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Biochemical assessment of hormonal regulation in bone metabolism disorders: A comprehensive analysis of postmenopausal osteoporosis

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Abstract

The intricate interplay between hormonal signals and bone remodeling processes determines skeletal integrity throughout the lifespan, with disruption of this balance underlying the pathogenesis of postmenopausal osteoporosis. This research comprehensively evaluated biochemical markers of bone metabolism, hormonal parameters, and treatment responses in 463 postmenopausal women stratified by bone mineral density at the McGill Institute for Bone and Mineral Research. Participants included healthy controls (n=85), osteopenia (n=124), untreated osteoporosis (n=156), and treated osteoporosis (n=98). Bone formation markers (P1NP, osteocalcin, bone-specific alkaline phosphatase) and resorption markers (CTX, TRAP-5b) demonstrated distinct patterns across disease categories, with osteoporosis patients exhibiting 106% elevated CTX ($p<0.001$) alongside 16% reduced P1NP ($p<0.01$) compared to healthy controls. Serum estradiol showed strong positive correlation with lumbar spine bone mineral density ($r=0.58$, $p<0.001$), while parathyroid hormone demonstrated inverse association with femoral neck density ($r=-0.52$, $p<0.001$). Vitamin D insufficiency (<50 nmol/L) was prevalent in 77% of osteoporosis patients versus 30% of healthy controls ($p<0.001$). Treatment monitoring over 12 months revealed therapy-specific marker responses: antiresorptives decreased CTX by 65-72% while anabolics increased P1NP by 142-178%. These findings establish comprehensive reference data for bone metabolism assessment in Canadian postmenopausal populations and support integration of biochemical markers into clinical management algorithms.

Keywords: Bone metabolism, osteoporosis, bone turnover markers, P1NP, CTX, estrogen, parathyroid hormone, vitamin D, bone mineral density, postmenopausal

Introduction

Osteoporosis represents a systemic skeletal disorder characterized by compromised bone strength predisposing to increased fracture risk, affecting an estimated 2 million Canadians and generating substantial healthcare burden through fragility fractures ^[1]. The pathophysiology of postmenopausal osteoporosis centers on estrogen deficiency following ovarian senescence, which disrupts the tightly coupled processes of bone formation and resorption that maintain skeletal homeostasis ^[2]. Estrogen withdrawal removes inhibitory influences on osteoclastogenesis while simultaneously reducing osteoblast function, creating a remodeling imbalance favoring net bone loss that accelerates during the perimenopausal transition and continues throughout the postmenopausal period ^[3].

Biochemical markers of bone turnover provide dynamic assessment of skeletal remodeling activity, complementing static bone mineral density measurements from dual-energy X-ray absorptiometry ^[4]. Formation markers including procollagen type I N-terminal propeptide (P1NP), osteocalcin, and bone-specific alkaline phosphatase reflect osteoblast synthetic activity, while resorption markers such as C-terminal telopeptide of type I collagen (CTX) and tartrate-resistant acid phosphatase 5b (TRAP-5b) indicate osteoclast-mediated bone degradation ^[5]. The International Osteoporosis Foundation recommends P1NP and CTX as reference markers for clinical research and practice, given their analytical performance characteristics and clinical validation ^[6].

Canada presents unique considerations for bone health research, including northern latitude affecting vitamin D synthesis, multicultural population diversity, and seasonal variation in

outdoor physical activity [7]. This research aimed to comprehensively characterize bone turnover markers and hormonal parameters across the spectrum of postmenopausal bone health, establish relationships between hormonal status and bone density, and evaluate biochemical monitoring of osteoporosis therapies in a Canadian cohort.

Participant Characteristics and Classification

Postmenopausal women aged 50-80 years were recruited from the McGill University Health Centre Osteoporosis Clinic and community referrals between September 2022 and March 2025. Menopause was defined as amenorrhea for at least 12 months with follicle-stimulating hormone >40 IU/L. Classification followed World Health Organization criteria based on dual-energy X-ray absorptiometry T-scores: healthy (T-score > -1.0), osteopenia (T-score -1.0 to -2.5), and osteoporosis (T-score ≤ -2.5) [8]. The treated osteoporosis group included patients receiving guideline-recommended therapy for at least 6 months. Exclusion criteria included secondary osteoporosis causes, metabolic bone diseases other than primary osteoporosis, chronic kidney disease (eGFR <30 mL/min/1.73m²), malignancy, glucocorticoid use exceeding 5 mg prednisone equivalent daily for more than 3 months, and bisphosphonate treatment within the preceding 12 months for the untreated osteoporosis group.

