

Parathyroid Hormone Suppression and Calcium Homeostasis Shift in Type 2 Diabetes with Osteoporosis: A Propensity Score-Matched Cross-Sectional Study

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Research Article

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Abstract

Purpose

The bone metabolic characteristics of type 2 diabetes mellitus (T2DM) with osteoporosis (OP) remain controversial. Previous studies often used "DM without OP" as controls, but such controls may confound patients using antiresorptive drugs for bone metastasis. This study re-evaluates bone metabolism in DM + OP after excluding drug confounders and using propensity score-matched (PSM) pure DM controls.

Methods

A retrospective cross-sectional study of hospitalized T2DM patients (2021–2024). The DM + OP group (n = 461) excluded bone metastasis cases. From 21,181 pure DM patients without antiresorptive drugs, 1,383 were 1:3 PSM-matched (age, sex). Serum bone turnover markers (beta-CTX, osteocalcin), 25(OH)VitD, PTH, calcium, and phosphorus were compared. HbA1c-stratified analysis was performed.

Results

After PSM, age (69.3 ± 8.8 years) and sex (15.2% male) were perfectly matched. PTH was 22.6% lower in DM + OP vs pure DM (40.3 vs 52.0 ng/L, $p < 0.001$, Cohen's $d = -0.434$). Serum calcium was slightly higher (2.21 vs 2.20 mmol/L, $p = 0.043$). Bone turnover markers (beta-CTX: 0.38 vs 0.38 ng/mL, $p = 0.580$; osteocalcin: 12.0 vs 11.0 ng/mL, $p = 0.141$) and 25(OH)VitD (24.7 vs 22.8 ng/mL, $p = 0.127$) showed no significant differences. In pure DM, HbA1c-osteocalcin showed a strong negative correlation ($r = -0.456$, $p < 0.001$), while this correlation was weaker in DM + OP ($r = -0.206$, $p = 0.006$), indicating "glycemic-bone turnover uncoupling."

Conclusions

After excluding antiresorptive drug confounders, BTMs showed no significant difference between DM + OP and pure DM controls, not supporting the classic "diabetic low bone turnover" hypothesis. PTH suppression with mild hypercalcemia is a distinct feature of DM + OP, suggesting possible CaSR sensitivity alteration or functional hypoparathyroidism. DM + OP also exhibits "glycemic-bone turnover uncoupling," indicating a qualitative change in bone metabolism regulation.

Introduction

Patients with T2DM have a 1.5- to 3-fold increased fracture risk compared with non-diabetic individuals [1], yet bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) is often normal or even elevated - the "DXA paradox" suggests bone quality impairment beyond BMD [2]. Bone turnover markers (BTMs) reflect dynamic bone metabolism and could theoretically compensate for BMD's

limitation in assessing bone quality. However, BTMs characteristics in DM + OP patients are highly contradictory: some reports show decreased bone resorption markers (low turnover) [3][4], while others show no significant difference from controls [5]. Advanced glycation end-products (AGEs) may affect bone quality through multiple pathways [6]. A meta-analysis noted that inter-study heterogeneity may partly stem from methodological differences [7]. Parathyroid hormone (PTH) metabolic abnormalities in T2DM are gaining attention [8]. We identified a neglected methodological issue: in large hospital EHR databases, "DM without OP" control groups may include patients using potent antiresorptive drugs (denosumab 120 mg, zoledronic acid) for tumor bone metastasis. These drugs can reduce BTMs by 50–80% [9], and if confounded in the control group would artificially alter baseline BTM levels, leading to systematic bias in between-group comparisons (Fig. 1). This study aimed to: (1) re-evaluate bone metabolic differences between DM + OP and pure DM controls after strictly excluding antiresorptive drug confounders and PSM matching for age and sex; (2) examine the pattern of PTH changes in DM + OP and its clinical significance; (3) explore the CaSR-mediated PTH suppression mechanism [10][11].

Methods

2.1 Study Design and Data Source

This was a retrospective cross-sectional study. Data were obtained from the electronic health record system of the Health Management Center and inpatient department of Shanghai Changzheng Hospital (2021–2024). The study protocol was approved by the Hospital Ethics Committee (approval No. 2022SL047).

2.2 Study Population and Group Definitions

DM + OP group: Inclusion criteria: (1) T2DM diagnosed by ICD-10 codes; (2) Osteoporosis diagnosed by ICD-10 codes; (3) at least one serum bone metabolism marker test during hospitalization. Exclusion criterion: malignant tumor with bone metastasis (based on denosumab Anjiawei 120 mg order records and ICD-10 tumor diagnosis codes). Final n = 461.

Pure DM control group: From 21,724 hospitalized patients with T2DM diagnosis but no OP diagnosis, layered screening was performed: (1) excluded 543 patients (2.5%) using antiresorptive drugs (denosumab Anjiawei 120 mg: n = 295; Prolia 60 mg: n = 51; zoledronic acid: n = 197); (2) screened those with bone metabolism marker records, yielding 13,050 as the PSM source population. After 1:3 PSM matching, n = 1,383 were included.

