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Micro-poro-elasticity of baghdadite-based bone tissue engineering scaffolds: A unifying approach based on ultrasonics, nanoindentation, and homogenization theory

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ABSTRACT

Microstructure–elasticity relations for bone tissue engineering scaffolds are key to rational biomaterial design. As a contribution thereto, we here report comprehensive length measuring, weighing, and ultrasonic tests at 0.1 MHz frequency, on porous baghdadite ($Ca_3ZrSi_2O_9$) scaffolds. The resulting porosity–stiffness relations further confirm a formerly detected, micromechanically explained, general relationship for a great variety of different polycrystals, which also allows for estimating the zero-porosity case, i.e. Young modulus and Poisson ratio of pure (dense) baghdadite. These estimates were impressively confirmed by a physically and statistically independent nanoindentation campaign comprising some 1750 indents. Consequently, we can present a remarkably complete picture of porous baghdadite elasticity across a wide range of porosities, and, thanks to the micromechanical understanding, reaching out beyond classical elasticity, towards poroelastic properties, quantifying the effect of pore pressure on the material system behavior.

1. Introduction

With an estimated 2.2 million yearly bone graft procedures for the treatment of critical size defects, bone is the second-most implanted material after blood [1]. Despite considerable progress over the years, the current gold standard, autografting [2], where bone from the patient is transplanted from one place to another, is limited by the amount of bone available, and may imply pre- and post-operative complications and morbidity, as well as the risk of infection [3]. The current clinical alternative, allografting, where cadaveric or synthetic bone is implanted, carries the risk of viral disease transmission, immunogenicity, and non-union [4]. This has motivated, for more than two decades, research in the field of bone tissue engineering [5–8], aiming at repairing damaged bone and restoring its functions [9] with the help of biocompatible materials cultivated with cells and corresponding growth factors [10]. Therefore, the scaffolds have to be designed in a way to provide sufficient porosity for good vascular and tissue ingrowth, while not overly compromising the overall mechanical properties of the implant, i.e. its stiffness and strength. This design process, involving also the biological properties of the implant material, turns out as very complex, and implies many design parameters whose interplay is extremely challenging to decipher in a classical 'trial-and-error' procedure, requiring a sheer innumerable multitude of in vitro and in vivo experiments. This challenging situation has given rise to the wish for rational, computer-aided design of biomaterials, regarding not only biological and cell transport aspects, but also mechanics. The present paper will concentrate on the latter aspect, thereby not being restricted to the measurement of some mechanical properties, but to a micromechanics theory-based understanding of an entire class of ceramic biomaterials, supported by a new set of experimental data making the aforementioned understanding feasible. More precisely, we will develop the micromechanics of porous baghdadite scaffolds [11] — these materials showed an in vivo osteoconductivity in critically sized defects induced into rabbit radius bones, which exceeds that of other scaffold types [12]. These developments will be described in the remainder of the present paper, which is organized as follows: porosity and ultrasonic test protocols together with their theoretical foundations will be dealt with in Section 2.1. For a deeper understanding of the resulting porosity–elasticity relations, Section 2.2 will cover a micromechanics formulation valid for a multitude of porous polycrystals, as developed in recent years [13–15], and its application to the newly collected experimental data. This will give access to the elastic properties of pure (dense) baghdadite. The methods section is then completed by a nanoindentation campaign allowing for an

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independent check of elasticity of pure baghdadite, as described in Section 2.3. The results of our comprehensive and consistent experimental–theoretical–computational multiscale mechanics approach to baghdadite scaffolds for bone tissue engineering are presented in Section 3, and further discussed in Section 4, in particular with respect to important theoretical and experimental features which allow for this consistent, unified view on the investigated bone biomaterial class.

