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BEYOND ANTIRESORPTION: CALIXARENE-METHYLENE-BISPHOSPHONIC ACIDS MODULATE BONE TURNOVER IN OVARIECTOMIZED RATS

Background/Aim. Antiresorptive therapy limits osteoclast-driven bone loss, but excessive suppression of turnover remains a concern. Calixarene-methylene-bisphosphonic acids (CMBAs) are supramolecular bisphosphonate-like compounds with potential osteoregulatory properties. This study evaluated C145 and C1249 in estrogen-deficiency-induced osteoporosis. **Methods.** Osteoporosis was induced by bilateral ovariectomy in female Wistar rats. After 12 weeks, animals received vitamin D₃, zoledronic acid, or C145/C1249 with vitamin D₃ for 12 weeks. Zoledronic acid, C145 and C1249 were administered orally at 40 µg/kg every 2 weeks. Serum deoxypyridinoline, CTX-1 and P1NP were assessed as bone-turnover markers. TRAP, cathepsin K, osteocalcin and β-catenin were analyzed in bone by RT-PCR and immunoblotting. Prothrombin time and activated partial thromboplastin time served as hemostatic safety endpoints. **Results.** Ovariectomy induced high-turnover bone loss with enhanced resorption and increased formation. P1NP increased by ~70% versus intact animals, whereas β-catenin mRNA decreased by 42%. Zoledronic acid produced the strongest antiresorptive effect and reduced P1NP by ~45% versus ovariectomized controls. C145 decreased CTX-1 by ~25%, while C145 and C1249 reduced P1NP by 20–30% but maintained it above intact values, indicating attenuation of excessive turnover without comparable suppression of formation. C1249 and C145 increased total β-catenin protein by ~15% and ~25%, respectively. These protein changes did not fully parallel mRNA responses, suggesting regulation beyond transcription; however, without assessment of β-catenin activation status or canonical Wnt target genes, they can't be interpreted as evidence of Wnt/β-catenin pathway activation. TRAP and cathepsin K changes were consistent with a less resorptive phenotype. Hemostatic parameters remained unchanged. **Conclusions.** C145 showed the most favorable profile, attenuating bone resorption while preserving residual bone-forming activity. Its effects were accompanied by partial restoration of β-catenin protein abundance, although activation of canonical Wnt/β-catenin signaling cannot be concluded. These findings support further evaluation of calixarene-based bisphosphonate analogues as modulators of pathological bone turnover. **Grants/Funding.** Funded by NAS of Ukraine grants to young scientists' research groups, 2024–2025, project No. 0124U002507.

Keywords: osteoporosis, ovariectomy, bone turnover, calixarene-methylene-bisphosphonic acids, C145, C1249, CTX-1, P1NP, β-catenin.

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