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Macroscopic anisotropic bone material properties in children with severe *osteogenesis imperfecta*

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ABSTRACT

Children with severe *osteogenesis imperfecta* (OI) typically experience numerous fractures and progressive skeletal deformities over their lifetime. Recent studies proposed finite element models to assess fracture risk and guide clinicians in determining appropriate intervention in children with OI, but lack of appropriate material property inputs remains a challenge. This study aimed to characterize macroscopic anisotropic cortical bone material properties and investigate relationships with bone density measures in children with severe OI. Specimens were obtained from tibial or femoral shafts of nine children with severe OI and five controls. The specimens were cut into beams, characterized in bending, and imaged by synchrotron radiation X-ray micro-computed tomography. Longitudinal modulus of elasticity, yield strength, and bending strength were 32–65% lower in the OI group ($p < 0.001$). Yield strain did not differ between groups ($p \geq 0.197$). In both groups, modulus and strength were lower in the transverse direction ($p \leq 0.009$), but anisotropy was less pronounced in the OI group. Intracortical vascular porosity was almost six times higher in the OI group ($p < 0.001$), but no differences were observed in osteocyte lacunar porosity between the groups ($p = 0.086$). Volumetric bone mineral density was lower in the OI group ($p < 0.001$), but volumetric tissue mineral density was not ($p = 0.770$). Longitudinal OI bone modulus and strength were correlated with volumetric bone mineral density ($p \leq 0.024$) but not volumetric tissue mineral density ($p \geq 0.099$). Results indicate that cortical bone in children with severe OI yields at the same strain as normal bone, and that their decreased bone material strength is associated with reduced volumetric bone mineral density. These results will enable the advancement of fracture risk assessment capability in children with severe OI.

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1. Introduction

Osteogenesis imperfecta (OI) is a genetic bone fragility disorder affecting between 1/20,000 and 1/5000 births (Byers and Steiner, 1992; Marini, 2011). There is no cure, and individuals are affected throughout their lifetime. OI type III, the most severe phenotype in individuals surviving birth, typically results in numerous bone fractures and progressive skeletal deformities, such as pronounced bowing of long bones (Sillence et al., 1979). Clinical management usually involves antiresorptive drugs and physical rehabilitation. Corrective surgery is sometimes used to straighten a bowed tibia or femur with the aim to improve mobility and prevent fracture. However, there is no quantitative method by which to assess fracture risk or the potential benefit of surgical or rehabilitative interventions in children with OI. Recent studies proposed using finite element models to quantify tibial and femoral fracture risk in children with OI (Fritz et al., 2009a, 2009b; Caouette et al., 2014, 2016). These models could prove useful to clinicians in determining safe activity levels or when to perform corrective surgery. However, a major challenge to these fracture risk assessment efforts remains the paucity of macroscopic-scale material property data in children with severe OI.

Macroscopic bone material properties have been studied in small groups of children with OI (Albert et al., 2013, 2014;

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Vardakastani et al., 2014; Imbert et al., 2015). Bone material strength and modulus of elasticity were confirmed to be reduced in these children compared to controls (Imbert et al., 2015). Abnormally elevated intracortical vascular porosity was also observed in children with OI (Jameson et al., 2013; Pazzaglia et al., 2013; Albert et al., 2014; Imbert et al., 2015), and was found to have a negative effect on cortical bone modulus and strength (Albert et al., 2014; Vardakastani et al., 2014; Imbert et al., 2015). These studies, however, were not focused specifically on children with severe OI, who tend to experience the most fractures, and only one study (Albert et al., 2014) examined anisotropy (*i.e.*, directional dependence) of the bone material properties.

The objectives of the current study were to: (1) characterize the anisotropic material properties of cortical bone in children with severe OI at the macroscopic scale; (2) compare these properties to those of pediatric controls; and (3) investigate relationships between material properties and measures of bone material density in this patient population. The results of this study will enable improved fracture risk assessment capabilities in children with severe OI.

2. Materials and methods

2.1. Bone specimens

Nine cortical osteotomy specimens were collected from the tibial or femoral diaphyses of seven children and adolescents (age 1–16 years) with severe OI (OI group), Table 1. Six of these children were diagnosed with OI type III. The seventh (donor 7) has a less common recessive form, OI type VIII, with clinical severity similar to that of OI type III. These specimens were obtained during routine surgical procedures at Shriners Hospitals for Children – Chicago under informed consent/assent and an approved IRB protocol (Western IRB WIRB#20160453, Marquette University #HR-2167). The specimens were fresh-frozen and stored below −20 °C prior to testing.

