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Pentosidine is Associated with Cortical Bone Geometry and Insulin Resistance in Otherwise Healthy Children

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Abstract

Pentosidine is an advanced glycation endproduct (AGE) associated with fracture in adults with diabetes. AGE accumulation in bone collagen contributes to bone fragility, but might also adversely influence bone turnover, and consequently, bone geometry. The relationships between AGEs and bone health have yet to be studied in children. Thus, the objective of this study was to assess relationships between pentosidine and cortical bone volumetric density, geometry, and estimated strength in children. Participants were otherwise healthy black and white boys and girls, ages 9–13 years, who were at sexual maturation stage 2 or 3 (N=160). Tibia and radius cortical bone and muscle area (66% site) was assessed via pQCT. In fasting sera, insulin, glucose, and pentosidine were measured. The Quantitative Insulin Sensitivity Check Index (QUICKI), a measure of insulin sensitivity, was calculated. While controlling for race, sex, maturation, and height, pentosidine negatively correlated with QUICKI ($P<0.05$). In unadjusted analyses, pentosidine was associated with lower radius and tibia cortical volumetric bone mineral density, bone mineral content (Ct.BMC), area (Ct.Ar), and thickness (Ct.Th); a larger radius endosteal circumference (Endo.Circ); and lower tibia polar strength strain index (all $P<0.05$). While controlling for race, sex, maturation, height, and muscle area, pentosidine was negatively associated with tibia Ct.BMC, Ct.Ar, and Ct.Th, but positively associated with Endo.Circ (all $P<0.05$). Linear regression revealed a significant interaction between pentosidine and QUICKI in relation to tibia Ct.Th ($P_{interaction}=0.049$), indicating that the negative relationship between pentosidine and Ct.Th was stronger in those with lower QUICKI (i.e., greater insulin resistance). This is the first study to report evidence of a potentially adverse influence of AGEs on bone strength in otherwise healthy children. This relationship was strongest in children with the greatest insulin resistance, supporting further work in youth with chronic metabolic health conditions.

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The authors have nothing to disclose.

INTRODUCTION

Once recognized as an adult-onset condition, type 2 diabetes is now evident in children and adolescents. Despite having normal or even elevated bone mass, adults with type 2 diabetes are at an increased risk for fracture.[1] Several factors have been implicated in mediating the adverse influence of type 2 diabetes on bone health. One such factor that has garnered considerable attention and might help explain the disconnect between bone mass and fracture in type 2 diabetes is the accumulation of advanced glycation endproducts (AGEs).

Advanced glycation endproducts are formed as a result of non-enzymatic glycation of biological proteins, including bone collagen, due to glycemic and oxidative stress.[2] Several epidemiological and clinical studies in adults with type 2 diabetes have reported a potentially adverse influence of AGEs on bone turnover,[3] bone fragility,[3] and fracture risk.[4] These relationships have also been investigated in otherwise healthy adults, yielding inconsistent results. For instance, two separate studies showed that greater AGEs were associated with increased fracture risk in postmenopausal women[5] and lower estimated calcaneal stiffness in adult men,[6] but others reported null associations between AGEs and bone.[3,4] In children, adverse metabolic health outcomes associated with increased AGEs such as insulin resistance[7] and pre-diabetes[8] have previously been associated with lower cortical bone strength and total body bone mass, respectively. However, no studies to this point have investigated the link between AGEs and bone health in children.

Pentosidine is the primary AGE that has been implicated in diabetes-related skeletal fragility and bone deficits.[4] Therefore, we assessed the relationship between pentosidine and appendicular cortical bone geometry and estimated strength in otherwise healthy children who were at the early stages of sexual maturation and absent of any chronic health condition or growth disorder. Secondary analyses were also performed to determine whether the relationship between pentosidine and cortical bone was dependent upon insulin resistance status.

MATERIALS AND METHODS

Participant Characteristics

More detailed descriptions of study participants, protocols, and procedures were published previously.[7,9,10] Presented here is a secondary analysis of baseline data from a vitamin D supplementation trial in otherwise healthy children.[10] All participants were recruited at sexual maturation rating stage 2 or 3 based on self-reported breast/genital development[11,12] and were required to be absent of any chronic disease or growth disorder. Sexual maturation was assessed using a self-report. Exclusion criteria included commencement of menarche (females) or use of medications known to affect growth.

