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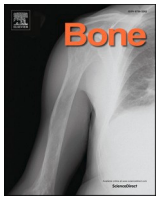

Full Length Article

Bone parameters in T1D and T2D assessed by DXA and HR-pQCT – A cross-sectional study: The DIAFALL study

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ABSTRACT

Introduction/aim: People with type 1 diabetes (T1D) and type 2 diabetes (T2D) have an increased risk of fractures due to skeletal fragility. We aimed to compare areal bone mineral density (aBMD), volumetric BMD (vBMD), cortical and trabecular measures, and bone strength parameters in participants with diabetes vs. controls.
Methods: In a cross-sectional study, we included adult participants with T1D (n = 111, MA = 52.9 years), T2D (n = 106, MA = 62.1 years) and controls (n = 328, MA = 57.7 years). The study comprised of DXA scans and HR-pQCT scans, biochemistry, handgrip strength (HGS), Timed Up and GO (TUG), vibration perception threshold (VPT), questionnaires, medical histories, alcohol use, and previous fractures. Group comparisons were performed after adjustment for sex, age, BMI, diabetes duration, HbA1c, alcohol, smoking, previous fractures, post-menopausal, HGS, TUG, and VPT.
Results: We found decreased aBMD in participants with T1D at the femoral neck ($p = 0.028$), whereas T2D had significantly higher aBMD at peripheral sites (legs, arms, $p < 0.01$) vs. controls. In T1D we found higher vBMD ($p < 0.001$), cortical vBMD ($p < 0.001$), cortical area ($p = 0.002$) and thickness ($p < 0.001$), lower cortical porosity($p = 0.008$), higher stiffness ($p = 0.002$) and failure load ($p = 0.003$) at radius and higher vBMD ($p = 0.003$), cortical vBMD($p < 0.001$), bone stiffness ($p = 0.023$) and failure load($p = 0.044$) at the tibia than controls. In T2D we found higher vBMD ($p < 0.001$), cortical vBMD ($p < 0.001$), trabecular vBMD ($p < 0.001$), cortical area ($p < 0.001$) and thickness ($p < 0.001$), trabecular number ($p = 0.024$), lower separation ($p = 0.010$), higher stiffness ($p < 0.001$) and failure load ($p < 0.001$) at the radius and higher total vBMD ($p < 0.001$), cortical vBMD ($p < 0.011$), trabecular vBMD ($p = 0.001$), cortical area ($p = 0.002$) and thickness ($p = 0.021$), lower trabecular separation ($p = 0.039$), higher stiffness ($p < 0.001$) and failure load ($p = 0.034$) at tibia compared with controls.
Conclusion: aBMD measures were as expected lower in T1D and higher in T2D than controls. Favorable bone microarchitecture and strength parameters were seen at the tibia and radius for T1D and T2D.

1. Introduction

Fractures cause substantial health issues globally, with an estimated 178 million new fractures annually and still increasing [3]. Furthermore, fractures, especially hip fractures, are associated with high morbidity and mortality, and every third woman and fifth man over the age of 50 will get a fracture [4–7].

In general, diabetes is associated with higher fracture risk. A study

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showed a relative risk (RR) at the hip of 4.93 (CI95%: 3.06–7.95) in people with T1D and a RR of 1.33 (CI95%1.19–1.49) in people with T2D and for non-vertebral fractures a RR of 1.92 (CI95%: 0.92–3.99) and a RR of 1.19 (CI95%:1.11–1.28), respectively [8]. Although, areal bone mineral density (aBMD) measured by dual-energy X-ray absorptiometry (DXA) has been reported to be decreased in T1D but to be normal or even increased in T2D [9]. Variations in aBMD do not explain the increased fracture burden in people with diabetes, as aBMD seems to underestimate the proportion of fractures observed in epidemiological research [10,11]. Morphological alterations in bone composition are a potential contributor to increased bone fragility and fractures in diabetes [12]. Furthermore, these changes are also associated with aging, sex, elevated BMI, alcohol use, smoking, different types of medication, muscle strength, and osteoporosis [13]. High-resolution peripheral quantitative computed tomography (HR-pQCT) is capable of non-invasive in vivo 3D characterization of bone microarchitecture, assessment of different volumetric BMDs (vBMD), cortical measures, and derived calculations of bone strengths parameters of the distal radius and tibia [14,15]. This novel technique has the ability to examine importantly and fracture-associated structural properties of cortical and trabecular bone and is superior in detecting skeleton changes compared to DXA [16]. In addition, HR-pQCT can predict bone strength by measuring failure load in finite element analyses (FEA). This is a computational approach that performs biomechanical simulations on scan data to estimate the failure load (fracture point) [17]. At present, it is unclear whether there should be another threshold for bone microarchitecture parameters in predicting fracture risk in diabetes when considering the presence of neuropathy, postmenopausal status, peak bone mass, and other factors [18–23]. However, gaining information on microarchitecture parameters and bone strength measures in combination with aBMD at central and peripheral skeletal sites could be a potentially helpful tool to estimate skeletal fragility and in time, predict fracture risk [24,25].

Therefore, the primary aim was to compare T1D and T2D participants with controls without diabetes on aBMD and bone mineral content (BMC) at central (femoral neck and spine (L1-L4)) and peripheral skeletal sites (arms and legs) and to estimate the corresponding T- and *Z*-scores for central sites. Furthermore, to determine bone microarchitecture parameters and bone strength at the distal radius and tibia in a comprehensive adjusted analysis for several potential cofounders. The analyses were adjusted for sex, age, BMI, diabetes duration, HbA1c, alcohol, smoking, previous fractures, postmenopausal status, handgrip strength (HGS), Timed Up and Go (TUG), and vibration perception threshold (VPT).