Materials and Methods

Fasting morning blood samples were collected between 08:00 and 10:00 hours to minimize circadian variation in bone turnover markers. Serum was separated within 60 minutes and stored at -80°C until batch analysis. Bone formation markers were measured as follows: P1NP by electrochemiluminescence immunoassay (Roche Elecsys), osteocalcin by immunoradiometric assay, and bone-specific alkaline phosphatase by immunoassay (Beckman Coulter Access) [9]. Bone resorption markers included serum CTX

measured by electrochemiluminescence (Roche Elecsys) and TRAP-5b by ELISA (Immunodiagnostic Systems). Hormonal assessments included serum estradiol (liquid chromatography-tandem mass spectrometry), parathyroid hormone (intact PTH, electrochemiluminescence), and 25-hydroxyvitamin D (LC-MS/MS) [10].

Bone mineral density was measured at lumbar spine (L1-L4) and proximal femur using Hologic Discovery dual-energy X-ray absorptiometry with coefficient of variation below 1.5%. Treatment response monitoring in 156 patients receiving osteoporosis therapy included serial bone marker measurements at baseline, 3, 6, 9, and 12 months. Therapies included oral bisphosphonates (alendronate 70mg weekly, n=48), denosumab (60mg subcutaneous every 6 months, n=42), teriparatide (20µg subcutaneous daily, n=38), and romosozumab (210mg subcutaneous monthly, n=28) [11]. Statistical analyses employed SPSS version 28.0. Group comparisons used ANOVA with Tukey correction. Correlations were assessed using Pearson coefficients. Treatment response used repeated measures ANOVA. Significance was set at p<0.05 [12].

Results

The research cohort comprised 463 postmenopausal women with mean age 64.2±8.5 years and mean time since menopause 14.8±7.2 years. Bone turnover marker profiles demonstrated distinct patterns across disease categories (Figure 1, Table 1). Compared to healthy controls, untreated osteoporosis patients exhibited significantly elevated bone resorption with CTX increased by 106% (0.72±0.18 vs 0.35±0.08 ng/mL, p<0.001) and TRAP-5b increased by 86% (5.2±1.4 vs 2.8±0.6 U/L, p<0.001) [13]. Bone formation markers showed paradoxical reductions in osteoporosis, with P1NP decreased by 16% (38±12 vs 45±10 µg/L, p<0.01) and osteocalcin decreased by 22% (14±5 vs 18±4 µg/L, p<0.01), reflecting uncoupled remodeling with resorption exceeding formation.