2. Materials and methods

2.1. Weighing and ultrasonic tests, for porosity and elasticity determination

Combining the sol–gel method for powder production with the polymer sponge replication method for the final scaffold processing [12], cylindrically shaped porous baghdadite samples of nominally 12 mm height and 6 mm diameter were made, and categorized with decreasing nominal porosities, into sample sets A to D. Their precise dimensions of height and diameter were measured by means of a digital sliding caliper, and these dimensions were used to compute the cylindrical volume V of each of the samples. Then, their mass m was weighed, giving access to the samples' mass density through

$$\rho = m/V. \tag{1}$$

Additional consideration of the (real) mass density of pure (dense) baghdadite, $\rho_{solid} = 3.48\ \text{g/cm}^3$ [16], allows for computation of the scaffold porosity as

$$\phi^{exp} = (1 - \rho/\rho_{solid}). \tag{2}$$

Thereafter, ultrasonic tests were performed in the pulse transmission mode, by means of a device consisting of a pulser receiver (5077PR, OlympusNDT), an oscilloscope (Waverunner 62Xi, Lecroy), and ultrasonic transducers. Following the protocol of [17,18] the pulser unit was set to emit an electrical square pulse up to 400 V. The piezoelectric elements inside the ultrasonic transducers transformed the electrical signals of a frequency f into corresponding mechanical signals, when operating in the sending mode, or they transformed mechanical signals back into electrical ones, when functioning as a receiver. Honey was used as a coupling medium. The time of flight t of the ultrasonic wave through the sample was accessed by the oscilloscope, and the travel distance through the specimen was equivalent to the scaffold's height h_s. These quantities provide direct access to the wave velocity v through

$$v = h_s/t. \tag{3}$$

According to the theory of plane waves in a 3D solid [19], the wave velocity gives access to the stiffness of the tested sample. The current study is restricted to longitudinal waves, where the directions of 'particle' displacement and of the wave propagation are parallel — in this case, the wave velocity gives access to the normal component C^{exp}_{1111} of the stiffness tensor, through

$$C^{exp}_{1111} = \rho v^2. \tag{4}$$

Table 1
Coefficients a^* and b^* defining linear relation (9) between Poisson's ratio of single crystals, v_s, and polynomial coefficients A_v, B_v, C_v, D_v, and E_v in porosity–Poisson's ratio relation (8).

q	a^*	b^*
A_v	−1.0521	0.2197
B_v	2.2684	−0.4645
C_v	−0.8121	0.1662
D_v	0.3602	−0.0718
E_v	0.2394	0.1496

Table 2
Polishing protocol with machine PM5 Logitech (Scotland).

Step	Particle size of sandpaper [μm]	Polishing time [min]	Type of arm movement	Plate speed [rpm]
1	6.5	3	Sweeping	18
2	2.5	5	Sweeping	25

What still needs to be specified is the size at which the aforementioned 'particle' is defined. In continuum (micro) mechanics [20], such a 'particle' is called material volume or representative volume element (RVE), with a characteristic length l_{RVE} being considerably larger than the inhomogeneities d within the RVE, and the RVE being subjected to homogeneous stress and strain states. Consequently, the characteristic length l_{RVE} needs to be much smaller than the scale of the characteristic loading of the medium, here the wavelength λ, which follows from wave velocity v and frequency f as

$$\lambda = v/f. \tag{5}$$

The aforementioned separation of length scales reads mathematically as

$$d \ll l_{RVE} \ll \lambda. \tag{6}$$

Accordingly, ultrasonic waves with wavelength λ detect the stiffness of a material with characteristic length l_{RVE}. More precisely, the '≪' signs in Eq. (6) need to refer to a ratio of $d/\lambda \le 0.03$, in order to access the normal stiffness component C_{1111} of the tested material with inhomogeneity size d, as was experimentally quantified in [18]. As for the aforementioned baghdadite samples, the inhomogeneity size relates to the pore diameters, amounting to about 500 μm, as accessed by scanning electron microscopy [12]. Thereby, the sample needs to be always representative of the material (i.e. it needs to consist of at least one entire RVE of the latter), so that $(h_s, d_s) \ge l_{RVE}$. Hence, the required scale separation between RVE-length and wavelength λ might well accomodate wavelengths which are much larger than the sample, while precisely delivering the elastic properties of the material making up the sample. In order to check different options for the determination of C^{exp}_{1111} according to Eq. (4), while considering scale separation conditions (6), the samples were sonified with a frequency of 0.1 MHz.

Table 3
Number of nanoindentation measurements per sample and per load.

Sample	Porosity [%]	Maximum load [mN]	Measurements
A2	94	10	22
A8		10	56
		15	39
		20	33
B8	85	10	50
		15	50
		20	50
		30	50
C3	81	10	50
		15	50
		20	50
		30	50
D1	66	10	300
		15	300
		20	300
		30	300