2. Material and method

2.1. Source of data

This study was conducted at Aalborg University Hospital in Denmark in collaboration with Aalborg University at Steno Diabetes Center North Denmark. To maintain a high study quality Coefficient of Variance (CV) was calculated and used as a validation method for each procedure [26,27]. CV percentages below 10 % were considered of high standard [28]. All data was collected and stored in Research Electronic Data Capture (REDCap).

2.2. Study population

This was a cross-sectional single-center study and consisted of people from the general population with T1D (n = 111), T2D (n = 106), and control persons without diabetes (n = 328). All participants were enrolled from the 1st of April 2019 until the 30th of June 2021. Participants were freely and openly recruited by social media and flyers at the local hospitals without direct contact and preference to disease status. Approximately 176 people were excluded according to the exclusion criteria (see below) before entering the study. Each participant met for one day of testing, and no participant dropouts were registered during the study day. More than 95 % of the study procedures were completed, and the study information was collected during the same study visit. Due to delayed approval of the HR-pQCT scanner (method described below), fewer participants were tested by this method (T1D: n = 109, T2D: n = 96, and Controls: n = 160).

Participants with T1D and T2D were identified by self-reports and previous HbA1c levels above 48 mmol/mol (6,5 %). If the diagnosis was questionable, the patient journal was evaluated and discussed between the investigator and sponsor to ensure the diagnosis. Post-hoc analyses of control persons revealed no HbA1c levels above 48 mmol/mol.

2.3. In- and exclusion

Participants with T1D and T2D were included if they were between 20 and 90 years of age and had more than one year of diabetes duration. Control persons were included if they were between 20 and 90 years of age and not diagnosed with diabetes. Participants were excluded if they had the following conditions (applicable for both T1D, T2D, and control persons): Maturity-onset Diabetes of the young, moderate to severe liver or kidney dysfunction (Alanin amino-transaminase (ALAT) > 250u/l or estimated Glomerular Filtration Rate (eGFR) <15 mmol/L/1,73m^2), pregnant or breastfeeding, active malignancy or terminal illness, current or previous alcohol- or drug abuse (within one year prior to inclusion), not able to understand Danish written or verbally, terms according to investigators judgment that made participants unsuitable to participate including lack of understanding or reduced physical ability, participated in other clinical studies or a current weekly exercise routine >10 h per week.

2.4. The study protocols

2.4.1. Questionnaire

An extensive questionnaire was handed out to each participant and completed on a tablet under standardized conditions. It included general questions regarding diabetes status, diabetic complications, osteoporosis, menopause, smoking status and alcohol consumption, previous fracture and medication.

2.4.2. Laboratory assessments and biochemistry

Blood samples were taken and handled by the Research bio. Med. Lap technologists at Aalborg University Hospital. Biochemistry included was: HbA1c, Creatinine, eGFR, Calcium-ion and ALAT. This laboratory is subject to rigorous quality testing according to international standards.

2.4.3. BMI

Body weight was calculated to the nearest 0.1 kg using a column scale (Seca Gmbh & co, Hamburg, Germany) with participants dressed in a light gown and no shoes. Height was measured to the nearest 0.5 cm using a stadiometer (Seca Gmbh & co, Hamburg, Germany). BMI was calculated as the person's weight in kilograms over their height in meters squared.

2.4.4. Handgrip strength

Handgrip Strength (HGS) was measured using a hydraulic dynamometer (SAEHAN Corporation, Gyungnam, South Korea) [29,30]. All participants were standing and had their arm in an extended position during testing. HGS was defined as the maximal grip strength achieved by verbally encouraging the participants. Each hand was used and the best of two trials was registered. CV was 4.8 %.

2.4.5. Timed Up and GO test

General mobility was assessed by the TUG test [31]. The participant started from a sitting position in a chair (seat height approximately 43–47 cm). Additionally, the participants were not allowed to use their

arms to help raise or sit in the chair. All participants were asked to perform the test barefooted one time for analysis. CV was 5.4 %.

2.4.6. Vibration perception threshold

Large-fiber neuropathy was assessed by VPT (Biothesiometry, Biomedical Instrument CO. Newbury Ohio 44,065, USA) [32,33]. The test was performed by slowly graduating the power (amplitude) until the participant registered the vibration on the proximal part of the first toe on each foot. The power was then turned down until the vibration was undetectable and registered. The test was repeated two times for analysis. CV was 2.3 %.

2.4.7. DXA imaging

A dual-energy X-ray Absorptiometry (DXA) (Hologic Horizon, type: 4500 Hologic Inc., Marlborough, MA, USA) was used to estimate aBMD and BMC, including *Z*- and T-scores at the femoral neck and spine (L1-L4). Each morning the DXA scanner was calibrated using a standard calibration block. The scanner uses two different energy beams, which allowed for two-dimensional quantification of the bone thickness and calculated aBMD and BMC measures of the region of interest. DXA scans included Whole Body, AP spine- and femoral neck DXA scan protocols. Effective doses for whole-body DXA examinations vary between 0.001 and 0.01 mSv. Images of the DXA scanner followed a manual and validated evaluation and were calculated by a standard protocol [34–36]. Analyzed DXA data including aBMD and BMC measurements for central (femoral neck, pelvis, spine (L1-L4), thoracic spine, lumbar spine) and peripheral sites (arms and legs). Thoracic spine, lumbar spine, and peripheral sites were derived from whole body DXA scans results. *Z*- and T-scores were estimated for the femoral neck and spine (L1-L4). The T-scores were computed in accordance with the international guidelines, using young females of Caucasian ethnicity as the basis of comparison CVs were between 0.1 %–0.5 % for different aBMD and BMC values after repositioning, and were comparable with previous literature [37].

