Diabetic Complications Consortium

Application Title: Determinants of Fracture Risk in Type 1 Diabetes

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1. Project Accomplishments:

Individuals diagnosed with Type 1 Diabetes (T1D) are ~4 (women) and ~2 (men) times more likely to suffer a low-energy fragility fracture than individuals without diabetes as estimated in a recent meta-analysis [1]. Therefore, the overarching goal of this pilot project is to identify possible deficits in cortical micro-/macro-structure, trabecular architecture, matrix-bound water, and resistance to micro-indentation in adults with T1D. To achieve this goal, we recruited subjects who were diagnosed with T1D between 8 years and 12 years of age and subjects without a history of diabetes such that the 2 groups were matched for sex, body mass index (BMI) and sex (Table 1). Advances in clinical imaging and other bone assessment techniques allow us to test for differences in "bone quality" among different groups in addition to areal bone mineral density (aBMD). As such, each subject underwent 3 dual-energy X-ray absorptiometry (DXA) scans of the hip, spine, and one-third radius and 1 magnetic resonance imaging (MRI) scan of the tibia diaphysis after a blood draw. Prior to the start of the project, the FDA stopped all clinical use of the micro-indentation instrument known as the OsteoProbe while they reviewed its safety. Therefore, we did not acquire the "bone quality" measurement from each subject's tibia diaphysis using this minimally invasive tool. Also limiting the original scope of the study, our access to a high-resolution, peripheral quantitative computed tomography (HR-pQCT) scanner was suspended after scanning 8 subjects because the sponsor of a clinical trial at our institution stopped paying the lease on the instrument meaning the manufacturer retrieved their scanner. In summary, we acquired aBMD of hip, spine, and radius, bound water concentration and pore water concentration of the tibia, and serum and plasma from 32 subjects, the target sample size.

Table 1. Subjects with T1D matched to subjects without diabetes based on sex, age, and BMI.

	Volunteers without Diabetes (Ctrl)				Type 1 Diabetes (T1D)				Ctrl vs T1D	
	Female		Male		Female		Male		Female	Male
	Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		p	p
Number	8		8		8		8			
Age (years)	36.7 ± 4.6		35.4 ± 3.3		35.0 ± 4.5		33.0 ± 3.2		0.47	0.16
BMI (kg/cm^2)	24.0 ± 4.2		29.4 ± 4.6		26.6 ± 5.6		28.1 ± 4.3		0.31	0.44*

P-values (p) from two-tailed t-tests except when data didn't pass the Anderson-Darling normality test or the F test for homogeneous variance between the two groups.

2. Specific Aims:

Only Specific Aim. Establish which bone characteristics related to fracture resistance differ between adults with T1D and age-matched adults without diabetes.

Results: From the Eskind Vanderbilt Diabetes Center and other IRB-approved recruitment strategies (ResearchMatch.org, Flyers, and Institutional research notifications email distribution), we enrolled 36 subjects with imaging data and blood draws being collected from 32 subjects (Table 1) because 3 subjects failed the screening and 1 did not show up for the scans. Out of the measurements from the 3 DXA scans, only aBMD of the ultra-distal radius (UDR) was significantly different between the 2 groups (Fig. 1). When accounting for sex and BMI of each subject, UDR aBMD was still significantly lower in the T1D than in the Control (Ctrl) group (Table 2). There was a trend of T1D subjects having lower aBMD of the femoral neck (FN) when the regression model included sex and BMI as covariates (Table 2).