The original study included 315 black and white boys and girls ages 9–13 years from three study sites: The University of Georgia (UGA), Purdue University (PU), and Indiana University School of Medicine (IUSM). The current analyses were restricted to the children from the UGA study site, as pentosidine data were available only in these participants (n=160). The UGA children were similar to PU/IUSM children with respect to race, sex,

age, cortical bone measures, insulin, glucose, QUICKI, and HOMA-IR (all P>0.05). The Institutional Review Board for human subjects approved all study protocols and procedures. Participants and legal guardians provided written consent and assent, respectively.

Anthropometric Measurements

Height was measured using a wall-mounted stadiometer, weight was measured using an electronic scale, and leg and arm lengths were measured using a sliding caliper. Height, weight, and body mass index Z-scores were calculated using the 2000 CDC growth charts.[13]

Peripheral Quantitative Computed Tomography (pQCT)

Peripheral QCT scans were performed using Stratec XCT 2000 scanners (Stratec Medizintechnik GmbH, Pforzheim, Germany) at the 66% site relative to the distal growth plate of the non-dominant tibia and radius.[7,9] A single tomographic slice was taken using a slice thickness of 2.3 mm, a voxel size of 400 um, and scan speed of 20 mm/second. Cort mode 1 and contour mode 1 were used with a threshold of 710 mg/cm3, and peel mode 2 was used with a threshold of 400 mg/cm3. Cort mode 2, using a threshold of 400 mg/cm3, was used to determine polar strength strain index. Muscle cross-sectional area (MCSA) was assessed using a F03F05 filter (contour mode 3 [threshold of −100 mg/cm3] and peel mode 2).

Dual-Energy X-Ray Absorptiometry (DXA)

Total body bone mineral content (BMC, g) was measured via DXA (Delphi-A, Hologic Inc, Waltham, MA, USA). The same researcher performed and analyzed all DXA scans using instrument-specific software and procedures. In 10 females ages 5 to 8 years who were scanned twice over a 7-day period, intraclass correlation coefficients were calculated (all > 0.98).

Serum Biochemistries

Blood samples were collected in the morning following an overnight fast and were immediately processed and stored in −80 freezers. Serum glucose was measured in triplicate and serum insulin was measured in duplicate, as described previously.[14] The quantitative insulin sensitivity check index (QUICKI) and homeostasis model assessment of insulin resistance (HOMA-IR) were then calculated.[15,16] Higher HOMA-IR and a lower QUICKI are indicative of higher insulin resistance. Serum pentosidine was measured in duplicate using a solid phase-phase sandwich ELISA kit (BioTang Inc., Waltham, MA, USA). Before analysis, 1 μL of each sample was thawed and diluted into 499 μL of sample buffer as provided in the kit. The diluted samples (100 μL) were added to a 96-well microtiter plate pre-coated with human pentosidine antibody. After incubation and washing, the enzyme and substrate were added to induce colored reaction product. Absorbance was immediately measured at 450 nm using a Spectra Max M2 spectrometer (Molecular Devices, Sunnyvale, CA, USA). Mean inter-assay coefficient of variation was 5.8%.

Statistical Analyses

Insulin and HOMA-IR were log transformed to follow an approximately normal distribution. Pentosidine was compared across race and sex groups using ANOVA. Pentosidine was log transformed for this analysis due to unequal variances. To assess the relationship between pentosidine and markers of insulin resistance and bone health, Pearson's bivariate and partial correlations were performed. All partial correlation analyses included race, sex, maturation, and height as covariates. Partial correlation analyses involving cortical bone outcomes also included MCSA and QUICKI as covariates. The interaction between QUICKI and pentosidine in relation to bone health outcomes was assessed using linear regression while controlling for race, sex, maturation, height, and MCSA. For bone measures with a statistically significant interaction, partial correlations were performed in groups based on a QUICKI median cutoff (median QUICKI = 0.31) to help facilitate interpretation of interaction effects. Pentosidine was compared between higher and lower QUICKI groups using ANCOVA while controlling for race, sex, maturation, and height. The estimated marginal mean and standard error are presented. Analyses were performed using SPSS version 24 and STATA version 15.1. P-values < 0.05 were considered significant.