2.4.8. HR-pQCT imaging

An HR-pQCT scanner (Xtreme CT I, SCANCO Medical, Switzerland) was used to scan the left radius and tibia by a standard in vivo protocol [14,38]. If a previously sustained radius or tibial fracture at the left side was reported, the contralateral side was scanned (app. 5 % of the scans). Participants were seated in a specially designed chair to immobilize the left leg or left arm in a carbon fiber shell during the measurement. An anteroposterior scout view of the scan side was acquired to position the specific region of measurement. A reference line was placed on the radial joint surface and the endplate of the distal tibia. The scan started 9.5 mm and 22.5 mm (for the radius and tibia, respectively) from the reference line in the proximal direction. The system stacked 110 parallel CT-slices with a nominal isotropic voxel size of 82 μm, thus delivering a three-dimensional representation of 9.02 mm bone to reconstruct images. The scan was three minutes, and the radiation dose was low (<3.0 μSv per site). All scans were graded regarding motion and scan quality. If the x-ray quality was graded five, the scan was repeated. A post hoc standardized quality control (grading) was made for all the scans [39,40]. The tibial and radial bone images were auto-contoured and overseen manually and modified when the contour visually deviated from the periosteal boundary. The images were automatically segmented and calculated from a standard evaluation, an ultra-distal cortical evaluation, and a finite-element analysis script provided by the manufacturer. The analyzed data included total vBMD (Tb.BMD), cortical BMD (Ct.BMD), trabecular BMD (Tb.BMD), cortical area (Ct.Ar), cortical thickness (Ct.Th), cortical porosity (Ct.Po), trabecular thickness (Tb.Th), trabecular number (Tb.N), trabecular separation (Tb.Sp) and finite-element analysis (FEA) measures (stiffness and failure load (FL)). Scan quality was graded as 1 (no motion artifacts), 2 (minor motion artifacts), 3 (moderate motion artifacts), 4 (severe artifacts) and 5 (extreme motion artifacts) [41]. Quality grade 1–4 was used in statistical analyses as sensitivity analyses did not change the overall outcomes compared with quality grade 1–3. CVs were between 0.02 % 4.35 %.

2.5. Statistics

Baseline characteristics were described as percentage of participants or mean with a standard deviation (SD) if normally distributed, and median with an interquartile range (IQR) if not. The distribution of continuous variables was examined by Histograms, q-q plots and box plots. For normally distributed data unpaired *t*-test was performed for intergroup comparisons. The resulting *p*-value was recorded and reported together with the mean and SD for the original data. The data were transformed with the natural logarithm if the assumption for normality was violated and rechecked. If still not normally distributed the Mann–Whitney *U* test was used to assess the difference between the two groups. Differences in categorical data were analyzed using a Chi-square or Fisher's exact test (when at least one cell in the contingency *table* had a cell count <5).

Multiple linear regression analyses were implemented for further analyses of the clinical and biochemistry measurements including bone data. First, simple multiple linear regression models were built with each clinical, biochemistry and bone score measurement as dependent variables, and diagnosis (T1D vs. control or T2D vs. controls) sex, age, and BMI as independent variables. Then, advanced multivariable models were built with each bone score measured by DXA or HR-pQCT as dependent variables, and sex, age, BMI, diabetes duration, HbA1c, alcohol, smoking, previous fractures, post-menopause status, HGS, TUG, VPT, metformin and insulin use and diagnosis (T1D vs. control or T2D vs. controls) as independent variables. The multiple linear regression models yielded beta-coefficients, 95%CI and *p*-values after assessing Pearson's correlation coefficient between potential independent variables. Each parameter was checked to see if it followed a normal distribution, and the residual plot for each linear regression model was inspected.

The models were robust as we performed several sensitivity analyses by discriminating for sex, age, presence of polyneuropathy measured by VPT and self-reported menopause status. This did not change the results of the outcomes between the groups (data not shown).

Statistical analyses were conducted in STATA version 17.0 (StataCorp, College Station, TX, USA) and a two sides p-value <0.05 was accepted as significant.

3. Results

3.1. General characteristics of the study population

Participants with T1D were younger than controls but no differences in age were observed between T2D and controls (T1D vs. controls, $p < 0.001$, T2D vs. controls, $p = 0.072$). Sex distribution was unevenly balanced as fewer women were included with T1D and T2D compared with controls (T1D vs. controls, $p = 0.002$, T2D vs. controls, $p = 0.005$). BMI was comparable between participants with T1D and controls but was higher in T2D vs. controls (T1D vs. controls, $p = 0.191$, T2D vs. controls, $p < 0.001$). Smoking was more frequent in participants with T1D compared to controls, but similar between T2D vs. controls (T1D vs. controls, $p = 0.003$, T2D vs. controls, $p = 0.232$). Alcohol consumption was lower in T1D and T2D compared with controls (T1D vs. controls, $p = 0.005$, T2D vs. controls, $p < 0.001$). Participants with T2D had less self-reported osteoporosis than controls ($p = 0.021$), but no differences were seen in post-menopause status between the groups. Few previous fractures were reported, and no differences were seen among the groups. Antidiabetic drugs were used as expected between insulin and non-insulin (Table 1).

3.2. Diabetes-related parameters

Participants with T1D exhibited inferior glycemic control with an

Table 1
General person characteristics.

