Developing Biomimetic Anisotropic Bioceramic Scaffolds through Computer-aided Design and 3D Printing for Bone Tissue Regeneration

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INTRODUCTION: Various bone tissue engineering (BTE) scaffolds have been developed for bone regeneration in human bodies and many of them are isotropic porous structures. Biomimetic scaffolds that mimic native tissue structures are shown to perform better in body tissue regeneration and hence have attract great attention in the tissue engineering field (C.Wang, et al., “3D printing of bone tissue engineering scaffolds”, *Bioact Mater*, 2020, 5(1): 82-91). Both cortical and cancellous bones are structurally anisotropic with anisotropic pore shape and pore distributions for withstanding heavy loads in specific directions in areas such as hip. Voronoi-structure based BTE scaffolds have random pore distributions and are shown to facilitate bone regeneration (Z.Zhao, et al., "Mechanical and permeability properties of porous scaffolds developed by a Voronoi tessellation for bone tissue engineering," *J. Mater. Chem. B*, 2022, 10(46): 9699-9712). Voronoi-type scaffold models are created via computer-aided design (CAD) and may be further improved to be biomimetic anisotropic structures for regenerating bone. As biphasic calcium phosphate (BCP) bioceramic is both osteoconductive and biodegradable (J.M.Bouler, et al., “Biphasic calcium phosphate ceramics for bone reconstruction: A review of biological response”, *Acta Biomater*, 2017, 53: 1-12), it is a promising biomaterial for BTE scaffolds. In this study, anisotropic Voronoi-type BTE scaffolds with longitudinally elongated structures were designed via CAD and their mechanical behaviour/properties were analyzed through computational simulation using the finite element analysis (FEA) method. The designed anisotropic scaffolds were fabricated using digital light processing (DLP, a 3D printing technology), and sintered scaffolds were assessed using compression tests.

METHODS: Pore-uniform Voronoi structure-based scaffolds (Φ10mm×10mm; strut thickness: 1.0mm) with porosities of 60, 70 and 80% were firstly designed by using nTopology software through seeding points stochastically in the Voronoi tessellation method. These uniform Voronoi-type scaffolds were then under manipulation by stretching the structures in the longitudinal direction (stretching factor: 2) but remaining unchanged in other directions, thereby achieving longitudinally elongated Voronoi-type scaffolds with the same porosity. Afterwards, precise meshing was performed and FEA was conducted on elongated Voronoi-type scaffold models using softwares nTopology and Ansys. A highly printable BCP ink was prepared for DLP 3D printing, featuring a solid loading of 70 wt.% to ensure printing efficiency and scaffold shape fidelity. A bottom-up DLP 3D printer was used to produce BCP scaffolds of the elongated Voronoi-type, with the printing parameters being systematically studied. As-printed BCP-based structures underwent debinding and sintering to ultimately form anisotropic BCP scaffolds. These anisotropic scaffolds were subjected to experimental assessments, mechanical and biological.

RESULTS: Elongated Voronoi-type scaffolds were successfully designed having different porosities (Fig.1). FEA showed that the stiffness and strength of elongated Voronoi-type scaffolds were influenced remarkably by their porosity. Von Mises stress distribution diagrams revealed that stress concentration areas mostly occurred around the connection nodes between struts in different directions (Fig.1). Compared with pore-uniform Voronoi-type scaffolds of the same porosity, the longitudinally elongated scaffolds had a higher load-bearing ability in the longitudinal direction, with 33.3%, 38.1% and 48.8% reduction on compressive strain for 60%, 70%, and 80% porosity, respectively. The high stress concentrated areas were dramatically decreased for elongated scaffolds as compared with uniform scaffolds, with the maximum von Mises stress being reduced by 28.8%, 27.7% and 26.7% for 60%, 70%, and 80% porosity, respectively. The high printability of BCP inks ensured high-fidelity of DLP 3D printed elongated Voronoi-type structures (Fig.2). High-fidelity was maintained for sintered BCP scaffolds without cracks or collapses. The compression test results of sintered BCP scaffolds were in agreement with FEA results.

DISCUSSION: Strengthening isotropic Voronoi-type scaffolds in one direction could be achieved by turning them into anisotropic scaffolds via CAD at the scaffold designing stage. Anisotropic, osteoconductive and biodegradable BCP bioceramic scaffolds could be successfully made according to these designs through DLP 3D printing and sintering. FEA and experimental results showed that these BCP scaffolds were mechanically stronger in the longitudinal direction. FEA analyses also pointed out significantly reduced stress concentrations in the longitudinal direction as compared to original isotropic Voronoi-type scaffolds, which is highly important for bioceramic-based BTE scaffolds. Integrating CAD and 3D printing, with the assistance of computational simulation, could effectively develop new anisotropic scaffolds for bone regeneration.

SIGNIFICANCE/CLINICAL RELEVANCE: Developing anisotropic, strengthened Voronoi-type BTE scaffolds could be realized through integrating CAD and 3D printing, which could be assisted by computational simulation such as FEA. BCP bioceramic, as an outstanding osteoconductive material, could be made into anisotropic, strengthened scaffolds to meet specific requirements for bone tissue regeneration in orthopedic and reconstructive surgeries.

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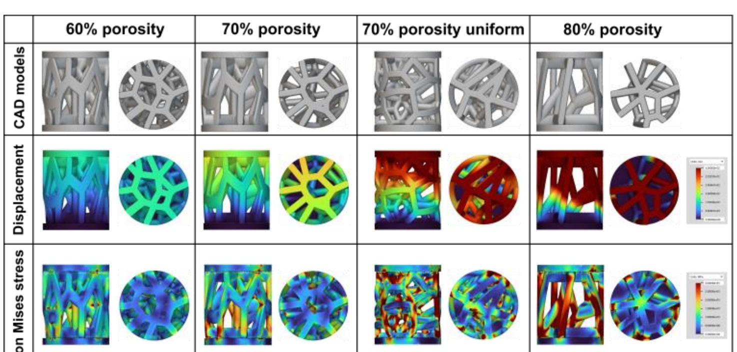

Fig.1 CAD-designed anisotropic Voronoi-type bone tissue engineering scaffolds of different porosities and computational simulation results for compressive loads.

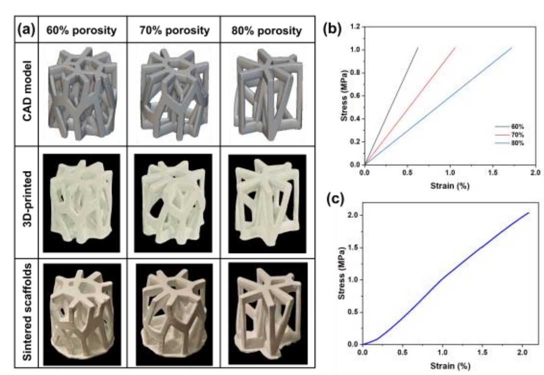

Fig.2 (a) Anisotropic biphasic calcium phosphate (BCP) scaffolds: designed, 3D printed, and sintered; (b) Stress-strain curves of anisotropic scaffolds predicted by computational simulation; (c) An experimental stress-strain curve of a sintered anisotropic BCP scaffold (70% porosity)