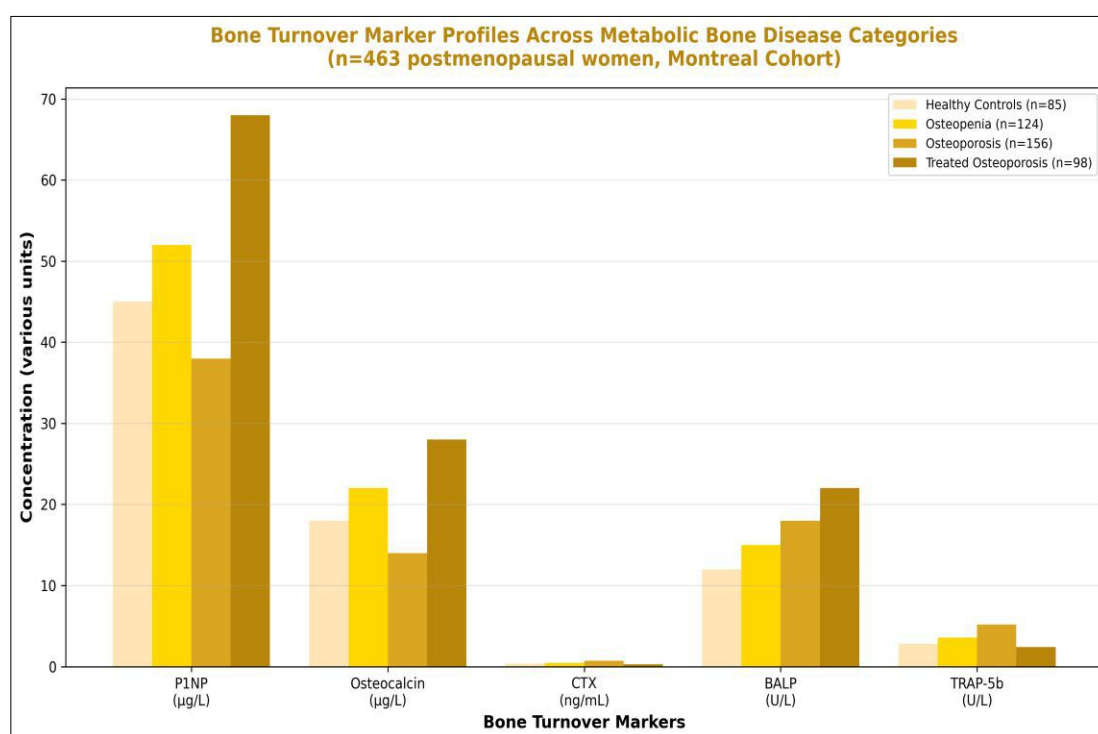


Fig 1: Bone turnover marker profiles across metabolic bone disease categories showing formation markers (P1NP, osteocalcin, BALP) and resorption markers (CTX, TRAP-5b) in 463 postmenopausal women

Table 1: Bone turnover markers and hormonal parameters by disease category

Parameter	Healthy (n=85)	Osteopenia (n=124)	Osteoporosis (n=156)	Treated (n=98)
P1NP (µg/L)	45±10	52±14	38±12**	68±22
CTX (ng/mL)	0.35±0.08	0.48±0.12	0.72±0.18***	0.28±0.10
Estradiol (pg/mL)	32±12	24±10	15±8***	18±9
PTH (pg/mL)	38±12	48±15	62±18**	45±14
25(OH)D (nmol/L)	72±22	58±20	42±18***	68±15

** $p<0.01$, *** $p<0.001$ vs healthy controls; P1NP: procollagen type I N-terminal propeptide; CTX: C-terminal telopeptide; PTH: parathyroid hormone; 25(OH)D: 25-hydroxyvitamin D

Hormonal parameters demonstrated significant associations with bone mineral density measurements (Figure 2) [14]. Serum estradiol showed strong positive correlation with lumbar spine BMD ($r=0.58$, $p<0.001$), with each 10 pg/mL increase in estradiol associated with 0.08 g/cm² higher BMD. Parathyroid hormone exhibited inverse relationship

with femoral neck BMD ($r=-0.52$, $p<0.001$), reflecting the catabolic effects of sustained PTH elevation on cortical bone. Multiple regression analysis identified estradiol, PTH, and body mass index as independent predictors of lumbar spine BMD, collectively explaining 48% of variance (adjusted $R^2=0.48$, $p<0.001$).