Variables	Participants with T1D (n = 111)	Participants with T2D (n = 106)	Controls (n = 328)
Age, years (SD)	52.9 (15.3)[a]	62.1(10.1)	57.7 (15.8)
Sex	–	–	–
Women, % (n)	57.7 (63)[a]	47.2 (50)[a]	62.8 (206)
Men (%) (n)	43.3 (48)	52.8 (56)	37.2 (122)
BMI, kg/m^2 (SD)	26.1 (5)	29.2 (4)[a]	27.4 (15)
Diabetes duration, years (SD)	26.44 (14.2)[a]	11.4 (9.3)	–
Diabetic complications			
Retinopathy, % (n)	8.1 (9)	5.6 (6)	–
Nephropathy, % (n)	0.0 (0)	3.7 (4)	–
Heart disease, % (n)	6.3 (7)[a]	13.2 (14)[a]	–
Neuropathy, % (n)	9.1 (10)[a]	13.2 (14)[a]	–
Foot ulcers, % (n)	0.0 (0)	0.9 (1)	–
More than one complication, % (n)	14.4 (16)	23.5 (25)	–
Total, % (n)	23.3 (26)[a]	36.8 (39)[a]	–
Smoking, alcohol and physical activity			
Smoking, % (n)	24.1 (26)[a]	8.1 (8)	7.4 (24)
Alcohol Units/month (SD)	18.4 (22)	16.6 (21)	23.9 (24)[a]
Physical activity[b] % (n)	50.4 (56)[a]	48.4 (51)[a]	67.4 (221)
Osteoporosis and fractures			
Osteoporosis, % (n)	12.6(14)	4.7 (5)[a]	11.5 (38)
Family history of osteoporosis, % (n)	25.2 (28)	17.9 (19)	24.4 (80)
Post-menopause, % (n)	26.1 (29)	19.8 (21)	25.9 (85)
Previous fractures, % (n)	8.1 (9)	7.1 (8)	6.1 (20)
Medication			
Antidiabetic drugs (not insulin), % (n)	0.0 (0)	67.9 (72)	–
Antidiabetic drugs, metformin, % (n)	0.0 (0)	49.1 (52)	–
Antidiabetic drugs, others[c], % (n)	0.0 (0)	23.5 (23)	–
Insulin use, % (n)	100 (111)	32.2 (34)	–
Corticosteroids, % (n)	0.0 (0)	2.8 (3)	0.1 (1)
Prolia, % (n)	0.0 (0)	0.0 (0)	0.1 (1)
Alendronate, % (n)	4.5 (5)	2.8 (3)	4.5 (15)

Data is presented as either percentages with a count (n) or as mean values with standard deviation (SD).
Abbreviations: T1D: Type 1 diabetes, T2D: Type 2 diabetes, SD: Standard deviation.
[a] Indicates a significant difference between groups (T1D vs. controls, T2D vs. controls or T1D vs T2D when no data on control persons is present).
[b] Physical activity in spare time more than twice and 30 min/week.
[c] Not insulin or metformin.

HbA1c level of 63.8 mmol/mol, which was significantly higher than the corresponding value of 54.7 mmol/mol observed in participants with T2D ($p < 0.001$) (refer to Table 2). Moreover, individuals with T1D had twice as long diabetes duration as those with T2D ($p < 0.001$). Despite the lower incidence of diabetic complications in T1D participants compared to those with T2D ($p < 0.001$) (refer to Table 1), neuropathy and heart disease were the two most prevalent complications. Additionally, roughly one-third of T2D participants regularly used insulin.

3.3. Clinical tests and biochemical assessment

A significantly higher HGS was seen in participants with T1D vs. controls in the crude analysis but the effect leveled when adjusted for sex, age and BMI. Opposite results were seen for T2 diabetic participants as the adjusted analyses showed a significantly lower HGS compared to controls ($p = 0.016$). The TUG test revealed a significantly slower walking speed among both T1D and T2D compared with controls when adjusted for sex, age and BMI (T1D vs. controls, $p < 0.001$, T2D vs. controls, $p = 0.032$). T1D and T2D diabetes participants had significantly higher VPT measures in the adjusted analysis (T1D vs. controls, $p = 0.008$, T2 vs. controls $p = 0.001$). There were no significant differences in eGFR, ALAT or calcium levels between the groups and they were within the normal range (Table 2).

3.4. aBMD at central and peripheral sites

Between participants with T1D and controls we found no differences in aBMD in the crude analyses except at the pelvis which was significantly lower ($p = 0.035$, Table 3). After correction for sex, age and BMI the aBMD at the femoral neck was significantly lower ($p = 0.038$) and stayed lower in multiple regression analysis ($p = 0.028$, Table 5). Although, there was a trend toward lower aBMD at the spine and legs in participants with T1D, findings were not significant. On the contrary, participants with T2D had significantly higher aBMD for all skeletal sites than controls in the unadjusted including the adjusted analyses for sex, age and BMI (Table 3). However, the effect disappeared in multiple adjustments for central sites at the femoral neck and spine including their t-scores, whereas peripheral sites stayed significantly higher. BMC was comparable with aBMD measures at all sites in the unadjusted analyses (Table 3).

3.5. HR-pQCT data at the distal tibia and radius

We performed HR-pQCT in 109 participants with T1D, 96 with T2D and 160 controls. All findings were compared unadjusted, minimal adjusted (age, sex, and BMI) and multiple adjusted (sex, age, BMI, diabetes duration, HbA1c, alcohol consumption, smoking, previous fractures, menopause, HGS, TUG, VPT, metformin and insulin use). However, the outcomes of the analyses stayed the same even after different adjustments, and therefore, referred to as significant or not.

3.6. Distal radius

At the distal radius, we found a significantly higher total vBMD ($p < 0.001$), cortical vBMD ($p < 0.001$), cortical area ($p = 0.002$) and thickness ($p < 0.001$) and a lower cortical porosity ($p = 0.008$) including a higher stiffness ($p = 0.002$) and failure load ($p = 0.003$) in T1D vs. controls (Tables 4 and 5).

For T2D participants we found a significantly higher total vBMD ($p < 0.001$), cortical vBMD ($p < 0.001$), trabecular vBMD ($p < 0.001$), cortical area ($p < 0.001$) and thickness ($p < 0.001$), a higher trabecular number ($p = 0.024$), and a lower separation ($p = 0.010$) including a higher stiffness ($p < 0.001$) and failure load ($p < 0.001$) compared with controls (Tables 4 and 5).

3.7. Distal tibia

We found a significantly higher total vBMD ($p = 0.003$) and cortical vBMD ($p < 0.001$), although none of the other microarchitectural parameters were significantly different comparing T1D with controls. Bone stiffness ($p = 0.023$) and failure load ($p = 0.044$) were also significantly higher (Tables 4 and 5).