Methodological Note

During data cleaning, 2.5% (543/21,724) of DM-only patients were found using antiresorptive drugs. If not excluded, BTM comparisons would be severely confounded.

2.3 Propensity Score Matching

Logistic regression was used to estimate each patient's propensity score (PS), with covariates of age and sex. Greedy nearest-neighbor matching at 1:3 ratio was adopted, with caliper set at 0.2xSD of logit(PS). After matching, standardized mean difference (SMD) was used to assess covariate balance, with SMD < 0.1 considered well-balanced.

2.4 Laboratory Measurements

All tests were performed in the Laboratory Department of Changzheng Hospital following standardized procedures: HbA1c by high-performance liquid chromatography; osteocalcin (OC) and beta-CTX by electrochemiluminescence immunoassay (Roche Cobas e601); 25(OH)VitD by chemiluminescence; PTH by electrochemiluminescence (reference range 15–65 ng/L); serum calcium and phosphorus by automated biochemical analyzer.

2.5 Statistical Analysis

Continuous variables are described as median (IQR), as all bone metabolism indicators were non-normally distributed (Shapiro-Wilk test $p < 0.05$). Between-group comparisons used Mann-Whitney U test. Effect sizes are reported as Cohen's d. HbA1c stratification: <7% (good), 7–9% (moderate), $\geq 9\%$ (poor). Spearman rank correlation was used to analyze associations between HbA1c and bone metabolism indicators. Two-sided $p < 0.05$ was considered statistically significant. All analyses were performed on the PSM-matched cohort.

Results

3.1 Baseline Characteristics and PSM Balance

Before PSM, the DM + OP group ($n = 461$) was significantly older (69.3 ± 8.8 vs 63.3 ± 12.0 years) and had a higher proportion of females (84.8% vs 35.6%), with SMDs of 0.56 and 1.12, respectively. After PSM, 1,383 patients were successfully matched from 13,050 pure DM patients (3:1). Age and sex were identical between groups (SMD = 0.000), indicating ideal matching (Table 1).

Table 1
Baseline characteristics of the PSM-matched cohorts.

Characteristic	DM + OP (n = 461)	Pure DM (n = 1,383)	p value	Cohen's d
Age, years (mean+/-SD)	69.3+/-8.8	69.3+/-8.8	1.000	0.000
Male, n (%)	70 (15.2%)	210 (15.2%)	1.000	0.000
HbA1c, %	7.7 (6.67–8.9)	7.4 (6.7–8.6)	0.075	0.155
beta-CTX, ng/mL	0.38 (0.23–0.62)	0.38 (0.28–0.59)	0.580	0.005
Osteocalcin, ng/mL	12.0 (9.0–17.0)	11.0 (8.67–14.8)	0.141	0.05
25(OH)VitD, ng/mL	24.7 (19.07–31.41)	22.82 (18.51–30.06)	0.127	0.133
Calcium, mmol/L	2.21 (2.14–2.28)	2.20 (2.12–2.27)	0.043*	0.12
Phosphorus, mmol/L	1.19 (1.05–1.32)	1.18 (1.05–1.32)	0.917	-0.004
PTH, ng/L	40.26 (27.92–54.03)	52.03 (34.03–94.61)	< 0.001***	-0.434

Values: median (IQR) unless otherwise stated. P-values from Mann-Whitney U test. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. PTH reference range: 15–65 ng/L.

The bone turnover markers including beta-CTX, osteocalcin, 25(OH)VitD, calcium, and phosphorus showed no significant differences between the two groups, as illustrated in (Fig. 2). The PTH distribution analysis revealed that the DM + OP group had a significantly lower PTH percentile distribution compared with the pure DM group, with a median PTH of 40.3 ng/L versus 52.0 ng/L, respectively ($p < 0.001$) (Fig. 3).

3.2 HbA1c Stratification Analysis

After HbA1c stratification, between-group PTH differences were most significant in the good glycemic control ($< 7\%$) and moderate (7–9%) subgroups. Notably, PTH in the pure DM control group showed a decreasing trend with worsening glycemic control (56.6 to 50.0 to 44.6 ng/L), whereas PTH in the DM + OP group was nearly constant across the three HbA1c strata (44.7 to 40.0 to 40.0 ng/L) - this "PTH floor effect" pattern is consistent with a non-significant HbA1c-PTH Spearman correlation in the DM + OP group ($r = -0.037$, $p = 0.618$) (Table 2).

Table 2
Bone metabolism markers stratified by HbA1c (PSM-matched).

Marker	< 7% DM + OP	< 7% Pure	p	7–9% DM + OP	7– 9% Pure	p	>=9% DM + OP	>=9% Pure	p
PTH, ng/L	44.66	56.57	0.005**	40.02	49.99	0.001**	40.04	44.63	0.228
Osteocalcin	14.0	14.75	0.338	12.0	11.0	0.733	11.0	9.0	0.023*
beta-CTX	0.40	0.55	0.047*	0.37	0.35	0.555	0.36	0.33	0.661
25(OH)VitD	26.71	22.59	0.127	24.34	23.54	0.868	23.28	22.70	0.579
Calcium	2.22	2.23	0.671	2.22	2.21	0.477	2.24	2.23	0.169
Phosphorus	1.19	1.23	0.115	1.17	1.20	0.319	1.22	1.16	0.359

Values: median. * $p < 0.05$, ** $p < 0.01$. HbA1c < 7%: DM + OP n = 76, Pure DM n = 235; 7–9%: DM + OP n = 106, Pure DM n = 298; >=9%: DM + OP n = 57, Pure DM n = 125.

