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Collagen glycosylation, hip structural analysis, and trabecular bone score in adolescents with type 1 diabetes: a cross-sectional study

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Abstract Both type 1 and type 2 diabetes mellitus (T1D and T2D) are associated with poor bone health and an increased risk of fracture in adults. However, there are limited data regarding the effects of diabetes on the growing skeleton, particularly during adolescence, the time of peak bone mineral accretion. The purpose of this study was to examine differences in markers of bone health and factors that influence bone health in White adolescents and young adults with well-controlled T1D ($n=17$; Average A1C 7.45 ± 1.15%) and control participants without T1D ($n=13$). Age across both groups was similar (17.41 ± 1.62 years for T1D vs. 17.46 ± 1.45 years for controls) as was BMI and height. Bone density was measured at the lumbar spine, whole body, and proximal femur sites using the GE HealthCare's Lunar iDXA (GE; v11-30.062) in all subjects. Hip structural analysis (HSA) was performed at the proximal femur and Trabecular Bone Score (TBS) was calculated from AP spine image using Trabecular Osteo Software from Medimaps. Markers of bone formation, resorption, serum sclerostin and urine pentosidine were measured in all subjects. No difference in total body bone mineral density (BMD), lumbar spine BMD, lumbar spine BMAD, dual femur BMD, HSA variables or TBS measures were noted between subjects with T1D and controls. However, duration of diabetes had a significant negative correlation (p: 0.035) with cross-sectional moment of inertia (a measure of resistance to bending forces) in subjects with T1D. IGF-1 levels were marginally lower in the group with T1D (p:0.06) and had a significant inverse relationship (r: -0.406, p:0.026) with mean hip axis angle; a known predictor of hip fractures. TBS score had a marginally significant negative correlation with urinary pentosidine (a marker for collagen glycosylation) across both groups after adjusting for age (r: -0.343, p: 0.07), suggesting increased collagen glycosylation has an adverse impact on bone microarchitecture.

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Introduction

Both type 1 and type 2 diabetes mellitus (T1D and T2D) are associated with poor bone health and an increased risk of fracture in adults [1]. However, there are limited data regarding the effects of diabetes on the growing skeleton, particularly during adolescence, the time of peak bone mineral accretion [2]. This age is important to study as factors that affect bone mineral accrual adversely could potentially be modified allowing us to optimize peak bone mineral mass, an important predictor of future osteoporotic fractures. Areal bone mineral density (BMD) measured by dual-energy X-ray densitometry (DXA) is commonly used as a surrogate measure for bone health. However, in patients with diabetes, BMD does not accurately predict fractures [3] suggesting there may be a deterioration in bone structure and quality (bone material properties) not reflected in DXA measures of areal BMD. Hip structural analysis (HSA) and trabecular bone score (TBS) are tools that use DXA measurements to evaluate hip geometry and spine microarchitecture, respectively. Both are adversely affected in adults with diabetes [4] and TBS has been shown to be an accurate predictor of fragility fractures in adults with diabetes [5]. Only one study has looked at HSA parameters in girls with T1D between ages of 10–16 years old and reported it was adversely affected [6]. TBS has not been examined in adolescents with diabetes.

Bone quality is influenced by various factors including advanced glycation end products (AGEs), serum sclerostin and insulin-like growth factor 1 (IGF-1) and reflected by markers of bone formation and resorption. Advanced glycation end products (AGEs) are formed by non-enzymatic reactions between reducing sugars and proteins, lipids, and nucleic acids. Pentosidine, a widely studied AGE, increases with age and is associated with increased bone fragility in adults [7]. Sclerostin is a protein produced by osteocytes that is a potent inhibitor of bone formation [8] and is known to be increased in patients with diabetes [9]. IGF1 stimulates bone formation and is reduced in T1D [10].

The objectives of this study were to determine the effects of T1D on AGEs, sclerostin, IGF-1, and markers of bone formation and resorption during adolescence and relate these measures to BMD, hip geometry, and TBS. We hypothesized that there would be increase in factors that adversely affect bone health in T1D and that these would be associated with impaired hip geometry and TBS scores and decreased BMD.