For comparison, cortical bone specimens were obtained from the femoral and tibial diaphyses of five deceased donors (control group, age 8–11 years, cause of death unknown).

2.2. Specimen preparation

Each specimen was cut into 2–12 rectangular beams (Table 1) using a precision sectioning saw (IsoMet™ Low Speed Saw, Buehler®, Lake Bluff, IL, USA) and a 0.3 mm-thick diamond blade (IsoMet 15HC Model 11-4244, Buehler®, Lake Bluff, IL, USA). The beams were 5–6 mm long, with the long beam axis being either parallel to the long diaphyseal axis (longitudinal beams) or in the circumferential direction of the outer cortex (transverse beams) (Albert et al., 2013). Beam depth (0.633 mm ± 0.042 mm) and base (1.021 mm ± 0.039 mm) were measured with a digital micrometer (Model 293-340, Mitutoyo Corporation, Japan).

2.3. Mechanical testing

The beams were tested in three-point bending on a custom-designed jig using methodology validated for small bone specimens (Albert et al., 2013). A span length of 4.0 mm was chosen to accommodate the small osteotomy specimens collected for this study. Mechanical testing was performed on an electromechanical testing machine (Model 3345, Instron®, Norwood, MA, USA) with a 50 N load cell (Model 2519-102, Instron®, Norwood, MA, USA). The test was controlled using Bluehill 2 Software (Instron®, Norwood, MA, USA). Beam deflection at mid-span was determined as the vertical displacement of the loading nose relative to the supports, measured with a linear variable differential transformer (Model 2601-092, Instron®, Norwood, MA, USA). Five cycles of preconditioning (0.05–0.5 N) were applied at a crosshead displacement rate of 0.2 mm/min, followed by a ramp to failure at a constant beam deflection rate of 2.0 mm/min. The beams were kept hydrated during the test using a drop of buffered saline, which remained in place on the tensile surface of the beam by surface tension for the duration of the test (less than 2 min). Load, crosshead displacement, and beam deflection were sampled at 100 Hz. Mid-span stress and strain at the tensile surface of the beam were calculated from the load and deflection data (ASTM-D790-07, 2006; Albert et al., 2013, 2014). The following material properties were calculated from the stress-strain data obtained during the ramp to failure using Matlab (R2012a, Mathworks, Natick, MA, USA), correcting for shear effects (see Supplement - Shear Effects

Table 1
Specimen description and donor details. For each specimen, the numbers of machined beams tested of each orientation relative to the long bone axis, *i.e.*, longitudinal (*L*) or transverse (*T*), is indicated. Of those beams, a subset (*numbers in parentheses*) was imaged by SRμCT following mechanical testing.

Donor	Gene affected	Specimen	Age (years)	Gender	Harvest site	Surgery notes	Beams tested (*Beams imaged*)	
							L	*T*
OI group								
1	*COL1A1*	OI 1	1	M	Tibia	Deformity correction	2 (0)	0 (0)
2	*COL1A2*	OI 2[a]	3	F	Femur	Deformity correction	2 (1)	2 (1)
		OI 3[a]			Femur	Deformity correction	4 (1)	2 (1)
3	Not available	OI 4	9	F	Tibia	Rod revision	1 (1)	1 (1)
4	Not available	OI 5	11	M	Femur[c]	Fracture two weeks prior	4 (2)	1 (1)
5	*COL1A1*	OI 6	13	F	Tibia	Deformity correction	2 (2)	1 (1)
6	*COL1A1*	OI 7[b]	13	M	Femur	Rod revision	4 (0)	3 (0)
		OI 8[b]	14		Tibia	Rod revision	2 (2)	0 (0)
7	*LEPRE1*	OI 9	16	M	Tibia	Deformity correction	6 (2)	3 (2)
Control group								
8	Normal	C 1	8	M	Femur	n/a	6 (2)	6 (2)
9	Normal	C 2	10	F	Femur	n/a	6 (2)	6 (2)
10	Normal	C 3	10	F	Tibia	n/a	6 (2)	6 (2)
11	Normal	C 4	11	F	Tibia	n/a	6 (2)	6 (2)
12	Normal	C 5	11	M	Femur	n/a	6 (2)	6 (2)

[a] Specimens OI 2 and OI 3 were obtained from contralateral femurs of the same donor (donor 2) during a bilateral corrective procedure.
[b] Specimens OI 7 and OI 8 were obtained from a single donor (donor 6) during surgical procedures that took place eight months apart.
[c] All specimens were obtained from the long bone mid-diaphysis, with the exception of specimen OI 5, which was obtained from the proximal region of the femur diaphysis.

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