The stratified analysis further revealed the "PTH floor effect" pattern, where PTH in the DM + OP group remained relatively stable across HbA1c strata, while PTH in pure DM controls decreased with deteriorating glycemic control (Fig. 4A). Additionally, correlation analysis between HbA1c and bone turnover markers demonstrated a distinct "glycemic-bone turnover uncoupling" phenomenon in DM + OP patients (Fig. 4B, Table 3).

Table 3
Spearman correlations between HbA1c and bone metabolism markers (PSM-matched).

Correlation pair	r (DM + OP)	p (DM + OP)	n (DM + OP)	r (Pure DM)	p (Pure DM)	n (Pure DM)
HbA1c - Osteocalcin	-0.206	0.005**	177	-0.456	< 0.001***	114
HbA1c - beta-CTX	-0.056	0.457	177	-0.301	< 0.001***	115
HbA1c - 25(OH)VitD	-0.119	0.112	177	-0.023	0.793	131
HbA1c - PTH	-0.037	0.618	179	-0.145	0.042*	195
HbA1c - Calcium	0.120	0.065	237	-0.004	0.928	651
HbA1c - Phosphorus	0.050	0.445	232	-0.073	0.077	585

Spearman rank correlation. The attenuation of HbA1c-OC correlation from Pure DM ($r = -0.456$) to DM + OP ($r = -0.206$) supports the "glycemic-bone turnover uncoupling" hypothesis.

The proposed mechanism underlying PTH suppression in DM + OP patients involves CaSR dysfunction mediated by AGEs, oxidative stress, and microvascular complications (Fig. 5). The clinical implications of our findings suggest that conventional DXA-based bone assessment may be insufficient for fracture risk prediction in DM + OP patients, necessitating a comprehensive triple-screening approach that integrates DXA, BTMs, and PTH measurements (Fig. 6). The correlation analysis further reveals the distinct metabolic pattern in DM + OP patients compared with pure DM controls (Fig. 7). A visual summary of the core findings is presented in (Fig. 8).

Discussion

Principal Findings

This study, after strictly excluding antiresorptive drug confounders and PSM matching for age and sex, yielded three core findings:

First, bone turnover markers in DM + OP patients showed no significant difference from pure DM controls. beta-CTX medians were identical (0.38 vs 0.38 ng/mL), and osteocalcin difference was not significant (12.0 vs 11.0 ng/mL, $p = 0.141$). This negative finding challenges the classic paradigm of "diabetic osteoporosis = low bone turnover."

Second, PTH suppression is the most robust feature of DM + OP. The effect size is medium ($d = -0.434$) and consistent across HbA1c strata. The Ca-PTH correlation is weak in both groups, supporting CaSR sensitivity alteration rather than a simple calcium feedback mechanism.

Third, DM + OP exhibits "glycemic-bone turnover uncoupling." The pure DM control group shows a clear HbA1c-osteocalcin negative correlation ($r = -0.456$), whereas this relationship is significantly attenuated in the DM + OP group ($r = -0.206$), suggesting that bone metabolism regulation has shifted from glucose-driven to CaSR/PTH-dominated mechanisms.

Revisiting the "Low Bone Turnover" Hypothesis

The "diabetic bone disease = low turnover" hypothesis dates back to the early 2000s [12][13]. Recent studies have confirmed that diabetes increases fracture risk despite normal or elevated BMD [14][15][16][17]. This study offers a new perspective: unrecognized drug exposure in the control group. Approximately 2.5% of "DM without OP" patients were actually using antiresorptive drugs (our cohort data). These drugs can reduce BTMs by 50–80% [18], and if confounded in the control group would artificially alter baseline BTM levels.

PTH Suppression: CaSR-Mediated Mechanism

PTH suppression is the most robust finding of this study. In the pure DM control group, PTH declined with worsening glycemic control (56.6 to 50.0 to 44.6 ng/L), consistent with the HbA1c-PTH negative correlation ($r = -0.145$, $p = 0.042$). However, in the DM + OP group, PTH was nearly constant across HbA1c

strata (44.7 to 40.0 to 40.0 ng/L), showing a "PTH floor effect." Bone turnover markers have been shown to predict fracture risk in diabetes [19][20]. Possible mechanisms include: (1) AGEs oxidatively modifying the CaSR extracellular domain [21][22]; (2) microangiopathy impairing parathyroid blood supply; (3) vitamin D-PTH axis shift.

Clinical Significance

PTH is a core regulator of normal bone remodeling. Chronic PTH suppression may lead to bone microdamage accumulation and increased fracture risk despite normal BMD [23][24]. We propose triple screening for DM + OP patients: DXA + BTMs + PTH, to improve fracture risk assessment accuracy [25][26].