Methods

This was a cross-sectional study of adolescents and young adults with and without T1D and who self-identified as White. Age range for study participants was 16–20 years and only adolescents who self-reported Tanner stages 4 or 5 for pubic hair were included. Signed informed consent was obtained from every young adult participant or parent (if subject was a minor) and assent was obtained from the minor, in accordance with the University of Oklahoma Health Sciences Center Institutional Review Board who approved the study. Recruitment was done between mid-2019 to end of 2020. Due to the significant effect of race and ethnicity on bone health, only subjects who identify themselves as Non-Hispanic White were recruited for this pilot study. Participants with T1D of at least two years duration and control subjects without diabetes were recruited from the University of Oklahoma Pediatric Diabetes and Endocrine Clinic. All enrolled subjects with T1D were prescribed intensive insulin management with 47% meeting ADA (American Diabetes Association) criteria for optimal control (HbA1c ≤ 7%) at enrollment. All subjects with T1D had evidence of pancreatic beta cell autoimmunity (i.e., positive GAD, islet cell, insulin, or Zn transporter antibodies) and met the ADA criteria for T1D. For the control group, enrolled subjects were T1D participants' siblings or other patients followed in the endocrine clinic whose conditions would not adversely impact bone health. A chart review was conducted to determine eligibility and rule out any contraindications for participating in the study. Duration of diabetes was also obtained from chart review. Fracture history was obtained by a simple questionnaire administered at study visit. Participants prescribed any medication that would impact bone health, including oral contraceptives, were excluded. Also excluded were patients with celiac disease, rheumatological disease, inflammatory bowel disease, patients prescribed systemic glucocorticoids for longer than two weeks, and subjects with a body mass index less than the 15th percentile for their age and sex. Because control subjects were recruited from the general endocrine clinic, they were more likely to have an endocrine condition (77%) compared to subjects with T1D (21%). The only other endocrine illness identified among both the control and T1D subjects was hypothyroidism or Hashimoto thyroiditis. Thyroid function tests in all subjects with thyroid disease were within acceptable limits with TSH between 1.0 and 6.0 microIU/mL for a year prior to enrollment. Fracture history and duration of diabetes was as reported by subjects at time of participation in study.

Enrolled subjects had bone density measured using GE Healthcare's Lunar iDXA (GE; v11-30.062) at the lumbar spine, whole body, and proximal femur. Bone Mineral Apparent Density (BMAD) was calculated for the Anterior-Posterior spine (AP spine) to account for the effect of height on DXA measurements using published formulas.Trabecular Bone Score (TBS) was calculated from AP spine image using Trabecular Osteo Software from Medimaps [11]. Hip structural analysis (HSA) was performed

at the proximal femur using HSA software in the DXA machine. Hip structural analysis variables that were calculated included strength index (SI), bucking ratio (BR) (an indicator of cortical bucking under compressive forces), section modulus (SM) (an indicator of bending strength for stress in direction of image plane), cross-sectional moment of inertia (CSMI) (an index of structural rigidity), and cross-sectional area (CSA) (a measure of resistance of bone to axial forces) [6].

A fasting blood sample was obtained, and serum was separated by centrifugation within one hour of collection and stored at -80 °C until analysis. Sclerostin, glucose, osteocalcin, IGF-1, CTX, insulin, and PINP were measured by ELISA (sclerostin, osteocalcin, IGF-1: ALPCO diagnostics; CTX, PINP: Novus Biologicals, Colorado and insulin: Millipore Sigma) according to manufacturer's protocol. The intra-assay CV for PINP and sclerostin was 9%, glucose was 7%, IGF-1 was 5%, and osteocalcin was 3%. All samples were analyzed as a single batch at the end of the study and standards and samples were run on each assay plate. A single urine sample was collected during the study visit. Urine was mixed thoroughly, and aliquots were stored at -80 °C until analysis. Pentosidine was extracted from urine using acetonitrile, and measured by LC-MS/MS in the OUHSC institutional core research facility using a method modified from Lee et al. [12]. A standard curve was prepared from commercially available purified pentosidine (Cayman Chemical, Ann Arbor, MI) and samples spiked with internal standard served as extraction efficiency controls.