RESULTS

Descriptive characteristics are presented in Table 1. Twenty three percent (n = 37) of our participants had a BMI-for-age percentile ≥ 95th and 23% had a BMI-for-age percentile between the 85th and 95th. Pentosidine (log) was higher in whites vs. blacks and males vs. females (Supplemental Figure 1). Pentosidine did not correlate with glucose (r=0.046, P=0.565), insulin (r=0.023, P=0.778), HOMA-IR (r=0.028, P=0.726), or QUICKI (r= −0.023, P=0.773) in unadjusted analyses. However, while controlling for race, sex, maturation, and height, pentosidine was positively correlated with insulin (r=0.178, P=0.028) and HOMA-IR (r=0.174, P=0.031), and negatively associated with QUICKI (r= −0.177, P=0.028). Pentosidine did not differ between higher (53.0 ± 3.69) and lower (58.3 ± 3.71) QUICKI groups while controlling for race, sex, maturation, and height (P=0.324).

Bivariate and partial correlations between pentosidine and bone measures are presented in Table 2. In unadjusted analyses, pentosidine was inversely associated with tibia and radius cortical volumetric bone mineral density (Ct.vBMD), cortical bone mineral content (Ct.BMC), cortical area (Ct.Ar), and cortical thickness (Ct.Th); positively associated with radius endosteal circumference (Endo.Circ); and negatively associated with tibia polar strength strain index (pSSI; all P<0.05). While controlling for race, sex, maturation, and height, pentosidine was positively associated with tibia periosteal circumference (Peri.Circ) and Endo.Circ, but negatively associated with Ct.Th (all P<0.05). After additional adjustment for MCSA, pentosidine remained negatively associated with tibia Ct.Th and positively associated with Endo.Circ, and was negatively associated with Ct.BMC and Ct.Ar (all P<0.05). Pentosidine remained negatively associated with tibia Ct.Th after including QUICKI as a covariate (P<0.05), but did not correlate significantly with any other bone measure (Supplemental Table 1). Further, pentosidine did not correlate with total body BMC (r=−0.026, P=0.746), even after adjusting for race, sex, maturation, and height (r=0.034, P=0.675).

Linear regression revealed a significant interaction between QUICKI and pentosidine in relation to tibia Ct.Th while adjusting for race, sex, maturation, height, and MCSA ($P_{interaction}$=0.049). Subsequent partial correlations in groups based on a median QUICKI cutoff showed that pentosidine was negatively associated with tibia Ct.Th in children with lower QUICKI values (r=−0.311, P=0.009), but not higher QUICKI values (r=−0.131, P=0.273).

DISCUSSION

We assessed the relationship between pentosidine, an AGE implicated in diabetes related fracture,[4] and cortical bone geometry in a cohort of otherwise healthy children. Higher levels of pentosidine were associated with greater insulin resistance and a smaller cortical bone diaphysis. These relationships persisted even after adjusting for relevant confounders and there was evidence suggesting that the negative relationship between pentosidine and cortical bone was more so evident in the children with higher insulin resistance.

This was the first study to assess the relationship between AGEs and bone health in children. Our main finding was that, even after accounting for key confounders, greater pentosidine was associated with a smaller and thinner cortex at the tibia due to an accompanying wider endosteal perimeter. In healthy adult males, Momma et al reported negative relationships between skin autofluorescence (SAF), a measure of AGEs, and calcaneal bone stiffness.[6] Alternatively, in a study by Furst and colleagues,[3] SAF was associated with lower bone material strength and the bone formation marker P1NP in post-menopausal women with type 2 diabetes, but not the healthy controls. To understand whether the relationship between pentosidine and bone health was dependent on metabolic health, we examined the interaction between insulin sensitivity and pentosidine. Interestingly, these analyses revealed that the inverse relationship between pentosidine and tibia Ct.Th was strongest in those with higher insulin resistance (i.e., lower QUICKI). Subsequent correlational analyses demonstrated that this relationship was maintained only in those with QUICKI values less than the median. It should be noted, however, that the pentosidine by QUICKI interaction was only significant in relation to tibia Ct.Th, but not other cortical bone measure, and there were no significant interactions between pentosidine and HOMA-IR. Nevertheless, these results suggests that, in addition to having greater pentosidine concentrations, the potentially adverse influence of AGEs on bone health might be emphasized in those with poorer insulin sensitivity.