Methodological Implications

This study reveals a methodological pitfall: antiresorptive drug exposure in control groups must be identified and excluded [27][28]. Recommendations: (1) use pharmaceutical order records as gold standard; (2) distinguish denosumab doses; (3) judge zoledronic acid indication by department/diagnosis.

Limitations

(1) Cross-sectional design; (2) Single-center retrospective data; (3) DM + OP group used antiresorptive drugs; (4) Lack of BMD data; (5) 1,25(OH)₂VitD and FGF23 not measured; (6) PSM only matched age and sex.

Conclusions

After excluding antiresorptive drug confounders and using PSM-matched pure DM controls, bone turnover markers in DM + OP patients showed no significant difference from controls - the classic "diabetic low bone turnover" hypothesis is not supported. PTH suppression (22.6% reduction) with mild hypercalcemia is a distinct feature of DM + OP, suggesting CaSR sensitivity alteration or functional hypoparathyroidism. DM + OP patients also exhibit "glycemic-bone turnover uncoupling." We recommend combined DXA+BTMs + PTH triple screening for DM + OP patients.

Declarations

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Supplementary Information

The online version contains supplementary material available at [DOI to be inserted by publisher].

Author contributions

Xiaotian Huang: Conceptualization, Methodology, Formal analysis, Writing – original draft. Yiwen Wang: Data curation, Investigation, Writing – review & editing. Hao Chen: Data curation, Investigation. Jiaoyang Zheng: Conceptualization, Supervision, Writing – review & editing. All authors read and approved the final manuscript.

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Data availability

The datasets generated and analyzed during the current study are not publicly available due to privacy and ethical considerations but can be available from the corresponding author upon reasonable request.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of Shanghai Changzheng Hospital (approval No. 2022SL047) and was conducted in accordance with the Declaration of Helsinki. The original ethics approval was granted for a study on denosumab treatment in postmenopausal osteoporosis, which was subsequently expanded to include the retrospective analysis of bone metabolism in patients with type 2 diabetes mellitus and osteoporosis. The requirement for informed consent was waived due to the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Figures

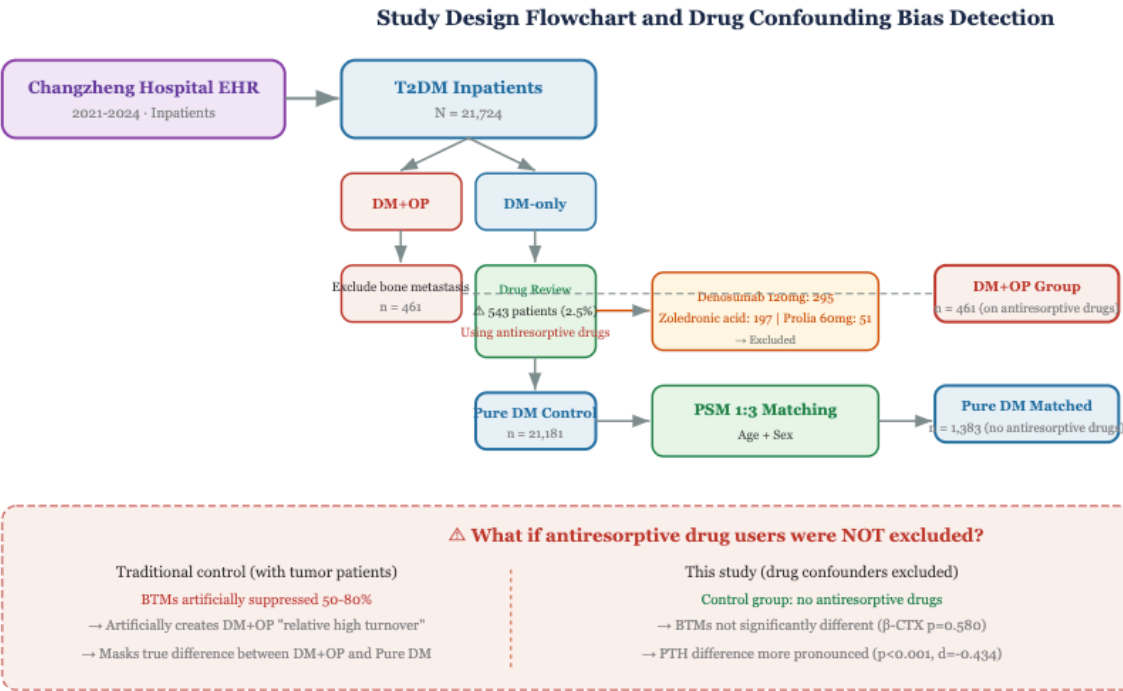


Figure 1

Study design flowchart and confounding-by-indication detection.