Participants' physical activity was assessed by the Bone-specific Physical Activity Questionnaire (BPAQ). The BPAQ is self-administered and designed to quickly obtain a comprehensive account of one's lifetime of bone-relevant physical activity [13]. Fracture history was obtained by a simple questionnaire administered at study visit. Nutrition data were obtained through the 7-day Food Frequency Questionnaire by NutritionQuest (https://www.nutritionquest.com/assessment) [14].

Statistics

Group statistics are indicated as mean ± SD for continuous measures or as percentages for categorical variables. Groups were compared using the Student t-test for continuous measures or chi-squared test for categorical measures. General linear models (glm) were used to measure associations adjusted for covariates; covariates for each model were selected as those with a significant association with the dependent variable. Correlation coefficients were calculated from the glm results. A threshold of 0.05 was set for statistical significance. Calculations were done in R (version 4.2.2, 2022-10-31, R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, (Vienna, Austria. URL https://www.R-project.org/) incorporating the gmodels package (version 2.18.1.).

Results

Baseline demographic, nutrition, and physical activity (Table 1)

Of the 30 enrolled participants, 17 (3 male and 14 female) with T1D were compared to 13 healthy control subjects (7 male and 6 female). There were no statistically significant differences in mean age, height, or BMI values between the groups. As expected, there was a difference in HbA1c values between the groups. Of the subjects with T1D, 35% reported having at least one fracture during their lifetime with 38% of the control subjects reporting at least one fracture. None of the reported fractures represented a major fragility fracture.

There was no significant difference in physical activity between groups as measured by the BPAQ questionnaire. Similarly, there were no significant differences in nutritional intake, including calcium and fiber intake, between the groups. (Supplementary Table 1)

Bone mineral density, hip structural analysis, and TBS measures (Table 2)

There was no difference between groups for total body less head BMD (TBLH BMD), lumbar spine BMD, lumbar spine BMAD, or dual femur BMD. Similarly, there was no difference in any of the HSA variables across groups. TBS measures did not significantly differ across groups. There was no significant effect of age (because the age range is narrow). We did do sex adjusted analysis, we went with the unadjusted results because age and sex

Table 1 Demographic, nutritional and physical activity measures for type 1 diabetic (T1D) and normoglycemic control subjects

Variable	T1D subjects *N* = 17	Control subjects *N* = 13	*p* value
Age (years, mean ± SD)	17.41 ± 1.62	17.46 ± 1.45	0.93
Sex (%male)	18	54	0.06
Height (cm, mean ± SD)	165.0 ± 9.5	169.6 ± 7.5	0.15
BMI (Kg/m2)	28.1 ± 6.1	27.1 ± 5.1	0.43
HbA1c (%)	7.45 ± 1.15	5.1 ± 0.47	< 0.01
History of fracture (n, (%) yes)	6 (35)	5 (38)	0.99
Daily calcium intake (grams, mean ± SD)	893 ± 394	1009 ± 557	0.53

Table 2 Bone mineral density (BMD), hip structural analysis and bone trabecular score variables among subjects with type 1 diabetes (T1D) and control subjects

Variable	T1D subjects *N* = 17	Control subject *N* = 13	*p* value
TBLH BMD (g/cm^2)	1.03 ± 0.12	1.06 ± 0.10	0.24
L1-L4 BMD (g/cm^2)	1.21 ± 0.18	1.24 ± 0.13	0.60
Bone mineral apparent density (g/cm3)	0.34 ± 0.05	0.33 ± 0.04	0.63
Femur neck BMD (g/cm^2)	1.10 ± 0.15	1.14 ± 0.16	0.50
Total femur BMD (g/cm^2)	1.10 ± 0.13	1.14 ± 0.14	0.49
Strength Index	1.41 ± 0.44	1.53 ± 0.36	0.41
Section modulus (mm3)	684 ± 150	756 ± 192	0.27
Cross Section Movement of Inertia (mm4)	10,572 ± 2937	12,528 ± 4689	0.20
Cross Sectional Area (mm^2)	158.1 ± 23.0	171.4 ± 32.2	0.21
Buckling Ratio	5.39 ± 2.57	5.38 ± 1.94	1.00
Trabecular Bone Score	1.53 ± 0.14	1.58 ± 0.11	0.35