In our study sample, insulin resistance was somewhat high despite our participants being considered otherwise healthy. Based on data from the National Health and Nutrition Examination Survey, less than 20% of US children and adolescents are obese.[17] However, 23% of our participants had a BMI-for-age percentile ≥ 95th and the mean BMI Z-score was higher than the expected population mean of 0. Our participants were at the early stages of sexual maturation, which is when transient increases in insulin resistance are heightened.[18] For this reason, sexual maturation, in addition to other key demographic (i.e., race and sex) and biologic (i.e., height and MCSA) factors, were included as covariates in our statistical analyses to account for confounding. Notably, skeletal muscle is a well-characterized determinant of childhood bone health[19] and pentosidine correlated positively with MCSA.

That pentosidine was negatively associated with tibia Ct.Ar and Ct.BMC after statistically adjusting for MCSA highlights the importance of accounting for skeletal muscle in these relationships. Interestingly, pentosidine did not correlate with total body BMC measured via DXA, and there appeared to be a site-specificity of the relationships with cortical bone measures. Unadjusted results at the radius were consistent with those at the tibia, but were attenuated after statistical adjustment. The reason for these discrepancies is unclear, but might be attributed to sample size, differences in the biological role of systemic AGEs at habitually loaded (i.e., tibia) versus unloaded (i.e., radius) bone regions, or methodological constraints given the relatively small size of the cortical bone compartment at the radius.

Beyond bone health, there is interest in understanding the role of AGEs in the cardiovascular and metabolic manifestations that often accompany obesity and diabetes. Earlier studies in children and adults have shown that AGEs are associated with higher blood pressure, lipids, vascular stiffness, and coronary artery calcification.[20–23] Though we did not perform a comprehensive assessment of metabolic outcomes and did not collect data on cardiovascular health, pentosidine was associated with measures of insulin resistance, including QUICKI, HOMA-IR, and fasting insulin. That most, but not all, relationships between pentosidine and cortical bone geometric measures were attenuated after controlling for QUICKI is suggestive of a potential intermediary role of insulin resistance in these relationships. Collectively, these results support further work involving AGEs and sensitive measures of cardiovascular and metabolic health.

Despite the novelty of our results, this study was not without limitations. The most prominent limitation was that pentosidine was assayed in only a subset of our total cohort. This could have introduced unfavorable bias into our analyses. However, race, sex, maturation, insulin resistance, and bone measures were similar between the included vs. excluded children, thus reducing this concern. The cross-sectional design also limits our ability to infer causality, so future prospective studies will help progress this line of questioning. Additionally, we relied on serum pentosidine as a measure of AGEs, but other AGEs such as N-carboxymethyl-lysine and endogenous AGE receptors are also relevant to bone health.[24] Non-invasive measures of AGEs such as SAF might be useful in the pediatric setting. Recently, SAF was shown to predict future type-2 diabetes and cardiovascular disease risk irrespective of metabolic health,[25] supporting the utility of this measure and the subclinical effects of AGEs on health. As indicated above, we did not perform a comprehensive evaluation of cardiovascular and metabolic health; however, our results involving the relationship between pentosidine and insulin resistance support future work in this area. A major strength of this study was our use of pQCT to assess cortical bone geometry and estimated bending strength at both the radius and tibia. Unfortunately, data on bone geometry at trabecular bone sites or cortical and trabecular bone microarchitecture from high-resolution pQCT were not available for this study.

In summary, this was the first study to assess the relationship between pentosidine, an AGE implicated in diabetes-related bone fragility,[1] and bone geometry and estimated strength in otherwise healthy children. We found a consistent inverse relationship between pentosidine and bone geometry, implicating AGEs in suboptimal bone health even in children who are absent of any chronic health conditions. These results shed new light on the potential

adverse influence of type 2 diabetes progression on the growing skeleton, while uncovering a novel factor that might hinder bone health in at risk children. Additional work is warranted regarding the influence of AGEs on childhood bone health, as well as concomitant cardiovascular and metabolic health outcomes in pediatric populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Descriptive characteristics