Findings for T2D vs. controls followed a similar pattern seen at the radius with a significantly higher total vBMD ($p < 0.001$), cortical vBMD ($p < 0.011$), trabecular vBMD ($p = 0.001$), cortical area ($p = 0.002$) and thickness ($p = 0.021$), a lower trabecular separation ($p = 0.039$) including a higher stiffness ($p < 0.001$) and failure load ($p = 0.034$) except for a higher trabecular number, which was not significantly increased.

4. Discussion

This is the first larger-scale study to assess central and peripheral aBMD measures head-to-head with bone microarchitecture and strength

Table 2
Clinical measures and biochemistry.

Variables	Participants with T1D (n = 111)	Participants with T2D (n = 106)	Controls (n = 328)	T1D vs. controls P-value	T1D vs. controls #P-value	T2D vs. controls P-value	T2D vs. controls #P-value
Clinical tests							
Handgrip strength kg (SD)	37.5 (11.6)	36.2 (11.7)	36.8 (11.6)	0.021	0.089	0.836	0.016
TUG sec (SD)	8.41 (3.1)	9.0 (2.5)	8.0 (1.9)	0.148	<0.001	0.017	0.032
VPT (SD)	15 (9.1)	20.4 (14.3)	14 (9.2)	0.270	0.008	0.026	0.001
Biochemistry							
HbA1c, mmml/mol (SD)	63.8 (12.2)*	54.7 (14.1)	35.2 (3.3)	–	–	–	–
eGFR ml/min (SD)	84.5 (10.1)	81.6 (9.5)	85.3 (12.2)	0.654	0.822	0.231	0.811
ALAT U/l (SD)	23.1 (31.1)	27.8 (20.5)	23.9 (12.2)	0.555	0.111	0.066	0.051
Calcium mmol/l (SD)	2.35 (0.09)	2.39 (0.09)	2.37 (0.08)	0.654	0.425	0.545	0.333

Data is presented as mean values with a standard deviation (SD).
P: Unadjusted t-test for two samples, Chi square or Mann-Whitney *U* test as appropriate.
#P: Adjustment for age, sex, and BMI by multiple linear regression. P-values in bold indicates a significant value.
Abbreviation: T1D: Type 1 diabetes, T2D: Type 2 diabetes, SD: Standard deviation, TUG: Timed Up and GO test, VPT: Vibration perception thresholds.

parameters at the distal radius and tibia in participants with long-standing T1D and T2D compared with controls stratified by several potential risk factors for increased skeletal fragility.

Compared to non-diabetic controls we observed a reduced aBMD at the femoral neck in T1D participants but high aBMD at all measured sites for T2D except the femoral neck and spine after multiple adjustments. In addition, favorable cortical and trabecular indices and higher bone strength and stiffness as modeled by FEA analyses at the distal radius and tibia were seen for both T1D and T2D participants.

In our cohort of T1D and T2D participants we found a significant aBMD reduction at the femoral neck including a trend of reduced aBMD at other central sites for T1D, whereas aBMD at both central and peripheral sites were increased in T2D. Except in the multiple regression analyses the effect disappeared at central sites. These results are in line with others, as e.g. meta-analysis showed that the femoral neck aBMD was modestly lower in T1D vs. controls but not significantly different at the lumbar spine [8,42] In addition, another recent study included people with T1D of all ages found no differences when compared with controls adjusted for sex, age and BMI at the lumbar spine or the femoral neck. However, postmenopausal women with T1D had lower aBMD at the femoral neck and lumbar spine, compared with postmenopausal women without diabetes [43]. These results are like ours, as the lower aBMD was seen in multiple adjustments.

T2D and aBMD at central sites were higher, as expected than controls, and similar results were seen adjusted for age, sex, and BMI. Although higher BMI increases aBMD in other studies, perhaps the increase was due to a lower lean mass measured by reduced strength parameters (TUG and HGS) as one study showed a stronger association between the ratio of muscle mass and fat mass with high aBMD [44]. Furthermore, in our analyses of advanced multiple adjustments the effect disappeared. Compared to controls anti-resorptive medication use was generally similar but low, they were less physically active, performed worse in physical test measured by HGS and TUG, had more presence of neuropathy and used more medication, especially metformin. Hence, we speculated that a higher aBMD at central sites were partly associated with metformin use or other antidiabetic drugs facilitating hypermineralization, although divergent studies exists [45,46]. Usually, postmenopausal status decreases aBMD [47]. Even though more women were present in our control group the ratio of post-menopausal to non-post-menopausal women were equally balanced and separate sensitivity analyses did not change the overall results in this study (data not shown). Hence, when correlating aBMD with the proposed estimated fracture risk at the hip (RR of 1.33 CI95%1.19–1.49) perhaps other causes like higher fall tendencies should be considered like these studies that found an increased risk of falls compared with controls without diabetes [8,48].

In general, we found no differences in *Z*-scores between T1D and controls. Although, significantly higher scores were seen for T2D vs. controls which were in line with several previous observations. Interestingly, the Z-score at the spine and femoral neck were close to zero and no significant difference was found testing the null hypothesis (data not shown). Hence, the controls and diabetic groups did not have significantly higher aBMD than the general population. Furthermore, in our study 11.5 % controls had self-reported osteoporosis (n = 38/328) whereas the average age-adjusted prevalence of self-reported osteoporosis aged 50 years was 12.6 % in 2018 [49]. Fewer cases of self-reported osteoporosis were registered in the T2D group, which was expected. Hence, our cohort of T1D, T2D and controls had healthier bone status.

