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Creation of bioactive glass (13–93) scaffolds for structural bone repair using a combined finite element modeling and rapid prototyping approach

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ABSTRACT

There is a clinical need for synthetic bioactive materials that can reliably repair intercalary skeletal tissue loss in load-bearing bones. Bioactive glasses have been investigated as one such material but their mechanical response has been a concern. Previously, we created bioactive silicate glass (13–93) scaffolds with a uniform grid-like microstructure which showed a compressive strength comparable to human cortical bone but a much lower flexural strength. In the present study, finite element modeling (FEM) was used to re-design the scaffold microstructure to improve its flexural strength without significantly lowering its compressive strength and ability to support bone infiltration in vivo. Then scaffolds with the requisite microstructures were created by a robotic deposition method and tested in four-point bending and compression to validate the FEM simulations. In general, the data validated the predictions of the FEM simulations. Scaffolds with a porosity gradient, composed of a less porous outer region and a more porous inner region, showed a flexural strength (34 ± 5 MPa) that was more than twice the value for the uniform grid-like microstructure (15 ± 5 MPa) and a higher compressive strength (88 ± 20 MPa) than the grid-like microstructure (72 ± 10 MPa). Upon implantation of the scaffolds for 12 weeks in rat calvarial defects in vivo, the amount of new bone that infiltrated the pore space of the scaffolds with the porosity gradient (37 ± 16%) was similar to that for the grid-like scaffolds (35 ± 6%). These scaffolds with a porosity gradient that better mimics the microstructure of human long bone could provide more reliable implants for structural bone repair.

1. Introduction

The repair of large structural bone defects such as segmental defects in the long bones of the limbs is a challenging clinical problem [1]. In comparison, small, contained bone defects are repairable with commercially available osteoconductive and osteoinductive filler materials [2,3]. To treat structural bone loss, clinicians use bone allografts, autografts and porous metals. These materials are limited by cost, availability, durability, infection risk, donor site morbidity, and uncertain healing. Consequently, there is a clinical need for synthetic bioactive implants that can reliably repair intercalary skeletal tissue loss in load-bearing bones.

Bioactive glasses have been investigated as one such material since they are osteoconductive, convert to hydroxyapatite in vivo, heal readily to host bone and soft tissues, and they are amenable to fabrication into porous three-dimensional (3D) architectures [4–8]. In the form of particles and weak scaffolds, bioactive silicate glasses such as the glasses designated 45S5 and 13–93 are approved by the Food and Drug Administration (FDA) for in vivo use, and they are used clinically to reconstitute non-structural bone defects [8].

Advances in rapid prototyping techniques (also referred to as solid freeform fabrication or additive manufacturing) have resulted in more innovative design and unprecedented control of scaffold microstructures [9]. Recent studies have shown the ability to create porous 3D scaffolds of bioactive silicate glasses (13–93 and 6P53B) with compressive strength comparable to human cortical bone using rapid prototyping methods [10–15]. Our previous study showed that 13–93 bioactive glass scaffolds, created with a uniform grid-like microstructure by robocasting, had a compressive strength (86 ± 9 MPa) and an elastic modulus (13 ± 2 MPa) comparable to the human cortical bone [13]. In comparison, the flexural strength of the scaffolds (11 ± 3 MPa) was much lower than cortical bone (~100 MPa). While those scaffolds showed the capacity to heal critical size segmental defects in rat femurs [16], improvement in their flexural strength could alleviate concerns about their mechanical reliability in vivo.

Finite element modeling (FEM) has been widely used to analyze the mechanical response of biomaterials [17–20]. In a recent study, FEM was used to simulate the mechanical response of models composed of

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hydroxyapatite or beta-tricalcium phosphate with a cubic geometry and uniform grid-like structure [17]. Regions of the structure with the highest local stress were determined under loading in compression, tension or shear and used to predict the strength of scaffolds with the same grid-like microstructure. Scaffolds created by a robocasting method were tested in compression to validate the FEM simulations. However, the FEM analysis and mechanical testing were limited to a cubic geometry and a uniform grid-like structure. The mechanical response of alternative geometries relevant to bending (flexure), an important loading mode in structural bone, and alternative structures relevant to the non-uniform microstructure of human long bones were not analyzed or tested.

The cross section of long bones of the limbs has a non-uniform microstructure, composed of a less porous outer region of cortical bone (porosity = 5–10%) and a more porous inner region of trabecular bone (porosity = 50–90%). As outlined above, our previous studies showed that a uniform grid-like microstructure provided bioactive glass (13–93) scaffolds with promising compressive strength and capacity to support bone infiltration but a flexural strength that was much lower than cortical bone [13,21,22]. Because the uniform grid-like microstructure is limited in its ability to mimic the microstructure of human long bones, an investigation of alternative microstructures is warranted. When compared to an approach based on trial-and-error experiments, FEM simulations could provide a more efficient approach to predict the mechanical response of a variety of alternative microstructures.