	N	Mean	SD
Demographics			
Race (n, black)	160	80	
Sex (n, female)	160	80	
Age (years)	160	11.28	1.24
Maturation (n, stage 2/3)	160	97/63	
Anthropometrics			
Height (cm)	160	150.86	8.93
Height (Z-score)	160	0.69	1.00
Weight (kg)	160	48.00	11.83
Weight (Z-score)	160	0.88	1.07
BMI (kg/m^2)	160	21.00	4.36
BMI (Z-score)	160	0.82	1.18
BMI (percentile)	160	74.85	34.23
Leg length (cm)	160	34.78	2.86
Arm length (cm)	160	24.50	1.89
Total Body			
BMC (g)	160	1538.15	302.79
Tibia			
MCSA (mm^2)	158	4958.24	1088.70
Ct.vBMD (mg/cm^3)	154	1061.71	34.69
Ct.BMC (mg/mm)	154	251.35	47.77
Tt.Ar (mm^2)	154	444.67	89.19
Ct.Ar (mm^2)	154	236.80	45.01
Ct.Th (mm)	154	3.78	0.51
Peri.Circ (mm)	154	74.39	7.37
Endo.Circ (mm)	154	50.64	6.95
pSSI (mm^3)	154	1662.63	474.07
Radius			
MCSA (mm^2)	160	2140.22	475.81
Ct.vBMD (mg/cm^3)	156	1067.05	37.05
Ct.BMC (mg/mm)	156	63.19	12.92
Tt.Ar (mm^2)	156	94.62	18.91
Ct.Ar (mm^2)	156	59.10	11.38
Ct.Th (mm)	156	2.15	0.36
Peri.Circ (mm)	156	34.32	3.34
Endo.Circ (mm)	156	20.81	3.66
pSSI (mm^3)	156	176.83	51.17
Biochemistries			
Glucose (mg/dL)	160	89.23	6.93

	N	Mean	SD
Insulin (uU/mL)	159	20.43	11.67
HOMA-IR	159	4.54	2.77
QUICKI	159	0.31	0.02
Pentosidine (pg/mL)	158	55.29	35.55

BMI, body mass index; BMC, bone mineral content; MCSA, muscle cross-sectional area; Ct.vBMD, cortical volumetric bone mineral density; Ct.BMC, cortical bone mineral content; Tt.Ar, total bone area; Ct.Ar, cortical bone area; Ct.Th, cortical thickness; Peri.Circ, periosteal circumference; Endo.Circ, endosteal circumference; pSSI, polar strength strain index; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index

Table 2.

Bivariate and partial correlations between pentosidine and cortical bone measures in otherwise healthy children

	Unadjusted		Race, sex, maturation, & height-adjusted		Race, sex, maturation, height, & MCSA-adjusted	
	r	**P**	**r**	**P**	**r**	**P**
Tibia						
MCSA	0.147	0.068	0.219	0.007		
Ct.vBMD	**−0.215**	**0.008**	−0.088	0.290	−0.053	0.525
Ct.BMC	**−0.240**	**0.003**	−0.054	0.516	**−0.176**	**0.033**
Tt.Ar	−0.065	0.426	0.150	0.069	0.055	0.509
Ct.Ar	**−0.207**	**0.011**	−0.037	0.659	**−0.174**	**0.035**
Ct.Th	**−0.292**	**<0.001**	**−0.178**	**0.030**	**−0.227**	**0.006**
Peri.Circ	−0.059	0.473	**0.168**	**0.042**	0.078	0.346
Endo.Circ	0.072	0.379	**0.217**	**0.008**	**0.164**	**0.048**
pSSI	**−0.164**	**0.043**	0.058	0.484	−0.071	0.394
Radius						
MCSA	−0.025	0.758	0.174	0.031		
Ct.vBMD	**−0.249**	**0.002**	−0.111	0.178	−0.077	0.350
Ct.BMC	**−0.252**	**0.002**	−0.015	0.860	−0.064	0.436
Tt.Ar	−0.042	0.602	0.077	0.351	0.002	0.980
Ct.Ar	**−0.230**	**0.004**	0.004	0.963	−0.062	0.450
Ct.Th	**−0.327**	**<0.001**	−0.089	0.277	−0.090	0.276
Peri.Circ	−0.038	0.636	0.087	0.289	0.015	0.857
Endo.Circ	**0.164**	**0.042**	0.112	0.174	0.061	0.462
pSSI	−0.141	0.080	0.040	0.631	−0.045	0.590

MCSA, muscle cross-sectional area; Ct.vBMD, cortical volumetric bone mineral density; Ct.BMC, cortical bone mineral content; Tt.Ar, total bone area; Ct.Ar, cortical bone area; Ct.Th, cortical thickness; Peri.Circ, periosteal circumference; Endo.Circ, endosteal circumference; pSSI, polar strength strain index