Table 3 Bone turnover markers and urinary pentosidine in type 1 diabetes (T1D) and normoglycemic control subjects

	T1D subjects *N* = 17	Control subject *N* = 13	*p* value
Osteocalcin (ng/ml)	19.4 ± 16.4	30.5 ± 32.0	**0.039**
IGF-1 (ng/ml)	336.7 ± 82.3	399.5 ± 91.8	0.064
Sclerostin (pmol/l)	24.0 ± 14.2	31.3 ± 22.8	0.21
PINP (pg/ml)	69.0 ± 78.5	53.5 ± 31.4	0.87
CTX (ng/ml)	0.15 ± 0.20	0.13 ± 0.08	0.75
Urinary pentosidine (ng/ml)	0.90 ± 0.78	1.21 ± 0.97	0.36

adjustments made no difference. (Supplementary Tables 2 and 3)

Serum and urine markers (Table 3)

There were no significant differences in levels of markers of bone formation or resorption between the groups. Similarly, groups did not differ for serum sclerostin, IGF-1, and urine pentosidine. However, serum osteocalcin levels were lower in subjects with T1D than controls (*p*: 0.04).

Determinants of HSA and TBS variables

In subjects with T1D, duration of diabetes had a significant negative correlation with cross-sectional moment of inertia (*r*= -0.513, *p* = 0.035). Cross sectional moment of inertia is a measure of resistance to bending forces and these results suggest longer duration of diabetes can adversely impact this measure. Similarly, serum osteocalcin had a significant correlation with BMAD in participants with T1D (*r*= -0.614 *p* = 0.045) after controlling for sex. BMAD is an estimate of volumetric bone density.

Among all subjects, TBS score had a marginally significant negative correlation with urinary pentosidine after adjusting for age (r: -0.343, p: 0.07) (Fig. 1). These data suggest that among all subjects, collagen glycosylation adversely affects bone microarchitecture as determined by TBS. IGF-1 levels had a significant relationship with mean hip axis angle (r: -0.406, *p*:0.026). Meta analysis by Fajar et al. has shown hip neck angle to be a significant risk factor for femoral neck fractures [15]. We did not measure 25 hydroxyvitamin D levels in our subjects.

Discussion

In this study, we observed that BMD in adolescents with T1D is equivalent to that of unaffected peers. This is different from the recent meta-analyses by Loxton et al. and Zhu et al. showing decreased bone mineral density in children with T1D [16, 17]. In the meta-analysis of Loxton et al., 38 studies were included and the mean age ± SD in those studies was 12.6 ± 2.3 years. Race, duration of diabetes, or HbA1c were not mentioned or used in the analysis. The meta-analysis published by Zhu et al. included nine articles overlapping with studies included in the paper published by Loxton et al. They reported that the findings of lower BMD in T1D children and adolescents are consistent in populations from Asia and South America but varied in North America and Europe. The inability to detect a difference in BMD in our study could be attributed to our smaller sample size and the fact that our participants had well-controlled T1D.

To date, only a single study has performed hip structural analysis in adolescents with T1D. Joseph et al. [6]