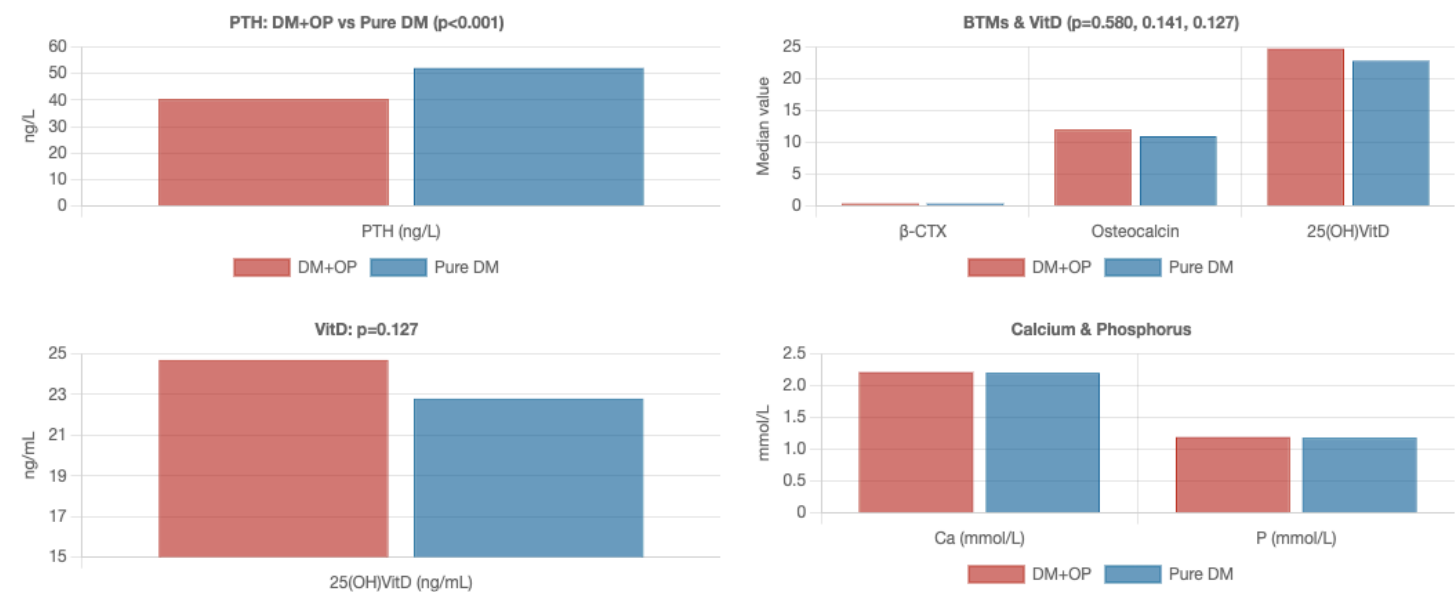


Figure 2. Box plots of bone metabolism markers. Boxes show IQR, middle line is median, whiskers show 1.5×IQR. (A) PTH significantly lower in DM+OP ($p < 0.001$, $d = -0.434$). (B) β -CTX and osteocalcin show no significant between-group differences. (C) 25(OH)VitD below 30 ng/mL in both groups. (D) Serum calcium slightly higher in DM+OP ($p = 0.043$).

Figure 2

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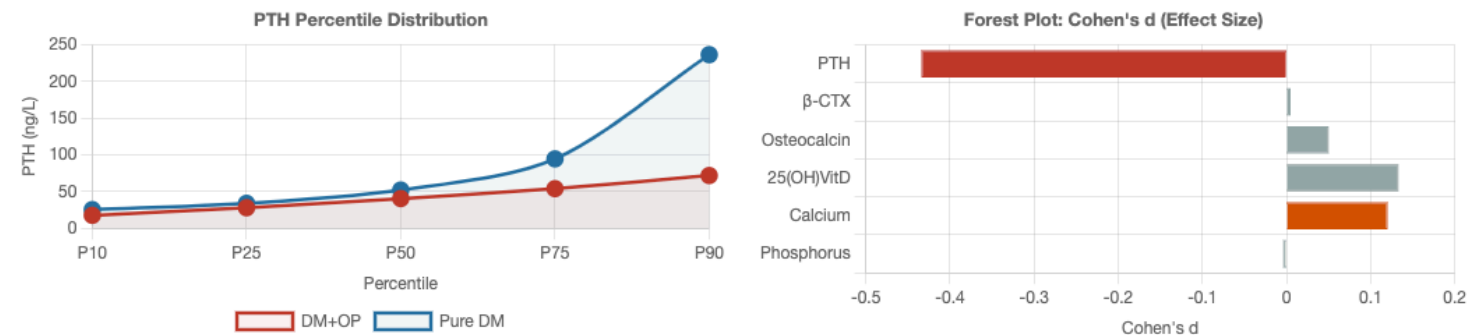


Figure 3. (A) PTH percentile distribution curves, DM+OP (red) shifted left, P75-P90 divergence suggests impaired PTH reserve. (B) Forest plot of Cohen's d for each indicator. PTH is the only indicator with medium effect size ($d = -0.434$); BTM effect sizes near zero.

