Towards Early Predictors of Fracture Risk in Type 1 Diabetes

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INTRODUCTION: 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 meta-analysis [1]. While there is an association between low areal bone mineral density (aBMD) and duration of T1D, this standard assessment of osteoporosis does not fully explain the elevated fracture risk in T1D [2]. Therefore, we investigated which imaging and serum markers were significantly different between adults with T1D and adults without diabetes, prior to the age in which osteoporosis typically becomes a major concern.

METHODS: To identify potential early predictors of osteoporosis in T1D, we recruited 16 adults between 29 years and 43 years of age who were diagnosed with T1D between 9 years and 17 years of age resulting in a duration (mean ± SD) of 21.7 ± 7.7 years. Matching for sex (8 Females / 8 Males per group) and age, we also enrolled 16 adults without a history of diabetes and between 30 years and 44 years of age. After non-fasting blood draws, each subject received dual-energy X-ray absorptiometry (DXA) scans of the hip, spine, and one-third radius to determine their aBMD and T-scores using a Hologic Horizon series W scanner. Then, using our recently published methods [3,4] and a Philips 3T scanner, ultra-short echo-time (UTE) magnetic resonance imaging (MRI) scans of the tibia diaphysis were acquired to measure bound water concentration (C_{bw}) and pore water concentration (C_{pw}) of cortical bone. Using a phantom which was included in each scan (Figure), these water concentrations were quantified as moles of protons (mol ^{1}H) per liter of bone (L). Extracted from blood, serum aliquots were analyzed by ELISA kits to measure the following: insulin-like growth factor 1 (IGF-1), bone resorption (CTX), bone formation (P1NP), tartrate-resistant acid phosphatase 5b (TRAcP 5b), osteoprotegerin (OPG), receptor activator of nuclear factor kappa beta ligand (RANKL), and fructosamine. Group differences in outcomes were tested for significance using a two-tailed, t-test if parametric assumptions were valid or Mann-Whitney test (^) if the distribution of the data per group did not pass the Anderson-Darling normality test. This study adhered to a protocol approved by the local IRB.

RESULTS SECTION: As intended, there was no difference in the age and body mass index (BMI) between the adults with T1D and the healthy controls (Table). Although the T1D subjects received insulin therapy (0.59 ± 0.21 units/kg/day), IGF-1 and fructosamine were significantly lower and higher, respectively, in the T1D group than in the Control group (Table). There were no significant differences in the turnover markers (CTX & P1NP), the OPG/RANKL ratio, and osteoclast activity (TRAcP 5b) between the groups. The T-score tended to be lower in T1D than in Control for all DXA regions of interest, except the lumbar spine (Table). By clinical definition ($-1 \leq$ T-score < -2.5), 4 T1D subjects (2 females and 2 males) had osteopenia at the femoral neck (FN); whereas, only 1 Control subject (a female) had osteopenia. In an analysis of covariance (ANCOVA) with sex as significant covariate (p<0.0001), the ultra-distal (UD) aBMD was significantly lower by -0.060 g/cm^2 (fitted estimate) in T1D than in Control. In another ANCOVA for the FN region of interest, sex (p=0.0184) significantly affected FN aBMD, but group did not (p=0.1233). With respect to UTE-MRI, bound and pore water concentrations trended toward being lower and higher, respectively, in T1D than in Control subjects (Table 1). Neither Sex (p>0.8) nor Group (p>0.2) were significant covariates in ANCOVAs of C_{bw} and C_{pw}. Among clinical factors in T1D (Duration, HbA1c, Daily insulin dose, IGF-1, and fructosamine), only daily insulin dose correlated with UD T-score (Spearman's r = 0.506, p = 0.0473) and IGF-1 significantly correlated with C_{bw} (Spearman's r = 0. 553, p = 0.0285).

DISCUSSION: There is a need for early predictors of the T1D-related increase in fracture risk as fracture incidence among those with diabetes is higher than normal across lifespan [5]. T-score and aBMD of the ultra-distal radius are possible early predictors as they were significantly lower in adults with juvenile-onset T1D than in the Control subjects (Table). Possibly contributing to the T1D-related increase in fracture risk, circulating IGF-1, an anabolic growth factor, and fructosamine, an advanced glycation end-product marker, were significantly lower and higher with T1D (Table). Although C_{bw} was significantly lower and C_{pw} significantly higher with osteoporosis in our recent study [4], these new imaging markers of matrix hydration and cortical porosity, respectively, were not significantly different between the 2 groups. They may however decrease and increase as the T1D subjects age and develop osteoporosis. A limitation of the study was the lack of other imaging techniques that may be sensitive to diabetic bone disease such as high resolution, peripheral quantitative computed tomography scans of the distal radius and tibia diaphysis.

SIGNIFICANCE/CLINICAL RELEVANCE: The present study suggests that DXA scans of the ultra-distal radius as well as circulating IGF-1 and fructosamine may be early predictors of bone fragility.

REFERENCES: [1] Shah VN et al., Diabetic Med. 2015;32: 1134‑1142. [2] Sellmeyer DE et al. Diabetes. 2016;65(7):1757-66. [3] Manhard M-K et al., Radiology. 2015;277(1): 221-9. [4] Nyman JS et al., Bone. 2023;In press. [5] Weber DR et al., Diabetes Care. 2015;38(10):1913-20.

Table. Mean ± SD or median (interquartile range) of selected outcomes per group.

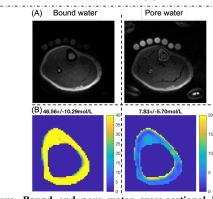| Characteristic	Unit	Control (n=16)	T1D (n=16)	p-value
Age	years	36.09 ± 3.92	34.07 ± 3.90	0.9799
BMI	kg/cm^2	26.73 ± 5.06	27.36 ± 4.89	0.7249
IGF-1	ng/ml	59.3 ± 18.5	40.6 ± 13.6	0.0028
Fructosamine	mmol/ml	185.7 ± 7.3	204.1 ± 9.9	<0.0001
OPG/RANKL	–	41.5 (17.4, 62.7)	36.1 (5.05, 66.0)	0.4230 ^
TRAcP 5b	U/L	2.05 (1.77, 2.45)	2.33 (2.06, 2.41)	0.1164 ^
CTX	ng/ml	0.117 (0.073, 0.19)	0.116 (0.048, 0.16)	0.5894 ^
P1NP	ng/ml	477.4 ± 168.7	494.1 ± 121.5	0.7507
FN T-score	–	0.48 ± 1.06	-0.11 ± 1.22	0.1567
Hip T-score	–	0.51 ± 0.97	0.13 ± 1.20	0.3386
L1-L4 T-score	–	0.19 ± 1.20	0.29 ± 1.28	0.8102
UD T-score	–	1.35 (0.28, 2.70)	0.20 (-0.25, 1.38)	0.0547 ^
D3 T-score	–	1.16 ± 1.27	0.61 ± 1.01	0.1861
C_{bw}	mol ^{1}H/L	28.0 ± 5.9	25.6 ± 5.4	0.2452
C_{pw}	mol ^{1}H/L	7.6 ± 1.7	8.1 ± 1.4	0.2870

Figure. Bound and pore water cross-sectional images by UTE-MRI. Double adiabatic full passage (left) and adiabatic inversion recovery (right) scans of each subject's lower leg with a neighboring calibration phantom provided 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).