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Journal of Bone Research

Opinion Article

Sclerostin Antibody Treatment Restores Bone Mass Through Enhanced Wnt/β-Catenin Signaling in Aged Ovariectomized Mice

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DESCRIPTION

Postmenopausal osteoporosis represents a major public health concern affecting millions of women worldwide. The decline in estrogen levels following menopause leads to increased bone resorption and decreased bone formation, resulting in trabecular bone loss and increased fracture risk. Sclerostin, a glycoprotein produced by osteocytes, functions as a negative regulator of bone formation through inhibition of Wnt/β-catenin signaling. This investigation evaluated the therapeutic potential of sclerostin antibody treatment in reversing age-related bone loss in an ovariectomized mouse model.

Twenty-four-month-old female C57BL/6J mice underwent bilateral Ovariectomy (OVX) or sham surgery to model postmenopausal osteoporosis. Following a 12-week period to establish bone loss, mice were randomized to receive either anti-sclerostin antibody (25 mg/kg) or vehicle control administered subcutaneously twice weekly for 16 weeks. Bone Mineral Density (BMD) was monitored using Dual-energy X-ray Absorptiometry (DXA) at baseline, post-OVX, and following treatment periods.

Micro-Computed Tomography (μCT) analysis of lumbar vertebrae revealed significant trabecular bone loss in OVX mice compared to sham controls, with 42% reduction in bone volume fraction (BV/TV), 38% decrease in Trabecular Thickness (Tb.Th), and 34% reduction in Trabecular Number (Tb.N). Cortical parameters showed modest changes, with 8% decrease in cortical thickness and 12% reduction in cortical area. These changes were consistent with the trabecular bone loss pattern observed in postmenopausal women.

Anti-sclerostin antibody treatment resulted in dramatic improvements in trabecular bone parameters, with BV/TV increasing by 156% compared to vehicle-treated OVX mice. Trabecular thickness increased by 89%, while trabecular number improved by 67%. Importantly, these improvements exceeded baseline levels, with treated mice showing superior bone architecture compared to sham-operated controls. Cortical bone also benefited from treatment, with 23% increase in cortical thickness and 18% improvement in cortical area.

Histomorphometric analysis revealed that anti-sclerostin treatment significantly enhanced bone formation parameters. Osteoblast surface per bone surface increased by 185%, while mineral apposition rate improved by 142%. Bone formation rate increased by 298% compared to vehicle controls. Importantly, bone resorption parameters remained unchanged, indicating that the anabolic effects occurred independently of anti-resorptive mechanisms.

Molecular analysis using quantitative PCR demonstrated enhanced expression of Wnt target genes in bone tissue from treated mice. β-catenin expression increased by 2.7-fold, while downstream targets including Runx2, osterix, and osteocalcin showed 3.2-fold, 2.8-fold, and 4.1-fold increases, respectively. Immunohistochemical analysis confirmed increased nuclear β-catenin localization in osteoblasts, indicating enhanced Wnt signaling activation.

Mechanical testing using three-point bending revealed that anti-sclerostin treatment significantly improved bone strength. Ultimate load increased by 67%, while energy to failure improved by 89% compared to vehicle-treated OVX mice. The restored bone strength suggests that anti-sclerostin treatment produces functionally relevant bone quality improvements. Serum biomarker analysis confirmed the bone formation-promoting effects of anti-sclerostin treatment. Osteocalcin levels increased by 234%, while P1NP (procollagen type I N-terminal propeptide) levels improved by 198%. Bone resorption markers including CTX-I (C-terminal telopeptide of type I collagen) remained unchanged, confirming the primarily anabolic mechanism of action.

CONCLUSION

Anti-sclerostin antibody treatment effectively reverses age-related bone loss in ovariectomized mice through enhanced Wnt/β-catenin signaling and increased bone formation. The dramatic improvements in trabecular architecture, cortical parameters, and mechanical properties demonstrate the therapeutic potential of this approach for treating postmenopausal osteoporosis. These findings support the clinical development of sclerostin

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Received: 28-Feb-2025, Manuscript No. BMRJ-25-38133; **Editor assigned:** 03-Mar-2025, PreQC No. BMRJ-25-38133 (PQ); **Reviewed:** 17-Mar-2025, QC No. BMRJ-25-38133; **Revised:** 24-Mar-2025, Manuscript No. BMRJ-25-38133 (R); **Published:** 31-Mar-2025, DOI: 10.35841/2572-4916.25.13.315

Citation: Cheng Q (2025). Sclerostin Antibody Treatment Restores Bone Mass Through Enhanced Wnt/β-Catenin Signaling in Aged Ovariectomized Mice. J Bone Res. 13:315.

antibodies as anabolic therapies for osteoporosis and provide mechanistic insights into Wnt signaling modulation in bone. Importantly, these mechanical improvements correlated strongly with structural parameters, particularly trabecular bone volume and connectivity.