Long-Duration Type 1 Diabetes Alters Bone Matrix Composition but Does Not Influence Microarchitecture or Mechanical Behavior in Femoral Trabecular Bone in Older Adults

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Increased hip fracture risk in type 1 diabetes (T1D) is not solely due to lower bone mineral density (BMD), indicating potential alterations in bone material contributing to mechanical deficiencies. T1D may affect bone mechanical properties through advanced glycation end product (AGE) accumulation and altered matrix composition. However, there is limited data on human trabecular bone in T1D. This study assesses trabecular bone tissue material behavior, AGE content, and composition in cadaveric femora from older adults with T1D and nondiabetic controls.

We acquired femora post-mortem from individuals with T1D ≥50 years (n=23; 13F/10M) and age- and sex-matched nondiabetic controls (n=19; 11F/8M). Trabecular cores (8mm diameter x16mm length) were extracted from femoral heads along the principal trabeculae direction. We performed μCT imaging (Scanco μCT40; 15 μm^3), assessed trabecular architecture and BMD, and conducted uniaxial compression tests. Combining μCT geometry and mechanical testing data, we computed apparent material properties: elastic modulus (E_{app}); yield stress (σ_y) and strain(ε_y); ultimate stress (σ_{ult}) and strain (ε_{ult}); toughness to ultimate (U_{ult}), yield (U_y), and post-yield (U_{py}). Total fluorescent AGEs (fAGEs) in trabecular bone were quantified by fluorometric assay, pentosidine (PEN) by HPLC, and matrix composition by Raman spectroscopy. Group differences were assessed by ANCOVA tests adjusted for age at death and sex (α=0.05). Associations between mechanical properties and compositional measures were tested in the combined cohort by Spearman correlations.

The T1D group had (mean±SD) HbA1c=7.7±1.1% and age at death=79.8±8.1yrs; age and sex did not differ between groups (p≥0.81). Trabecular architecture (p≥0.71), BMD (p=0.84), and mechanical behavior (p≥0.14) were similar. T1D trabecular bone had greater AGE content (fAGE +42%, p=0.003; PEN +73%, p=0.002), and altered Raman composition (**Table**) compared to controls. While fAGEs and PEN were not independently associated with any mechanical property, BMD was positively associated with ε_y, ε_{ult}, U_{ult}, U_{py} (p<0.04); crystallinity was positively associated with E_{app}, σ_y, σ_{ult}, and U_{ult} (p<0.04).

Long-duration T1D altered femoral head trabecular bone composition but neither bone structure nor compressive mechanical behavior. In bone, mineral (i.e, BMD) has a greater influence under compressive loading, while collagen and AGEs play a larger role under tension. Despite elevated fAGE and PEN levels in T1D, similar BMD between groups explains the lack of differences in trabecular compressive mechanical properties.

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Table: μCT, compression, AGE content, and Raman metrics for trabecular bone from T1D and nondiabetic

	Control N = 17[1]	T1D N = 20[1]	p-value[2]
μCT			
BMD (mg/cm^3)	293 (235, 359)	294 (240, 344)	0.839
BV/TV (%)	27 (21, 34)	26 (21, 33)	0.844
Tb.N (1/mm)	1.81 (1.65, 2.10)	1.81 (1.64, 2.21)	0.846
Tb.Th (mm)	0.172 (0.155, 0.201)	0.178 (0.168, 0.194)	0.710
Tb.Sp (mm)	0.58 (0.52, 0.62)	0.57 (0.49, 0.62)	0.962
Conn.D (1/mm^3)	23 (16, 29)	25 (16, 36)	0.532
Compression Testing			
Apparent Elastic Modulus, E_{app} (GPa)	0.99 (0.70, 1.39)	0.87 (0.65, 1.08)	0.173
Yield Stress, σ_y (MPa)	31 (25, 37)	27 (24, 30)	0.147
Yield Strain, ε_y (%)	3.09 (2.47, 4.00)	3.94 (3.32, 4.58)	0.940
Ultimate Stress, σ_{ult} (MPa)	37 (31, 42)	33 (26, 38)	0.170
Ultimate Strain, ε_{ult} (%)	5.18 (4.13, 6.07)	5.55 (4.14, 6.30)	0.536
Toughness to Yield, U_y (mJ/mm^3)	0.42 (0.32, 0.65)	0.47 (0.38, 0.57)	0.266
Toughness to Ultimate, U_{ult} (mJ/mm^3)	1.09 (0.85, 1.50)	0.93 (0.65, 1.37)	0.756
Toughness Post-Yield, U_{py} (mJ/mm^3)	0.50 (0.31, 0.75)	0.35 (0.21, 0.75)	0.600
AGEs			
Total fAGEs (ng quinine/mg coll)	259 (200, 315)	367 (281, 423)	**0.003**
Pentosidine (mmol/mol coll)	1.62 (1.35, 2.12)	2.80 (2.36, 4.27)	**0.002**
Raman metrics			
Mineral-to-matrix (v_1PO_4/Proline)	13.63 (12.59, 16.00)	13.03 (12.47, 13.54)	**0.025**
Carbonate substitution (CO_3/v_1PO_4)	0.196 (0.191, 0.200)	0.203 (0.196, 0.212)	0.085
Crystallinity	0.0573 (0.0556, 0.0580)	0.0552 (0.0538, 0.0567)	0.195
Hydroxyproline/Proline (Hyp/Pro)	0.73 (0.72, 0.75)	0.77 (0.74, 0.78)	**0.012**
1670/1690 cm^{-1}	2.79 (2.52, 2.99)	3.08 (2.70, 3.51)	0.145
GAG/Amide III	0.46 (0.43, 0.47)	0.42 (0.40, 0.44)	**0.004**
GAG/v_1PO_4	0.049 (0.045, 0.052)	0.043 (0.036, 0.045)	**0.004**
Lipid content (~1298 cm^{-1} / Amide III)	0.77 (0.70, 0.83)	0.78 (0.74, 0.90)	0.286

[1] *Median (IQR); n(%);* [2] *ANCOVA (age and sex)*