Arm and leg aBMDs have seldomly been investigated in diabetes. We found higher peripheral measures in T2D but similar in T1D compared with controls, respectively, and the. Results remained the same even after adjustment. The peripheral aBMD measures were comparable with the vBMD parameters from the HR-pQCT scans for T2D but not for T1D as peripheral tibial and radial vBMDs were higher compared with controls. This could indicate that a normal bone mass in T1D was attained before reaching peak bone mass and therefore might mineralize bone differently, as indicated by the HR-pQCT data at peripheral sites. We speculated that these findings were associated with a longer diabetes duration and an earlier average debut as seen in T1D.

To our knowledge, this is one of the largest studies of T1D and HR-pQCT imaging. We found that participants with T1D had higher cortical vBMD, cortical area, thickness, and a lower cortical porosity at the radius whereas only cortical vBMD was increased at the tibia compared with controls. These results were initially surprising as previous studies have found opposing results. One small study found larger trabecular area, lower cortical and trabecular vBMD measures in T1D with the microvascular disease compared to controls but non-significant results without [50]. Another found that poor glycemic control in girls with T1D increased cortical porosity and decreased trabecular number and density [51]. A third, by Lilian Sewing et al., with long-standing T1D found a decrease in cortical measures and strength at the distal tibia but not the radius in the presence of diabetic neuropathy [52]. However, in our study, only a few diabetic complications were reported, including microvascular and neuropathy, and glycemic control was acceptable despite 26 years of diabetes duration. In short, the cohort was considered relatively healthy. In addition, we adjusted for several known risk factors for skeletal fragility and performed several sensitivity analyses which did not change the overall outcome.

Participants with T2D had higher cortical and trabecular vBMD compared with controls. In addition, cortical area, cortical thickness and trabecular number were higher and trabecular separation was lower at the radius and tibia.

Table 3
DXA scans of participants with T1D, T2D and controls without diabetes.

	Participants with T1D (n = 111)	Participants with T2D (n = 106)	Controls (n = 328)	T1D vs controls (*p*-value)	T2D vs controls (p-value)
Bone mineral density (g/cm2) mean (SD)					
Central sites					
Femoral neck aBMD	0.79 (0.14)	0.85 (0.13)	0.78 (0.15)	0.565	0.001
Spine (L1-L4) aBMD	1.01 (0.15)	1.13 (0.20)	1.02 (0.18)	0.694	0.002
Pelvis aBMD	1.20 (0.17)	1.32 (0.19)	1.26 (0.20)	0.035	0.001
Thoracic spine aBMD	0.87 (0.11)	0.93 (0.16)	0.85 (0.13)	0.058	<0.001
Lumbar spine aBMD	1.08 (0.15)	1.15 (0.25)	1.08 (0.19)	0.742	0.011
Peripheral Sites					
Arms aBMD	0.82 (0.10)	0.84 (0.11)	0.81 (0.12)	0.091	0.018
Legs aBMD	1.22 (0.17)	1.33 (0.18)	1.26 (0.20)	0.916	<0.001
Bone Mineral Content (g) mean (SD)					
Central sites					
Femoral neck BMC	4.17 (0.92)	4.58 (0.87)	4.19 (0.95)	0.836	0.002
Spine (L1-L4) BMC	65.8 (14.7)	75.6 (22.3)	66.6 (17.3)	0.909	0.001
Pelvis BMC	265.7 (78.7)	274.9 (70.7)	265.2 (84.0)	0.993	0.031
Thoracic spine BMC	126.6 (27.7)	143.5 (37.1)	125.0 (29.3)	0.783	<0.001
Lumbar spine BMC	59.8 (15.3)	64.9 (64.9)	59.5 (16.0)	0.555	0.088
Peripheral Sites					
Arms BMC	191.5 (50.3)	202 (52.2)	185.0 (53.4)	0.211	0.003
Legs BMC	469.1 (108.7)	511.0 (115.2)	470.8 (121.2)	0.339	0.001
Estimated T- and *Z*-scores mean (SD)					
Femoral neck T-score	−0.71 (1.16)	−0.29 (1.06)	−0.77 (1.19)	0.543	0.001
Femoral neck Z-score	0.19 (1.02)	0.91 (1.01)	0.29 (1.00)	0.434	0.001
Spine (L1-L4) T-score	−0.37 (1.33)	0.68 (1.79)	−0.34 (1.66)	0.835	0.001
Spine (L1-L4) Z-score	0.45 (1.38)	1.79 (1.86)	0.73 (1.52)	0.126	0.001

Data is presented as mean values with standard deviation (SD) or percentage (%) including test of differences between groups.
P: Unadjusted T-test for two samples, Chi square or Mann-Whitney U test as appropriate.
Abbreviation: T1D: Type 1 diabetes, T2D: Type 2 diabetes, SD: Standard deviation, A: Area, BMD: Bone mineral density. W) Data derived from a whole body DXA scan.

These findings suggest an increased density in the trabecular and cortical compartments and a more compact bone in participants with T2D. However, divergent studies exist regarding T2D and changes in trabecular and cortical bone parameters. One previous study adjusted for sex and obesity showed that older people with T2D had lower cortical vBMD and higher cortical porosity at the tibia not at the radius, but trabecular indices were more favorable in T2D than people without T2D [53]. Another on well-treated people with T2D with a short diabetes duration showed that inadequate glycemic control was negatively correlated with cortical bone measures of the radius but increased trabecular number at both sites [54]. A small study found that people with T2D compared to controls had 10 % higher vBMD adjacent to the cortex at both sites and higher trabecular thickness in the tibia [55]. Another, recent study on older women with T2D found a higher aBMD, cortical vBMD and cortical area compared with controls whiteout diabetes [18]. Hence, in our study, we added extensive adjustments of well-known risk factors to the analyses, and still, bone microarchitecture remained more favorable in T2D. These results of better-estimated stiffness and failure load at the distal radius and tibia in T1D and T2D point toward a more protective and appropriate effect of mass distribution and bone microarchitecture. Although divergent studies exist, some highlighted reduced strength parameters at the distal tibia while others increased at the radius, implying a weight bearing and non-weight bearing difference, as we also proposed [18,21,56]. Yet, there is compelling evidence indicating a differing fracture risk at the radius and tibia in T1D and in T2D. In a recent meta-analysis, Wang and colleagues reported a significant increase in ankle fractures in people with T1D which was more pronounced than in T2D [25]. Vilaca et al. showed that diabetes is associated with increased risk of ankle fractures and decreased wrist fractures, but most data were obtained from T2D [24]. Bone strength is determined by bone mass and quality and is an important determinant of fracture risk. We observed a low bone mass at the femoral neck in T1D and comparable bone mass for central sites after comprehensive adjusted analyses for T2D, which indicated a potential pattern of reduced lower extremity strength. In addition, the upper extremity aBMDs were also more compelling than the lower aBMDs.

