Cortical Bone Post-Yield Energy Absorption is Reduced in Older Adults with Long-Duration Type 1 Diabetes

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INTRODUCTION: Type 1 Diabetes (T1D) is associated with an increased risk of fracture compared to non-diabetics, with up to a 7-fold increased risk for hip fracture [1]. However, the factors contributing to skeletal fragility in T1D are not well understood, and no studies have assessed bone mechanical properties in older adults with T1D, in whom fracture risk is highest. The aim of this study was to compare cortical bone mechanical properties in the excised femora of older adults with long-duration T1D and non-diabetic controls.

METHODS: Whole femora were acquired post-mortem from the Joslin Medalist Study [2,3], a unique cohort of individuals with long-duration T1D (≥ 50 years) (n = 21). Non-diabetic control femora of similar age-, race- and sex were obtained from a commercial tissue bank (n = 14). Patients with end stage renal disease, lower limb amputation, or history of bone metastases were excluded. Cortical beams were extracted from the proximal midshaft, polished to exact dimensions (2x2x40mm), and assessed via microCT, cyclic reference point indentation (cRPI) and 4-point bending. First, the mid-section of the cortical beams was scanned (Scanco μCT 40; 12 μm^3 isotropic voxel) and tissue mineral density (Ct.TMD) and cortical porosity (Ct.Po) were measured. Next, ten cRPI tests were performed on the periosteal surface of each beam, with each indentation test consisting of 20 cycles at 2 Hz with a 10N peak force (BioDent, Active Life Scientific, BP2 probe). The average value of the replicate cRPI measurements was calculated for each specimen. Finally, monotonic 4-point bending was performed using a servohydraulic system (Instron 8511) with a ramp rate of 3mm/min, with upper and lower spans set to 9 and 27 mm, respectively. Force, displacement, and geometry data were used to calculate the apparent material properties of the cortical bone. Non-parametric, unpaired Mann Whitney tests were used to determine differences between groups ($p<0.05$).

RESULTS: The T1D specimens included 11 women (52%) and 10 men (48%), with an average HbA1C = 7.8%, mean T1D duration = 67.3 years (range 56-77), age at onset = 12.4 years, and median age at death = 79.8 years (range 67-94). The control group was comprised of 8 women (57%) and 6 men (43%); age and sex distribution were not significantly different between groups ($p = 0.77$ and 0.78, respectively). No significant differences in cRPI or microCT measures were detected between groups (**Table 1**, cRPI data not shown). Yet, the ability of the cortical bone to absorb energy and plastically deform during bending was diminished in T1D compared to non-diabetic controls. Specifically, toughness to maximum force (-28%, $p=0.04$, **Fig. 1**) and toughness to fracture (-27%, $p=0.04$, **Fig. 2**) were lower in T1D versus non-diabetics. In contrast, elastic properties such as bending modulus were not different between T1D and non-diabetic controls.

DISCUSSION: The results of this study suggest that long-duration T1D compromises the post-yield energy absorbing capacity, but not elastic behavior, of cortical bone in the femoral mid-diaphysis. In bone, reduced toughness and post-yield behavior are attributed to altered matrix collagen such as increased advanced glycation end-products (AGEs). AGEs are elevated in diabetic patients due to long-term hyperglycemia [4], and previous studies in aging and type 2 diabetes have correlated increased AGE content with diminished cortical bone toughness [5-7]. Further investigation is necessary to determine the cause of the significant decrease in post-yield properties in the current T1D specimens. Future work will incorporate evaluation of the matrix and mineral composition of T1D femoral bone compared to non-diabetic controls via quantification of AGEs and Fourier-transform infrared (FTIR) imaging.

SIGNIFICANCE/CLINICAL RELEVANCE: Although the growing issue of skeletal fragility in patients with T1D is widely recognized, there is a lack of information regarding how T1D increases fracture risk. The presented data provide evidence to suggest that the mechanical implications of T1D manifest in post-yield energy absorption deficits in cortical bone, which may contribute to the increased fracture risk in patients with T1D.

REFERENCES: [1] Shah et al., Diabetes Med., 2015. [2] Keenan et al., Diabetes Care, 2007. [3] Maddaloni et al., Acta Diabetologica, 2017. [4] Starup-Linde et al., Diabetes Metab Syndr Obes, 2019. [5] Nyman et al., J Orthop Res., 2007. [6] Wang et al., Bone, 2002. [7] Hunt et al., JBMR, 2019.

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Table 1. Mechanical and mineral properties of cortical bone in long-duration T1D and non-diabetic controls.

Characteristic	T1D N = 21[1]	Control N = 14[1]	p-value[2]
4-Point Bending			
Bending Modulus (GPa)	18.15 (17.17-19.48)	18.67 (16.77-19.92)	0.86
Ultimate Stress (MPa)	184.2 (168.6-208.9)	210.0 (184.9-225.9)	0.10
Yield Stress (MPa)	116.8 (96.47-130.7)	124.9 (109.4-133.6)	0.52
Toughness to Yield (mJ/mm^3)	0.03 (0.02-0.04)	0.03 (0.03-0.04)	0.56
Toughness to Maximum Force (mJ/mm^3)	0.18 (0.13-0.23)	0.25 (0.16-0.29)	**0.04**
Toughness to Fracture (mJ/mm^3)	0.19 (0.14-0.25)	0.26 (0.18-0.30)	**0.04**
Post Yield Toughness to Fracture (mJ/mm^3)	0.15 (0.11-0.21)	0.22 (0.14-0.26)	0.05
Post Yield Displacement (mm)	0.78 (0.64-1.07)	1.01 (0.74-1.28)	0.18
Fracture Stress (MPa)	181.4 (166.4-207.5)	202.1 (180.5-222.5)	0.12
MicroCT			
Cortical Tissue Mineral Density ($mgHA/cm^3$)	1090 (1084-1096)	1092 (1078-1108)	0.61
Cortical Porosity (%)	5.70 (4.84-8.21)	6.15 (4.74-8.25)	0.70

[1]Median (IQR), [2]Mann Whitney test, $p<0.05$ are in bold

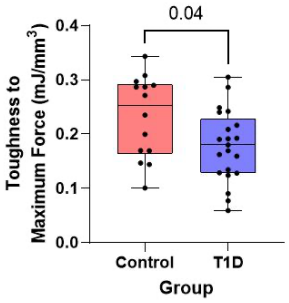

Fig 1. Toughness to maximum force comparison between nondiabetic control and long-duration T1D. Median ± IQR with whiskers extending from the minimum to the maximum.

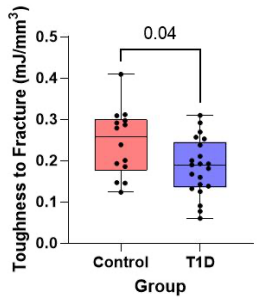

Fig 2. Toughness to fracture comparison between nondiabetic control and long-duration T1D. Median ± IQR with whiskers extending from the minimum to the maximum.