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Enhanced regeneration of large segmental bone defects via hierarchically structured bioactive scaffolds

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ABSTRACT

Repairing large segmental bone defects poses significant challenges in reconstructive surgery, due to the need for scaffolds that balance robust mechanical properties with effective bone regeneration performance. Hierarchically structured scaffolds designed to mimic the native bone microenvironment have shown significant potential but often fail to fully address this balance. In this study, we propose an approach by integrating autogenous lyophilized platelet-rich fibrin (L-PRF)—a rich source of platelets and growth factors—with a 3D-printed β-tricalcium phosphate (β-TCP) ceramic framework to manufacture a hierarchically structured bioactive L-PRF/β-TCP composite scaffold. The β-TCP ceramic framework ensures robust mechanical support, while the L-PRF offers an extracellular matrix (ECM)-like bioactive microenvironment that enhances cellular responses and enables a sustained release of autologous bioactive factors. Comprehensive *in vitro* and *in vivo* assessments demonstrate the superior efficacy of the scaffold in promoting bone regeneration, positioning it as a highly promising bioactive material for large segmental bone defect repair in bone tissue engineering.

1. Introduction

Repairing large segmental bone defects poses significant challenges in reconstructive surgery, primarily due to the complex structural, mechanical, and biological demands necessary for effective tissue regeneration[1–3]. Traditional repair options, such as autografts, allografts, and synthetic substitutes, each have critical limitations. Autografts, regarded as the gold standard, are constrained by donor site morbidity and limited availability. Allografts, while bypassing these limitations of autografts, are associated with risks of immune rejection and inconsistent integration with host tissue[4,5]. Synthetic materials, despite their versatility, often fail to meet the requirements for large bone defect repairs, due to limited bioactivity, inadequate vascularization, and insufficient mechanical support under physiological loads. These factors frequently lead to delayed or incomplete bone regeneration[2,3,6].

In recent years, bone tissue engineering (BTE) scaffolds have opened new avenues for addressing these challenges, combining advanced structural designs with multifunctional properties[1,7–9]. Among these, three-dimensional (3D) printing[10,11], has revolutionized the field by enabling the fabrication of customized scaffolds, particularly with calcium phosphate-based bioceramics such as β-tricalcium phosphate (β-TCP)[12,13]. These scaffolds can closely mimic the mechanical and

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