The objective of the present study was to re-design the uniform grid-like microstructure used in our previous studies and determine whether alternative microstructures can impart higher flexural strength to 13–93 glass scaffolds without compromising their compressive strength and ability to support bone infiltration. FEM was used to simulate the mechanical response in flexure and compression for models with a variety of structures. Then scaffolds with the optimal microstructures predicted by FEM were created by robocasting and tested in four-point bending and in compression to validate the predictions of the FEM simulations. Scaffolds with the optimal microstructures were also implanted for 12 weeks in rat calvarial defects to evaluate their ability to support bone infiltration in vivo.

2. Materials and methods

2.1. Design of scaffold architecture

A uniform grid-like microstructure, in which the glass filaments in adjacent layers were arranged at right angles with reference to the *x* and *y* axes, was used as the reference structure and our approach was to modify the spatial arrangement of the filaments. The diameter of the glass filaments (330 μm) used in the FEM simulations was the same as the filaments in the uniform grid-like scaffolds created by robocasting in our previous studies [13,16,21,22]. In view of our interest in improving the flexural strength of the bioactive glass scaffolds while maintaining the promising compressive strength, the flexural mechanical response of the structures was analyzed first. Then the response of selected structures was analyzed in compression.

For the FEM analysis in flexure, a beam was selected as the macroscopic external shape of the physical model because this geometry is commonly used in the measurement of flexural strength by four-point bending. The external dimensions of the model (Fig. 1) were selected to avoid the use of excessive computing power and time. However, the dimensions of the model were still large enough to allow the use of enough layers to create a porosity gradient in the structure and to create scaffolds with similar dimensions for experimental four-point bending tests.

Each model was composed of 13 alternating orthogonal layers of parallel filaments. The length and angle of the filaments and the spacing between the parallel filaments were defined for each layer. With

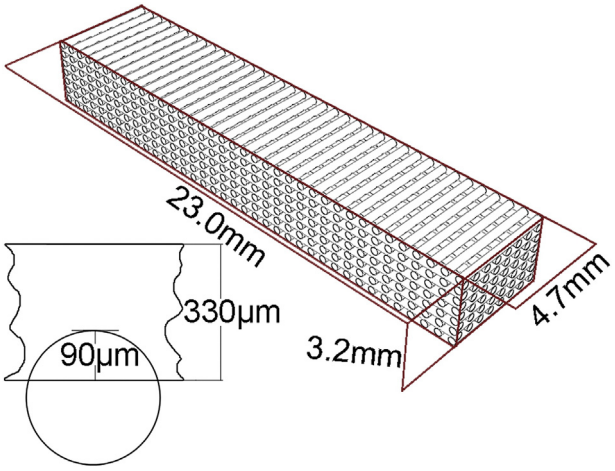

Fig. 1. The external shape and dimensions of the models used in FEM simulations of the flexural mechanical response. Each filament had a diameter of 330 μm and the thickness of the partially overlapped region between the filaments in adjacent layers was 90 μm.

different arrangements of the filaments in each layer, 11 different 3D models were designed (Table 1). The models all had the same external dimensions. Ten models were composed of 7 layers of short (S) filaments along the *x* axis and 6 layers of long (L) filaments along the *y* axis. The assignments L1 to L4 were used to describe the arrangement of the long filaments while S1 to S3 were used describe the arrangement of the short filaments. For example, L3S1 designated the model in which the long filaments had the L3 arrangement and the short filaments, orthogonal to the long filaments, had the S1 arrangement. In the eleventh model, designated S45°, the filaments in the adjacent layers were arranged at 45° to the *x* and *y* axes. In this model, the 13 alternating orthogonal layers consisted 4 layers each with a lower porosity on the top and the bottom of the model and 5 layers with a higher porosity in the middle. Except for the L4S1 model, all the models had the same porosity (~43% as determined from the models by the software). For the L4S1 model, additional long filaments were added to the two outermost layers of the L1S1 structure, resulting in a lower porosity (~33%). The center-to-center distance between adjacent filaments in each layer of the models is given in Table S1.

Based on the results of FEM simulations in flexure, 3 models were selected for analysis in compression. Models with the L3S1 and L4S1 structures were selected because the FEM simulations showed that these structures had a higher flexural strength than the uniform grid-like L1S1 structure. In addition, the uniform grid-like L1S1 structure was analyzed for comparison. Each model was composed of 19 alternating orthogonal layers of parallel filaments (Fig. 2). All three models had the same external shape (a cube with each side equal to ~5 mm). The glass filaments were identical to those described for the flexural analysis. The cross sections of the structures (*xy* plane) were identical to the L1S1, L3S1 and L4S1 models and the load was applied in the *z* direction.

2.2. Finite element simulations

Finite element simulations were carried out using ABAQUS/CAE 6.12-1 software (Dassault Sytemes Simulia Corp., Providence, RI). All 11 models in Table 1 were analyzed in flexure while the 3 models in Fig. 2 were analyzed in compression. The filaments in all the models were assumed to be composed of a dense homogeneous material with a Young's modulus of 70 GPa and a Poisson's ratio of 0.25, values which are comparable to those of a silicate glass [23].

For the simulations in flexural loading, 4 rigid cylinders with a diameter of 2.0 mm were generated to simulate the fixture used in the four-point bending test (Fig. 3). The two upper cylinders, each 5 mm from the midline, served as the inner span, while the two lower cylinders, 10 mm from the midline, served as the outer span. The cylinders were