Figure 3

See image above for figure legend

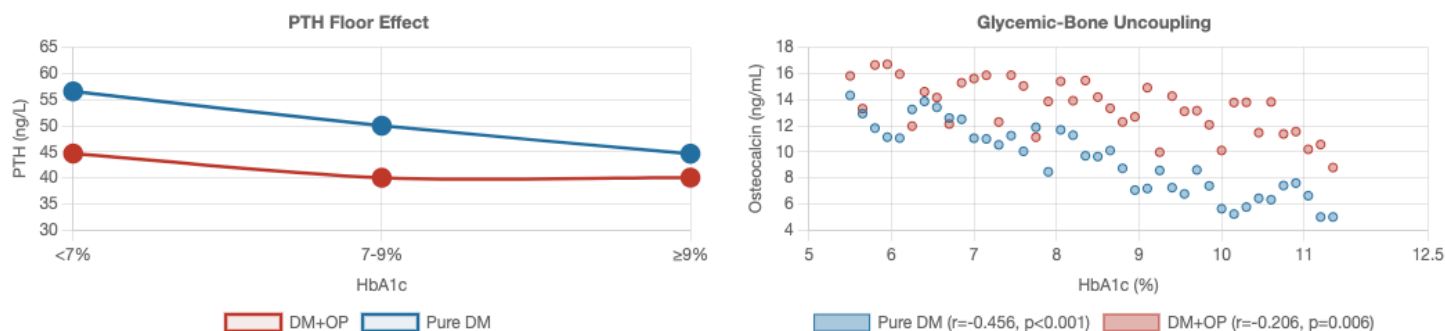


Figure 4. (A) PTH floor effect: Pure DM PTH declines with worsening HbA1c (blue line), DM+OP PTH nearly constant across strata (red line), suggesting loss of glucose-responsive PTH regulation. (B) Glycemic-bone turnover uncoupling: Pure DM shows strong HbA1c-osteocalcin negative correlation ($r=-0.456$), DM+OP shows attenuated correlation ($r=-0.206$), indicating shift from glucose-driven to CaSR/PTH-driven bone metabolism.

Figure 4

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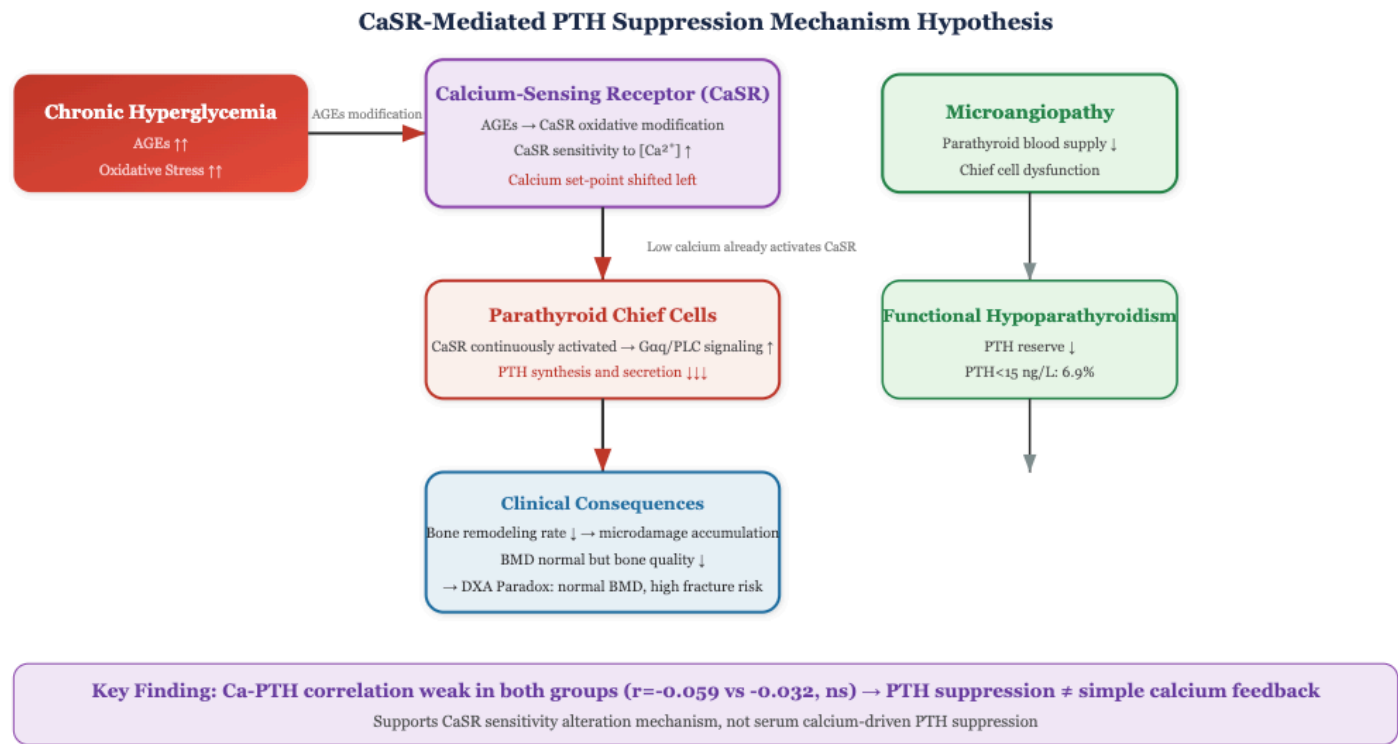


Figure 5. Proposed dual-pathway mechanism: CaSR hypersensitivity (left) + functional hypoparathyroidism (right) → PTH suppression → impaired bone quality despite normal BMD (DXA paradox).