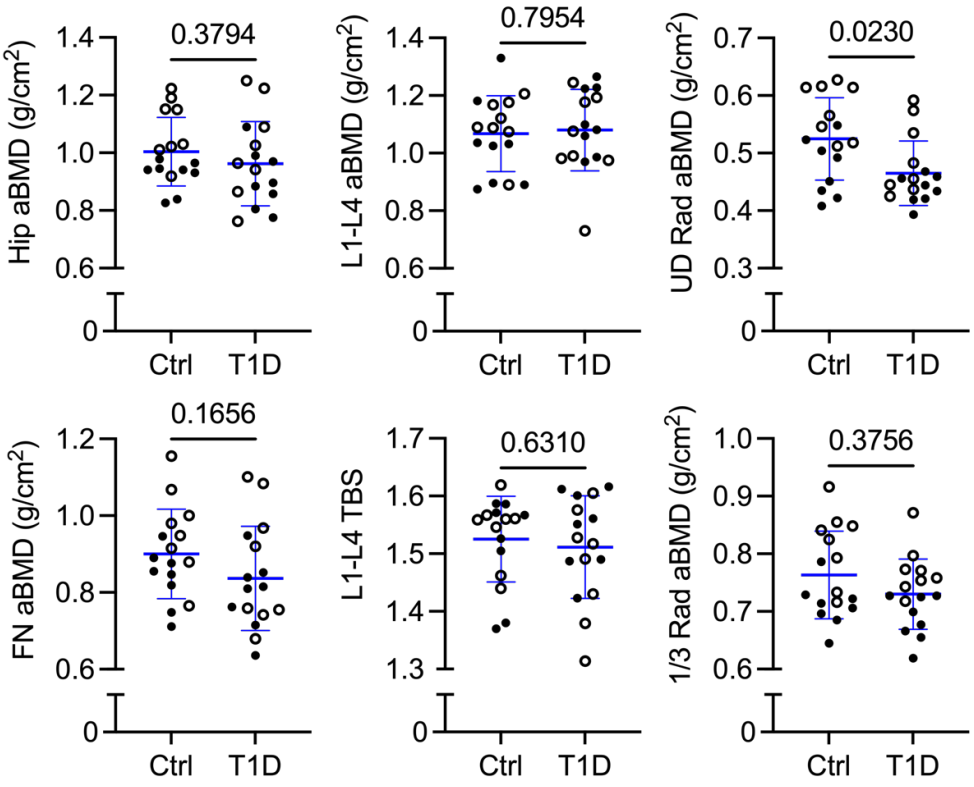

Figure 1: Comparison of areal bone mineral density (aBMD) by DXA. There were no differences in aBMD of the hip and femoral neck (FN) between adults without diabetes and adults with T1D (left row). aBMD and trabecular bone score (TBS) of the lumbar spine were also similar between the 2 groups (middle row). From the radius scan, the aBMD of the ultra-distal region was significantly lower in the T1D than in the Ctrl group (right row). P-values are from two-tailed t-tests above horizontal line. Closed and open symbols indicate female and male subjects, respectively.

Table 2: Regression coefficients (β) and corresponding p-values from linear regressions in which DXA-derived properties were dependent on Group, Sex, and Body Mass Index of the of subject (i.e., aBMD = β0 + β1 x Group + β2 x Sex + β3 x BMI*).*

Property	Intercept, add β0	If T1D, add β1	If Male, add β2	add β3 x BMI	Adj-R^2
Hip aBMD	+0.692, p<0.001	-0.048, p=0.215	**+0.103, p=0.017**	**+0.010, p=0.028**	0.350
FN aBMD	+0.653, p<0.001	*-0.068, p=0.097*	*+0.076, p=0.085*	*+0.008, p=0.088*	0.306
L1-L4 aBMD	+0.881, p<0.001	+0.008, p=0.871	+0.007, p=0.627	+0.007, p=0.176	0.067
L1-L4 TBS	+1.665, p<0.001	-0.011, p=0.708	+0.000, p=0.987	-0.005, p=0.110	0.011
UDR aBMD	+0.516, p<0.001	**-0.059, p=0.003**	**+0.084, p<0.001**	-0.001, p=0.526	0.531
1/3rdR aBMD	+0.700, p<0.001	*-0.033, p=0.066*	**+0.094, p<0.001**	+0.000, p=0.760	0.499

As for the MRI scans, we acquired maps of bound water concentration and pore water concentration within the cortex of the tibia mid-diaphysis (Fig. 2). These images require specialized pulse sequences and ultra-short time-to-echo (UTE) acquisition of signals to detect water residing in the pores of bone or bound to the matrix [2]. Since the technique is not a standard UTE-MRI scan, processing of the data is ongoing.

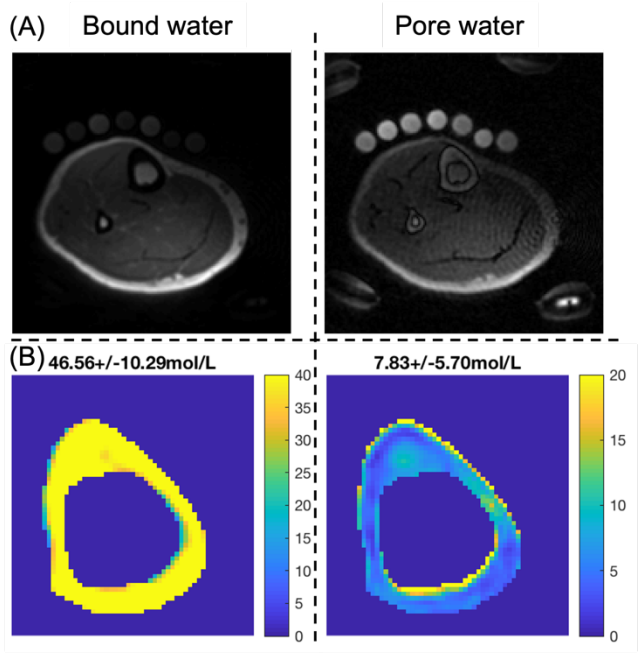

Figure 2: Bound and pore water cross-sectional images by UTE-MRI. Using double adiabatic full passage (left) and adiabatic inversion recovery (right) scans of a subject's lower leg with a neighboring calibration phantom, we acquired images of bound and pore water, respectively (A). These images were then converted to false color maps based on a concentration scale in mol ^{1}H per liter of bone (B).