It has been reported that long-term hyperglycemia favors accumulations of Advanced glycation end-products (AGEs) and causes non-enzymatic cross-links of collagen type 1 which seems to impair bone tissue toughness [57–59]. The hypermineralization and the build of AGEs cause excessive brittleness and accumulation of bone micro-cracks increasing the risk of fractures as observed in other studies of T1D and T2D [57–65]. DXA and HR-pQCT scans measure the solid part of the bone structures (trabecular and cortical density), while modifications in the bone matrix are immeasurable by these methods. A recent study reported a <5 % decrease in the bone material strength measured by OsteoProbe in a cohort of T1D men [66]. If the observed decrease in tissue material properties that constitute a necessary input for FEA analysis was confirmed, it would imply an overestimation of bone strength for the T1D group by a similar amount and probably even out the higher vBMD.

This present study's findings should be interpreted within the context of its strengths and limitations. First, participants with diabetes were mainly recruited from the outpatient clinics and through social medias and flyers. This probably limited the recruitment to a more well-regulated and responsive group and subsequently underestimated the study findings. Second, in questionnaire-based studies recall bias must be considered. However, the use of medication and diabetic complications were probably equally underreported between the groups. Although, the degree of diabetic complications could have been underestimated as participants with diabetes reported these only. Hence, microvascular complications could have been underestimated. Third, participants with T1D were younger and contained a higher

Table 4
HR-pQCT scans of participants with T1D, T2D and controls without diabetes.

Variable exposure, mean (SD or Percentage)	Participants with T1D (n = 109)		Participants with T2D (n = 96)		Controls (n = 160)		T1D vs. controls (p-value)		T2D vs. controls (p-value)	
	Radius	Tibia	Radius	Tibia	Radius	Tibia	Radius	Tibia	Radius	Tibia
Volumetric bone mineral density (vBMD) measures										
Total (Tt.BMD), mg HA/cm3	301.1 (69.3)	281.6 (61.3)	322.5 (57.4)	300.6 (46.0)	275.4 (61.6)	263.1 (53.6)	0.002	0.014	<0.001	<0.001
Cortical (Ct.BMD), mg HA/cm3	904.0 (62.5)	849.2 (77.1)	894.1 (57.3)	834.7 (71.1)	867.4 (67.6)	809.9 (80.3)	<0.001	<0.001	0.001	0.008
Trabecular (Tb.BMD), mg HA/cm3	146.3 (46.9)	162.9 (40.3)	168.4 (35.8)	181.1 (32.1)	139.8 (43.2)	156.1 (38.3)	0.240	0.184	<0.001	<0.001
Cortical (Ct.) measures										
Cortical area[a] (Ct.Ar), mm^2	58.8 (16.3)	122.3 (36.0)	64.5 (16.5)	136.6 (33.3)	52.5 (16.7)	114.4 (33.8)	0.001	0.052	<0.001	<0.001
Cortical thickness[b] (Ct.Th), mm	0.88 (0.17)	1.20 (0.27)	0.92 (0.16)	1.30 (0.22)	0.81 (0.16)	1.16 (0.24)	<0.001	0.159	<0.001	<0.001
Cortical porosity[c] (Ct.Po), $*10^2$ %	0.02 (0.01)	0.08 (0.03)	0.03 (0.01)	0.09 (0.03)	0.04 (0.02)	0.09 (0.04)	<0.001	0.061	0.865	0.162
Trabecular (Tb.) measures										
Thickness (Tb.Th), mm	2.58 (0.82)	6.46 (1.55)	2.70 (0.78)	6.72(1.48)	2.66 (0.77)	6.62 (1.38)	0.300	0.300	0.429	0.589
Number[d] (Tb.N), mm^{-1}	1.99 (0.43)	2.07 (0.34)	2.22 (0.30)	2.25 (0.24)	1.99 (0.39)	2.07 (0.37)	0.457	0.782	<0.001	<0.001
Separation[e] (Tb.Sp), mm	0.46 (0.13)	0.43 (0.09)	0.39 (0.09)	0.38 (0.05)	0.46 (0.13)	0.43 (0.10)	0.377	0.989	<0.001	<0.001
Finite-element analysis (FEA) measures										
Stiffness [f] $*10^3$, N/mm	8.7 (2.7)	22.6 (56.0)	9.8 (2.2)	25.2 (52.5)	8.1 (2.6)	21.2 (52.9)	0.010	0.035	<0.001	<0.001
Failure load[g] (FL) $*10^{-7}$, N	4.25 (1.30)	5.80 (3.58)	4.75 (1.12)	6.91 (3.13)	3.91 (1.24)	5.26 (3.61)	0.022	0.049	<0.001	<0.001
Scan Quality, yes (%)										
Grade 1	13 (11.9)	29 (26.6)	12 (12.5)	18 (18.7)	24 (15.0)	41 (25.6)	–	–	–	–
Grade 2	58 (53.2)	62 (56.8)	50 (52.0)	61 (63.5)	66 (41.3)	94 (58.7)	–	–	–	–
Grade 3	26 (23.8)	11 (10.1)	21 (21.9)	12 (12.5)	37 (23.1)	16 (10.0)	–	–	–	–
Grade 4	9 (8.2)	7 (6.4)	9 (9.3)	5 (5.3)	26 (16.5)	7 (4.3)	–	–	–	–
Grade 5	3 (2.7)	0 (0.00)	4 (4.1)	0 (0.0)	7 (4.3)	2 (1.2)	–	–	–	–