Figure 5

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DXA Paradox and Triple-Screening Strategy

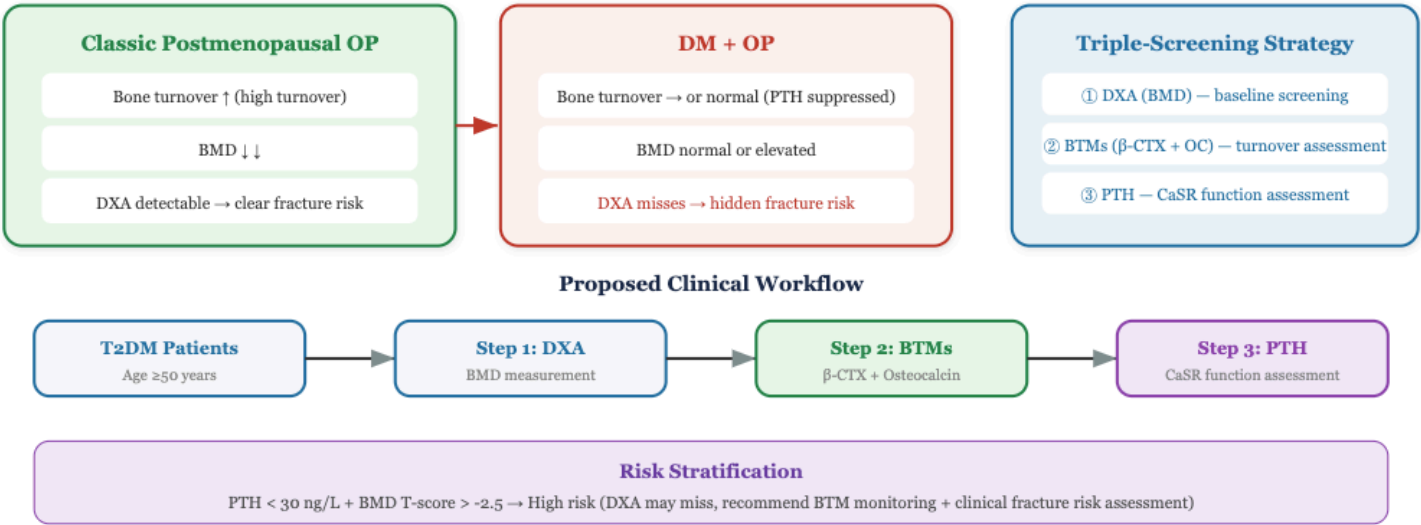


Figure 6. DXA paradox illustrated and proposed triple-screening workflow. In DM+OP, normal BMD does not exclude high fracture risk; PTH and BTMs add orthogonal information.

Figure 6

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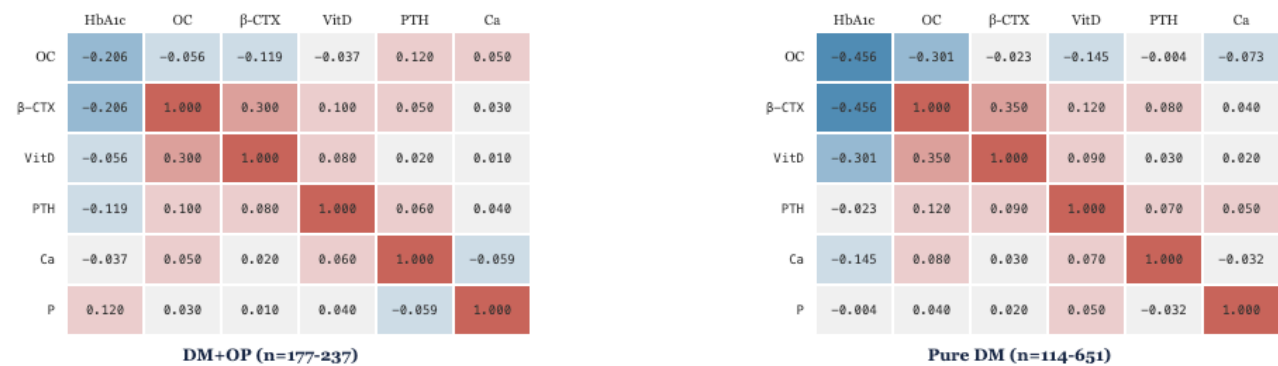


Figure 7. Correlation matrix heatmap. Left: DM+OP group, Right: Pure DM control group. Color intensity represents |Spearman r|, red=negative correlation, blue=positive correlation. Pure DM shows clear HbA1c-osteocalcin strong negative correlation ($r=-0.456$), while DM+OP shows significantly attenuated correlation ($r=-0.206$), demonstrating glycemic-bone turnover uncoupling.

