Gelatin-based hydrogel creates a rejuvenating microenvironment to enhance osteoporotic bone regeneration

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INTRODUCTION: The regeneration ability of osteoporotic bone is impaired and there is a delay in osteoporotic bone defect healing. To address this challenge, we propose a gelatin-based hydrogel that supports the osteogenic differentiation of endogenous mesenchymal stem cells (MSCs) in an osteoporotic bone defect rat model.

METHODS: The study had been approved by the institutional animal experimentation ethics committee. Our hydrogel is created through host-guest complexation between the aromatic residues of gelatin and acrylated β-cyclodextrin (β-CD) monomers, resulting in supramolecular gelatin hydrogel referred to as GelCD hydrogel. After that, we incorporated human fetal MSCs secretome (HFS) into GelCD hydrogel (GelHFS) to mimic a rejuvenated niche. We evaluated the biomechanical properties and biocompatibility of both GelCD and GelHFS hydrogels. The effectiveness of hydrogels in promoting bone regeneration was tested using an osteoporotic bone defect rat model. Specifically, we ovariectomized Sprague-Dawley rats and, after three months, created bone defects in their distal femurs. Post-surgery, rats were grouped into control, GelCD, and GelHFS, based on whether they received no implant, GelCD hydrogel, or GelHFS hydrogel, respectively. Bone regeneration was then assessed via micro-CT, histology, double fluorescence labeling, and immunohistochemistry.

RESULTS SECTION: Our results revealed that GelHFS hydrogel has a significant impact on MSCs behaviors, enhancing MSCs spreading, migration, and osteogenic differentiation via the integrin β1-induced focal adhesion pathway. In osteoporotic bone defect rats, GelHFS hydrogel implantations led to significant increases in bone volume and bone mineral density of the newly formed tissue as early as 2 weeks post-surgery, compared to the GelCD group ($P<0.001$). Moreover, the GelHFS group demonstrated superior biomechanical properties, including significantly higher stiffness and ultimate load, compared to the GelCD group after 8 weeks of implantation ($P<0.05$ and $P<0.05$, respectively). Consistent with the *in vitro* findings, the GelHFS hydrogel was found to recruit integrin β1-expressing endogenous cells, thereby facilitating new bone formation. GelHFS hydrogel also displayed an accelerated degradation behavior in osteoporotic bones when compared to GelCD hydrogel.

DISCUSSION: Our findings reveal that GelHFS hydrogel establishes a rejuvenating microenvironment, effectively attracting endogenous cells and promoting osteogenic differentiation of MSCs, which subsequently results in the formation of new bone tissue. Furthermore, the results indicated that GelHFS hydrogel exhibited a temporally coordinated degradation pattern, which corresponded to the formation of new bone at the defect site.

SIGNIFICANCE/CLINICAL RELEVANCE: These insights indicate that GelHFS hydrogel may serve as a promising bone graft to facilitate bone regeneration in cases of osteoporotic bone defects.

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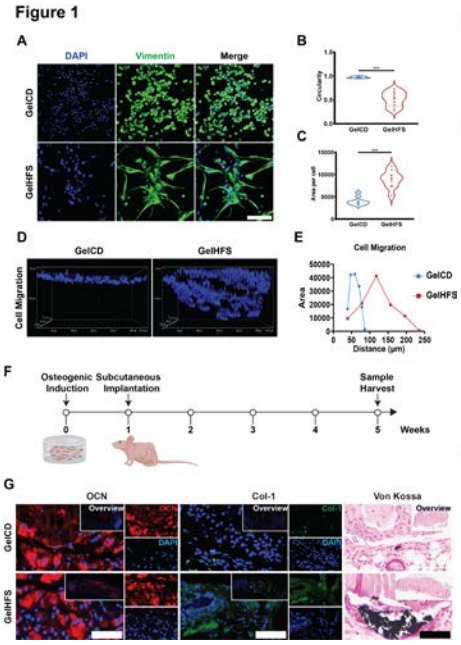
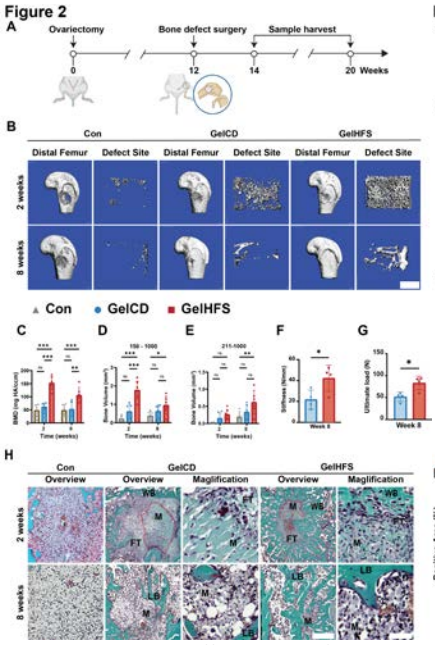
IMAGES AND TABLES:





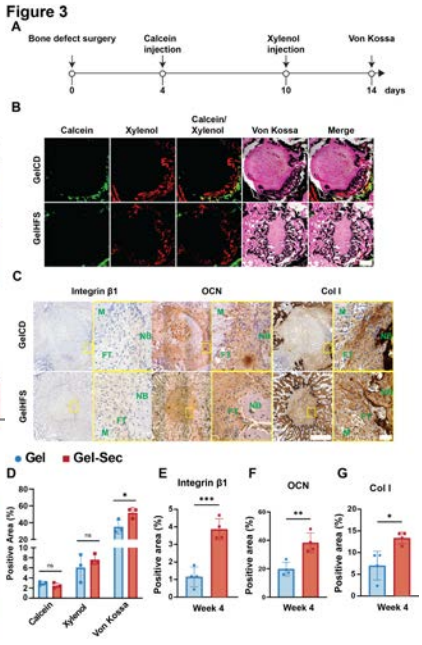


Figure 1. GelHFS hydrogel promotes spreading, migration and osteogenic differentiation of MSCs
Figure 2. GelHFS hydrogel enhances bone regeneration in osteoporotic model
Figure 3. GelHFS hydrogel recruits integrin β1+ cells into the defect site