Magnesium Nanocomposite Hydrogels Demonstrating Controllable Gelation and Tissue Integration Accelerate Necrotic Bone Regeneration

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INTRODUCTION: Nowadays, a critical side effect observed in patients undergoing long-term bisphosphonate (BPs)-administration is the increased risk of predisposing BPs-related osteonecrosis of the jaw (BRONJ), this refers to the presence of necrotic bone in the jaw with multiple pathological mechanism including impaired healing capacity, diminished angiogenesis, susceptibility to infections and M1 macrophage polarization. Given the urgency to explore potential treatments that can alleviate BRONJ progression and promote mandible regeneration after necrotic debridement, magnesium (Mg) implants and the degraded products Mg^{2+} have garnered attention. Previous studies have reported the ability of Mg^{2+} to regulate various cellular functions, combat inflammation, and upregulate genes favoring osteogenesis and angiogenesis. In this study, taking into account the significance of aesthetic restoration of facial structures, we report a strategy for tuning the gelation kinetics of Amidation reactions by bioactive nanoparticles, magnesium-oxide nanoparticles (MgO-NPs), which are utilized to fabricate controllable crosslinked hydrogels with enhanced mechanical strength and superior osteopromotive capabilities for mandible regeneration and further uncover the healing mechanism.

METHODS: A modified version of Polyethylene glycol hydrogel (PEG) called Magnesium Nanocomposite (PBR@MgO) hydrogel was developed. The precursor solution was uniformly mixed with MgO nanoparticles (NPs) to precisely control the gelation time, ensuring injectability for minimal invasive therapy. The PBR@MgO hydrogels were characterized for their mechanical properties, degradation behaviors, and cellular functions, including osteogenic and angiogenic properties, through quantitative PCR (qPCR) and immunofluorescence (IF) staining. Subsequently, we successfully established a BRONJ rat model and evaluated the therapeutic efficacy of PBR@MgO hydrogel using radiography and histology techniques. The underlying mechanism was further explored through RNA bulk sequencing. Finally, the treatment effect was also verified in a large animal model, the porcine mandible defect.

RESULTS SECTION: By incorporating MgO nanoparticles, the PBR@MgO hydrogel demonstrated controllable gelation behavior, ensuring injectability, strong adhesion, improved mechanical properties, and rapid functionality in hemorrhage situations. *In vitro*, The introduction of MgO NPs and the crosslinked RGD peptide improved the cell adhesion, infiltration, osteogenic and angiogenic differentiation than conventional PEG hydrogels. *In vivo*, PBR@MgO hydrogel implantation augmented mandible formation in BRONJ with enhanced osteogenesis-angiogenesis coupling, the regenerated bone harbored more abundant Type H vessels and associated Osx^{+} osteoprogenitor cells in PBR@MgO group. Notably, the promotion of mandible formation was also observed in the porcine mandible defect model.

DISCUSSION: In the context of the multifactorially induced disease BRONJ, Mg plays a crucial role in various aspects including osteogenesis, angiogenesis, inflammation inhibition, and maintenance of bone homeostasis. Leveraging the therapeutic potential of Mg, we developed a PBR@MgO hydrogel demonstrating controllable gelation, improved mechanical strength, and osteopromotive properties, making it a promising candidate for addressing bone regeneration in pathological conditions and offering potential benefits in minimally invasive surgery.

SIGNIFICANCE/CLINICAL RELEVANCE: Controllable crosslinked and strong osteoinductive ability provide the PBR@MgO hydrogel with promising clinical translation potential in multifactorially induced BRONJ treatment and complex maxillofacial tissue reconstruction.

REFERENCES: [1] Guo J, et al. Bioact Mater. 2022;22;21:175-193. [2] Ensrud KE. JAMA. 2021;5;325(1):96. [3] Rupel K, et al. Oral Oncol. 2014;50(11): 49-57. [4] Zhang Y, Xu J, et al. Nat Med. 2016;22(10):1160-1169. [5] Zheng N, Xu J, et al., Mat. Today, 2022; 52:43-62

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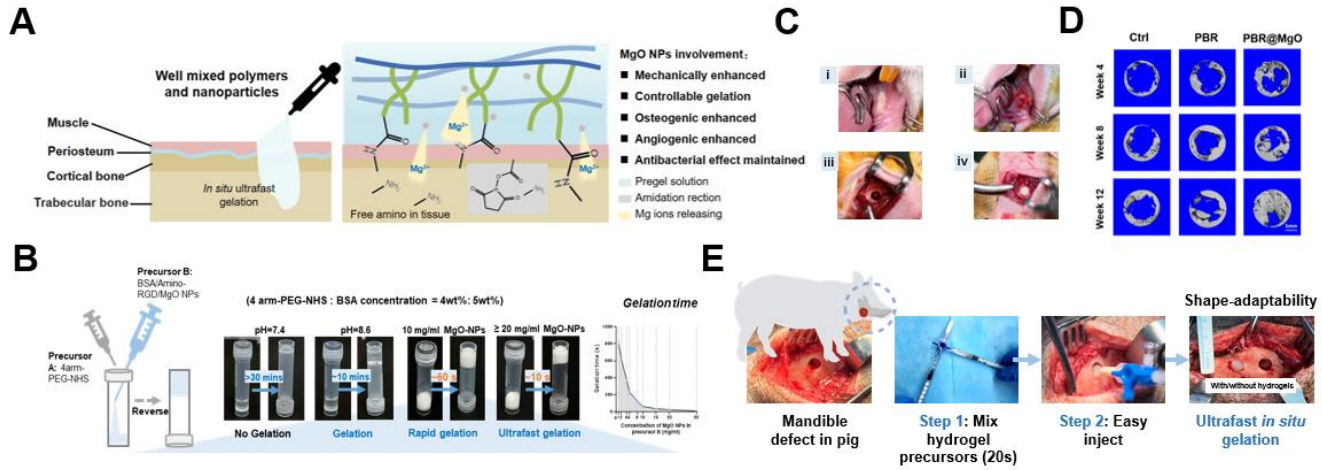
IMAGES AND TABLES:



(A) Illustration of hydrogel design. (B) Demonstration of controllable gelation property. (C) Surgical procedures involving mandible defect creation and implant fixation in BRONJ. (D) 3D Micro-CT reconstruction of mandible defect area after the implantation of hydrogels. (E) Surgical imaging of the treatment to mandible defect, injecting hydrogels and defect filling.