Figure 7

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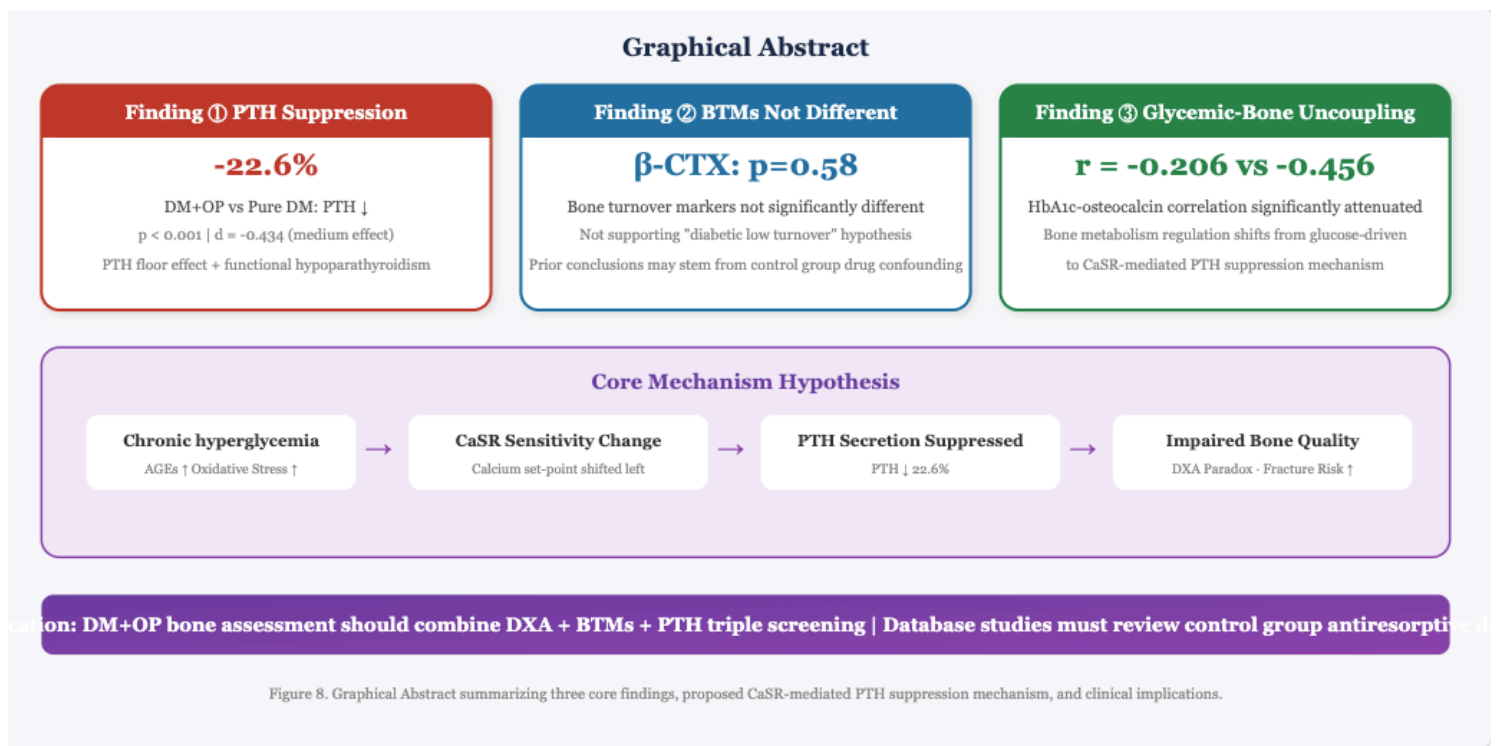


Figure 8

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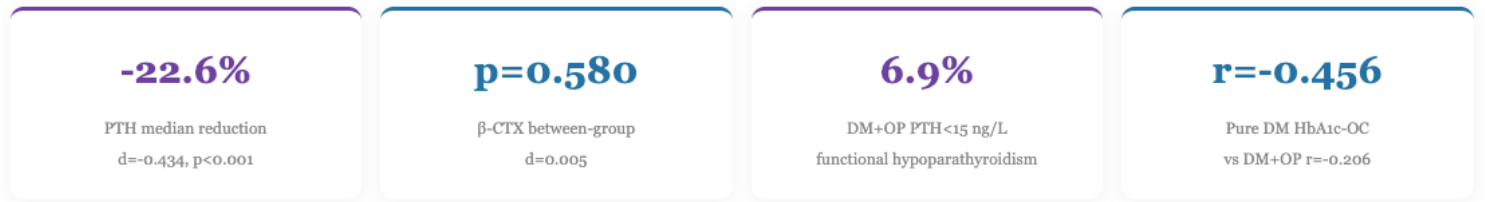


Figure 9

Unnumbered image in the Discussion Section

Supplementary Files

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