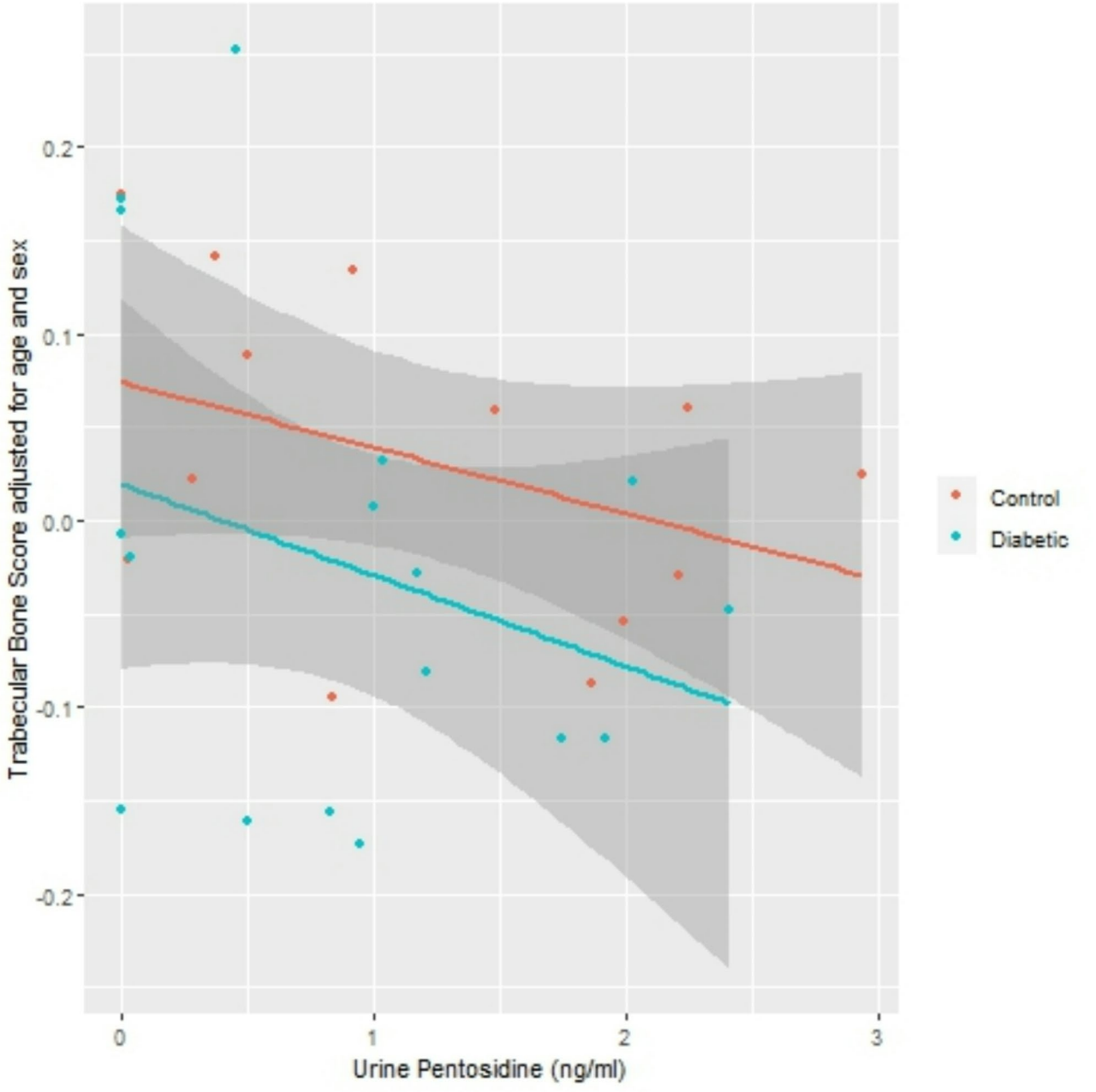

Fig. 1 Urinary Pentosidine and Trabecular Bone Score for type 1 diabetic and normoglycemic control subjects

reported lower CSA, CSMI, SM, and cortical thickness at the narrow neck among 62 girls with T1D aged 10–16 years of age compared to 61 same-aged girls without T1D. However, we did not find any difference in hip structural parameters in participants with T1D compared to controls; this could again be because our subjects had well-controlled diabetes. In our study, mean HbA1c and duration of diabetes were 7.5% and 7.4 years, respectively, compared to 8.4% and 4.8 years in their study. We also observed a negative correlation of CSMI with duration of diabetes (not reported by Joseph et al.) suggesting decreased structural rigidity in subjects with longer duration of diabetes even in well-controlled subjects as participants in our study had 3 years longer duration of diabetes and thus a longer time for these physiological changes to emerge.