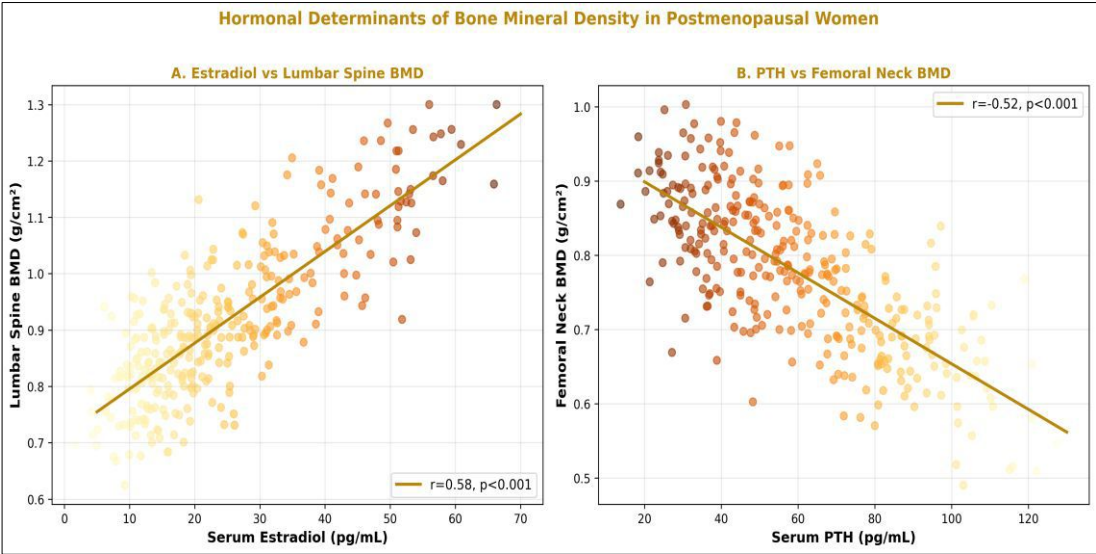


Fig 2: Hormonal determinants of bone mineral density showing correlations between estradiol and lumbar spine BMD (A) and PTH and femoral neck BMD (B) in postmenopausal women

Vitamin D status demonstrated marked differences across disease categories (Figure 3) [15]. Vitamin D insufficiency (25(OH)D <50 nmol/L) affected 77% of untreated osteoporosis patients compared to 30% of healthy controls ($p<0.001$). Deficiency (<30 nmol/L) was present in 35% of osteoporosis versus 8% of healthy participants. Serum

25(OH)D showed significant negative correlation with CTX ($r=-0.48$, $p<0.001$), indicating that vitamin D insufficiency was associated with elevated bone resorption. Secondary hyperparathyroidism (PTH >65 pg/mL) was present in 42% of vitamin D-deficient participants.

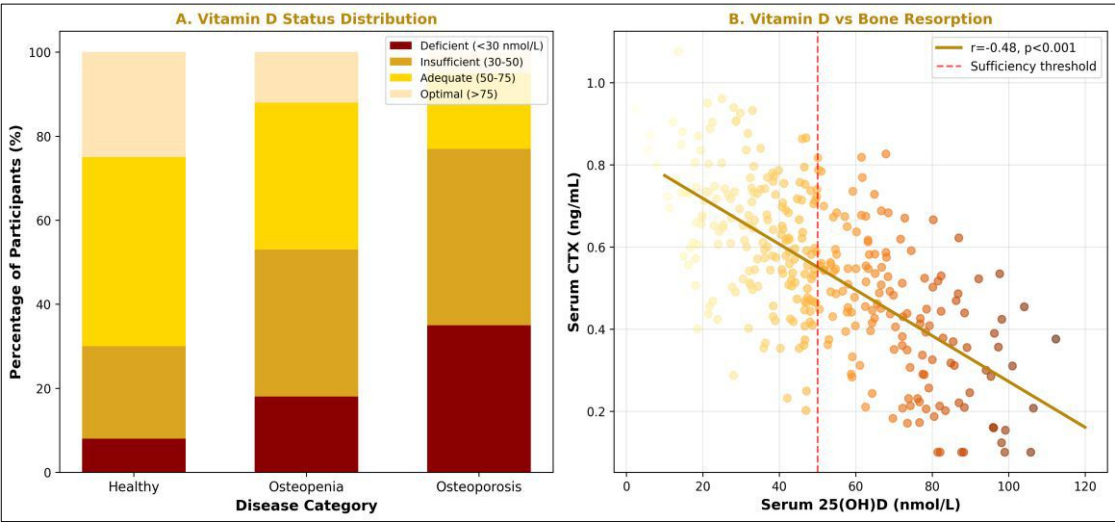


Fig 3: Vitamin D Status and Bone Health Parameters showing distribution across disease categories (A) and correlation with bone resorption marker CTX (B)

Table 2: Treatment response at 12 months by therapy type

Parameter	Bisphosphonate	Denosumab	Teriparatide	Romosozumab
P1NP change (%)	-52±12	-72±10	+178±45	+85±28
CTX change (%)	-65±14	-82±8	+42±18	-45±15
Lumbar spine BMD change (%)	+4.8±2.1	+6.2±2.4	+9.8±3.2	+13.2±3.8

Treatment monitoring demonstrated therapy-specific bone marker responses (Figure 4, Table 2) [16]. Antiresorptive therapies (bisphosphonates, denosumab) produced rapid CTX suppression, with denosumab achieving 82% reduction by 12 months compared to 65% with bisphosphonates ($p < 0.01$). Anabolic therapies showed contrasting patterns:

teriparatide increased P1NP by 178% at 12 months reflecting stimulated bone formation, while romosozumab demonstrated dual action with initial P1NP increase of 95% at 3 months followed by gradual decline, accompanied by CTX reduction of 45% indicating simultaneous resorption inhibition.