At present, bound and pore water measurements are available for some of the male subjects. Based on these preliminary, it appears T1D lowered bound water concentration but did not affect pore water concentration (Fig. 3).

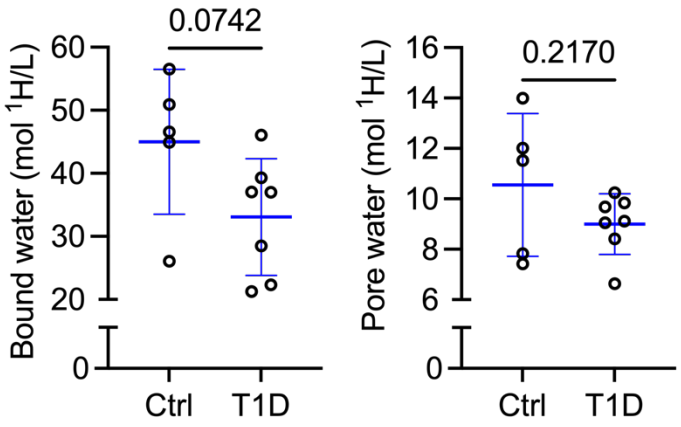

Figure 3: Preliminary comparison of bound (left) and pore water (right) concentrations between the control group and T1D group. Taking the mean concentration of all pixels within the image stack of the cortex (i.e., excluding marrow and surrounding soft tissue), bound water appeared to be more sensitive than pore water in detecting T1D-related differences in bone quality.

Discussion: DXA-derived aBMD, the clinical gold-standard for predicting a patient's fracture risk, does not appear to be sensitive to deficits in bone caused by juvenile-onset Type 1 Diabetes, at least not between the age of 29 years and 44 years. Of the clinically relevant sites, the ultra-distal radius, a trabecular-rich site and prone to a low-energy fracture, may provide an early indicator of a patient's risk of osteoporosis. Although we were not able to acquire high resolution, volumetric images of bone from all subjects in this study (1 Control and 7 T1D subjects only), two recent studies involving HR-pQCT scans of i) juvenile-onset T1D subjects or ii) T1D subjects with a duration of at least 25 years vs. age-, sex-, and BMI-matched control subjects found: lower total volumetric bone mineral density (vBMD), trabecular vBMD, trabecular bone volume fraction, and trabecular thickness (distal radius) in T1D subjects with median duration of 11 years [n=15; 32 ± 8 years (21–52 years)] [3] and lower cortical thickness and cortical vBMD (distal tibia) in T1D patients with a mean ± SD duration of 37.7 ± 9.0 [n=59; 59.9 ± 9.9 years] [4]. In the study with the younger population, there wasn't a difference in aBMD (hip nor spine), while aBMD was significantly lower in aBMD (hip and spine) between T1D patients than in the control subjects.

As for "bone quality" measurements using the impact micro-indentation device known as the OsteoProbe, a recent study reported that the group of male T1D subjects had significantly lower Bone Material Strength Index (BMSi) than the age-matched group without diabetes: T1D: 83.2 (72.0–85.1) BMSi vs controls 87.4 (85.3–91.2) BMSi, p = 0.004 [5]. In this study, there were 33 men between 18 and 65 years of age (43 ± 12 years) with T1D and 28 healthy male controls (42 ± 12 years). The age of diagnosis and duration of T1D (mean ± SD) was 19.3 ± 11.6 and 23.0 ± 10.2, respectively. BMI was not exactly matched between the groups: T1D: 25.9 ± 3.2 vs. Control: 24.1 ± 2.4, p=0.017.

Ongoing work and future directions: To gain insight into how juvenile-onset T1D affects, the collected serum and plasma will be analyzed for the following circulating markers: CTX (bone resorption), P1NP (bone formation), Sclerostin (inhibitor of bone formation), RANKL (osteoclast activity), OPG (inhibitor of RANKL), OC (osteoblast differentiation), c-peptide

(endogenous insulin production), IGF-1 (growth factor), IGFBP-3 & IGFBP-1 (binding proteins of IGF-1), pentosidine (crosslinking advanced glycation end-product or AGE), and CML (non-crosslinking AGE). We anticipate markers of bone formation and bone resorption to be lower and higher in T1D than control subjects, respectively. As indicators of AGE accumulation in tissue, we also expect there to be more circulating CML and pentosidine with T1D, while the indicator of anabolism IGF-1 will be lower. CML may directly correlate with bound water concentration. If successful, preliminary data generated in this project would be used to apply for funding to identify the root cause of diabetic bone disease.

References Cited:

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3. Publications:

Nothing directly related to this project to report at present. Data analysis is still ongoing.