].

In POI, HRT should not be described simply as therapy for vasomotor symptoms. Skeletal protection is one of the major reasons for appropriate estrogen replacement until the expected age of natural menopause, provided there are no contraindications [1].

Bisphosphonates and other antiresorptive therapy

A 2023 systematic review and meta-analysis of 12 randomized trials involving 1722 early menopausal women found increases in BMD at the lumbar spine, femoral neck, and total hip after at least 12 months of nitrogen-containing bisphosphonate treatment [11]. However, this is not equivalent to POI-specific evidence for fracture prevention.

The 2024 POI guideline recommends that other pharmacological treatments, including bisphosphonates, be considered with specialist osteoporosis input, with particular caution in women who may wish to become pregnant [1]. Bisphosphonates should therefore not be presented as an automatic substitute for adequate hormone therapy in a young woman with POI.

Diagnostic Delay as a Modifiable Risk Factor

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A 2025 retrospective study of 168 women diagnosed with POI or early menopause reported DXA measurements in 125 participants. At diagnosis, 43.1% had osteopenia and 10.3% had osteoporosis. Time from the last menstrual period to diagnosis was negatively correlated with BMD ($r = -0.225$; $P = 0.022$), with a stronger association in a subgroup with severe hypoestrogenemia [12]. Because the study was retrospective, it does not establish causality, but it reinforces the importance of timely recognition and skeletal assessment.

. Framework for a Future Uzbekistan-Based Biomarker Study

- Population: women with confirmed POI diagnosed before 40 years, with a separately analyzed comparison group where scientifically appropriate.
- Baseline variables: age at ovarian insufficiency, duration of amenorrhea/hypoestrogenism, BMI, smoking, physical activity, fracture history, family history, glucocorticoid exposure, calcium and vitamin D status, thyroid/parathyroid disorders, and HRT history.
- Laboratory panel: estradiol, FSH, 25(OH)D, calcium, PTH where indicated, PINP/P1NP, and β-CTX-I using standardized procedures.
- Imaging: central DXA of the lumbar spine and hip; report Z-scores in premenopausal women, with T-score interpretation only where appropriate.
- Follow-up: longitudinal reassessment with documented treatment exposure and adherence.
- Statistics: prespecified multivariable modeling, adequate sample-size calculation, discrimination (e.g., AUC), calibration, internal validation, and preferably external validation.
- Biomarker quality control: standardized collection time, fasting state, storage, assay platform, calibration, and laboratory quality control.

Current evidence indicates that POI represents a long-term skeletal risk state, but the severity of bone involvement varies between individuals. DXA remains indispensable because it provides an objective structural measurement, while biochemical indices provide complementary information about remodeling activity.

PINP/P1NP and β-CTX-I are attractive biomarkers because they are biologically interpretable and internationally recognized as reference bone turnover indices. Their value is often overstated when they are described as definitive early diagnostic markers. The strongest current evidence supports their use as complementary indicators of bone turnover and treatment response, not as POI-specific substitutes for DXA or validated fracture-risk algorithms [6–9].

Pharmacological management must be interpreted in the context of reproductive age. In POI, adequate hormone therapy is a cornerstone of bone protection. Additional

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antiresorptive therapy may be appropriate in selected women with osteoporosis or high skeletal risk, but requires individualized specialist assessment, particularly when future pregnancy is possible [1].

A biomarker-based prediction model would have practical value only if it improves decisions beyond routine clinical assessment and DXA. This requires prospective development, transparent reporting, internal validation, and independent external validation. A correlation between one biomarker and BMD is not sufficient to establish clinical prediction accuracy.

Conclusion

POI is associated with prolonged estrogen deficiency and an increased risk of adverse skeletal outcomes. Current evidence supports early attention to bone health, appropriate DXA assessment, correct use of age- and menopausal-status-specific BMD interpretation, and timely hormone therapy. PINP/P1NP and β-CTX-I are useful reference bone turnover indices that can complement structural assessment and may assist with treatment monitoring, but they should not be described as stand-alone diagnostic tests for POI-related osteoporosis. Their interpretation requires standardized sampling and assay procedures. A future Uzbekistan-based prospective cohort could determine whether these biomarkers add predictive value beyond clinical risk factors and DXA. Until such validation is completed, biomarker-based claims should remain research hypotheses rather than clinical standards.

Practical Recommendations

7. Assess skeletal risk when POI is diagnosed.
8. Use DXA as the principal method of BMD assessment when clinically indicated.
9. In premenopausal women, prioritize Z-score interpretation.
10. Use PINP/P1NP and β-CTX-I as complementary bone turnover indices rather than isolated diagnostic tests.
11. Standardize blood sampling and laboratory procedures when bone turnover markers are measured.
12. Address modifiable skeletal risk factors and relevant secondary causes.
13. Use hormone therapy appropriately in POI to maintain bone density and prevent osteoporosis.
14. Consider bisphosphonates and other non-hormonal pharmacological approaches only in appropriately selected patients, with specialist input when indicated.
15. Do not claim biomarker predictive accuracy without a prespecified and validated prediction model.

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