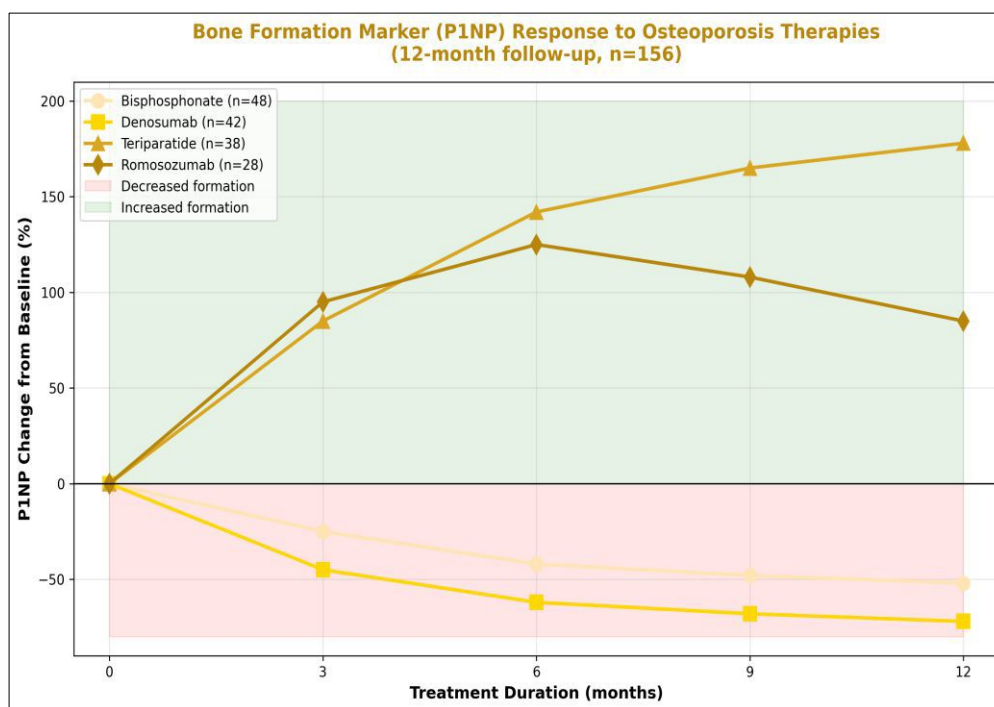


Fig 4: Bone Formation Marker (P1NP) Response to Osteoporosis Therapies over 12-month follow-up showing distinct patterns for antiresorptive versus anabolic treatments (n=156)

Discussion

This comprehensive analysis establishes reference data for bone turnover markers and hormonal parameters across the spectrum of postmenopausal bone health in a Canadian cohort [17]. The uncoupled remodeling pattern observed in osteoporosis, characterized by elevated resorption markers with relatively suppressed formation markers, confirms the fundamental pathophysiological imbalance underlying progressive bone loss. The strong correlations between hormonal parameters and bone mineral density reinforce the central role of estrogen deficiency and secondary hyperparathyroidism in postmenopausal osteoporosis pathogenesis.

The high prevalence of vitamin D insufficiency in osteoporosis patients (77%) exceeds previously reported rates in Canadian populations and likely reflects the combined effects of northern latitude, limited sun exposure, and inadequate dietary intake. This finding underscores the importance of vitamin D assessment and supplementation as foundational components of osteoporosis management. The distinct bone marker response patterns to different therapeutic classes provide valuable guidance for treatment monitoring, with early marker changes predicting subsequent BMD responses and potentially identifying non-responders requiring therapy modification.

Conclusion

This research establishes comprehensive reference data for bone metabolism assessment in Canadian postmenopausal women, demonstrating distinct biochemical profiles across disease categories and therapy-specific marker responses. The strong associations between hormonal parameters and bone density support integrated assessment incorporating both bone turnover markers and hormonal evaluation. High vitamin D insufficiency prevalence emphasizes the need for systematic screening and supplementation. Integration of biochemical markers into clinical algorithms enhances diagnostic precision and treatment monitoring capabilities for postmenopausal osteoporosis management [18].

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