We found no differences in serum sclerostin, PINP, CTX, and urine pentosidine between subjects with T1D and controls. Franceschi et al. reported increased PINP in subjects with T1DM compared to controls [18]; 96 children with T1D were included in this study (45 male, 51 female with mean age of 10.5 ± 3.1 years and 10.3 ± 3.2

years, respectively). Thus, the mean age of children with T1D in this study was much lower than those in our study. Additionally, the subjects with T1D in their study were significantly younger than their control subjects ($p < 0.05$) and thus the increased PINP might merely reflect age-related differences in bone turnover. Similar to our study, these authors did not observe any difference in sclerostin or CTX levels between subjects with T1D and control subjects. Sclerostin was found to be elevated in subjects with T1D aged 12.3 ± 4.7 years compared to similar age control subjects in a recent study done by Wedrochecwicz et al. [19]. Participants (though well matched in their study) ranged across all Tanner stages, and this could have influenced the results.

We found serum IGF-1 to be marginally lower (p: 0.06) in those with T1D, consistent with prior reports showing a reduction in circulating IGF-1 in children and adolescents with T1D [20]. IGF-1 had a significant negative correlation with hip axis angle in our study. Elevated hip axis angle is a predictor of osteoporotic neck fractures in adults in a metanalysis done by Fajar et al. [15]. These data suggest lower IGF-1 levels that are characteristically seen in subjects with T1D could contribute to bone fragility by adversely influencing hip geometry. A study by Jaisson et al. showed increased serum pentosidine levels in children with T1D [21]. The difference in our findings may reflect the smaller sample size and better glycemic control.

We found that serum osteocalcin was lower in our participants with T1D as has been previously reported [22, 23]. The present study expands upon this by demonstrating a significant relationship between serum osteocalcin and BMAD (calculated volumetric spine BMD), a significant predictor of vertebral fractures in children [24]. A relationship between osteocalcin and spine BMD has been shown before in postmenopausal women with osteoporosis [25, 26], but not in adolescents with T1D.

Our study describes the relationship between urinary pentosidine and TBS (a measure of bone microarchitecture) in adolescents with and without T1D. The AGE pentosidine has been linked to bone health in a variety of circumstances. Trabecular pentosidine correlates positively with adverse biomechanical properties in human vertebrae [27]. Urinary pentosidine predicts vertebral fractures in elderly Japanese women [28] and negatively correlates with TBS in adults with T2D [29, 30]. A recent article by Kindler et al. showed higher serum pentosidine levels were associated with smaller and thinner tibial cortex [31]. Given the abundance of literature relating pentosidine with indices of bone health, we consider our findings to be biologically and potentially clinically significant even though the statistical significance was borderline ($p = 0.07$). Our finding of the relationship between urinary pentosidine and TBS across all subjects is in line with these reports. Some of the limitations of our study include the small sample size. However, our subjects were very well matched in terms of race, age, body weight and height, potentially overcoming this limitation. Our power is low, so we have to treat non-significant results with caution. We also did not measure 25-hydroxy vitamin D levels in our subjects. Due to the limited sample size, we could not do sex-matched comparisons, however analysis separately based on sex did not reveal any differences in males and females for any of the parameters. Tanner stage pubic hair was determined by self-report (after being shown pictures of various tanner stages). This could be biased and would be another limitation for our study.

Conclusion

In this study we demonstrate that adolescents and young adults with T1D with good control (A1C < 7.5%) have similar BMD compared to age, race matched controls but their hip geometry, specifically CSMI, is adversely affected by a longer duration of diabetes. The pathophysiology underlying adverse hip geometry with longer duration of diabetes needs to be explored further. This study did not find any difference in bone turnover markers or serum sclerostin between the two groups.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01677-w.

Supplementary Material 1

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by S.K, J.C, H.W. The first draft of the manuscript was written by S.K and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate

The study was approved by University of Oklahoma Health Sciences center IRB for ethical approval and all subjects gave informed consent/assent to participation.

Consent to publication

Not applicable as no identifiable individual information is present.

Competing interests
The authors declare no competing interests.

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