

From Structure to Function: Restoring Mechanical Performance During Bone Regeneration

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Abstract

Understanding how mechanical function is restored during bone regeneration is essential to assess the limits of current strategies and to inform future approaches for effective bone repair. In this study, rat cranial defects (3 mm in diameter) were treated using three well-established strategies: autologous bone grafts (BG), providing both osteoconductive and osteoinductive support and still considered the clinical gold standard; biphasic calcium phosphate (BCP), providing only osteoconductive support; and BCP combined with total bone marrow (BCP+TBM), introducing additional osteoinductive potential. A multiscale characterization strategy combining in situ synchrotron scattering, nanoindentation, microcomputed tomography, and histology was employed to monitor the time- and space-resolved evolution of structural and mechanical properties throughout regeneration, from the crystal to the bone-matrix scale, for the various treatments. This comparative approach aimed to assess the extent to which the addition of TBM to a synthetic scaffold improves the mechanical recovery of regenerated bone. The results show that BCP alone fails to restore bone mechanical properties after 20 weeks of regeneration, while the

addition of TBM significantly enhances regeneration, although it does not reach the performance of autologous bone grafts. While limited bone formation is observed at defect edges for BCP implants, the addition of TBM promotes increased bone formation around BCP grains, with a bone mass increase of 31% for BCP+TBM and 24% for BCP-alone at 20 weeks post-surgery (compared with 35-40% for BG), and favors the development of lamellar tissue, although the remodeling remains incomplete throughout the neoformed bone. At this stage, both implant strategies lead to a similar mechanical response of the hydroxyapatite crystals in the regenerated and adjacent native bone. Notably, although structural organization and crystallographic orientation of hydroxyapatite relative to native bone are restored, this recovery does not translate into full restoration of mechanical function at the bone-matrix scale (indentation modulus of 22 GPa for native tissue, 5.1 GPa for BCP-regenerated tissue, and 7.1 GPa for BCP+TBM-regenerated tissue), even for autologous BG (7.4 GPa for regenerated tissue). These findings reveal a critical decoupling between crystallographic organization and tissue-level mechanical performance during regeneration. This work provides fundamental insight into the limitations of current approaches and highlights the need for improved designs that control bone regeneration beyond structural reconstruction alone. It demonstrates the importance of coupled multiscale mechano-structural analyses for deciphering bone regeneration processes. Designing next-generation biomaterials for functional bone regeneration will require moving beyond structural mimicry toward implants that actively guide tissue formation through coupled mechanical and biological cues, including the spatiotemporally controlled delivery of osteoinduction and osteogenesis inducers.

Keywords:

bone regeneration implant materials mechanical properties synchrotron X-ray diffraction nanoindentation