Data is presented as mean values with standard deviation (SD) or percentage (%) including test of differences between groups.
P: Unadjusted T-test for two samples or Chi square U test as appropriate.
Abbreviations: T1D: Type 1 diabetes, T2D: Type 2 diabetes, SD: Standard deviation HA: Hydroxyapatite, HR-pQCT: high resolution peripheral quantitative computed tomography.
[a] Mean area occupied by cortical bone.
[b] Calculated directly.
[c] Calculated using void-voxel.
[d] Mean number of trabeculae per unit length.
[e] Mean distance between trabeculae.
[f] Whole bone stiffness.
[g] Estimated maximum load.

percentage of men than the control group. It could also be speculated that this group perhaps was healthier than the general patient with T1D. However, judged by the z-score, the entire cohort had a better bone health than general people. Fourth, approximately, half of the control group had the HR-pQCT scan done. Although, the distribution between sex did not change, but the age of the control group rose from approximately 57 to 63 years. Hence, the control group was older, and age is a well-known predictor of skeletal fragility. However, the adjusted analyses for age and sex showed more significant results, and higher beta-coefficients were seen. In addition, several sensitivity analyses were performed including women and men separately, but they did not change the study results. Fifth, the HR-pQCT parameters were limited to the distal radius and tibia, and as bone mechanics is a complex interplay between components of skeletal fragility these findings cannot transfer to other sites. In line with this, the low number of fractures reported is a limitation of this study. We could not perform analyses on subsets of fracture types such as peripheral or forearm fractures and make direct comparisons between the scan location and fracture site. Finally, the quality of the HR-pQCT images used for reconstructing bone geometry and microstructures is an important factor in the reliability of HR-pQCT models [67]. In our study only the best quality graded images were used. The strength calculated from the HT-pQCT analysis is estimated from a linear analysis (Pistoia criterion) and represents only a pragmatic surrogate of a non-linear FEA analysis required to assess bone strength reliably. The maximum force is more sensitive to image artifacts than stiffness. In previous experimental and computational analyses of elderly distal radius or tibia, the stiffness and strength correlated highly, and similar results were shown in this study.

5. Conclusion

In summary, we investigated the bone health of participants with T1D and T2D compared to non-diabetic controls by assessing central and peripheral aBMD measures, bone microarchitecture, and strength parameters. We found that participants with T1D had a reduced aBMD at the femoral neck and a trend of reduced aBMD at other central sites, whereas participants with T2D had high aBMD at all measured sites. However, the effect of higher aBMD at central sites for T2D disappeared in advanced multiple adjustments, whereas the higher peripheral measures remained. Both T1D and T2D participants had favorable cortical and trabecular indices and higher bone strength and stiffness as modeled by FEA analyses. We also found that the peripheral aBMD measures were comparable with the vBMD parameters from the HR-pQCT scans for T2D but not for T1D. Overall, these study findings suggest that people with T1D and T2D have different bone health profiles, and that bone health should be carefully monitored in both types of diabetes and highlights the need for further research to investigate the mechanisms underlying these findings.

Funding

No external funding was applied to this study.

Ethics approval

The methods used have been tested and performed in several studies both in Denmark and abroad, and no long-term side effects have been

Table 5
Adjusted multiple linear regression of each test presented as beta-coefficients, CI95% (in brackets) and p-values.

	T1D vs. Controls				T2D vs. Controls			
Scan modality	Sex, age and BMI adjustment		Multiple adjustment[i]		Sex, age and BMI adjustment		Multiple adjustment[i]	
	Beta coef. (CI95%)	P-value	Beta coef. (CI95%)	P-value	Beta coef. (CI95%)	P-value	Beta coef. (CI95%)	P-value
DXA scan								
Central sites								
Femoral neck aBMD	−0.02 (−0.51 to −0.01)	0.035	−0.07 (−0.14 to −0.01)	0.028	0.04 (0.01–0.07)	0.003	0.01 (−0.06–0.05)	0.798
Femoral neck T-score	−0.19 (−0.41–0.03)	0.099	−0.67 (−1.13 to −0.29)	0.005	0.27 (0.01–0.51)	0.035	−0.28 (−0.82–0.21)	0.257
Spine (L1-L4) aBMD	−0.03 (−0.06–0.01)	0.322	−0.01 (−0.10–0.08)	0.098	0.06 (0.02–0.11)	0.001	0.04 (−0.03–0.14)	0.139
Spine (L1-L4) T-score	−0.17 (−0.51–0.17)	0.331	−0.02 (−0.76–0.72)	0.066	0.64 (0.26–1.02)	0.001	0.19 (−0.62–1.01)	0.533
Pelvis aBMD	−0.03 (−0.07–0.11)	0.161	−0.05 (−0.14–0.01)	0.252	0.07 (0.02–0.11)	0.001	0.11 (0.01–0.21)	0.028
Thoracic spine aBMD[h]	−0.02 (−0.01–0.04)	0.141	−0.02 (−0.04–0.02)	0.089	0.08 (0.04–0.11)	<0.001	0.11 (0.04–0.17)	0.001
Lumbar spine aBMD[h]	−0.01 (−0.04–0.04)	0.825	−0.01 (−0.09–0.05)	0.052	0.08 (0.03–0.13)	<0.001	0.10 (0.00–0.21)	0.045
Peripheral sites								
Arms aBMD[h]	0.02 (−0.01–0.04)	0.151	0.04 (−0.01–0.09)	0.125	0.04 (0.01–0.06)	0.021	0.07 (0.01–0.12)	0.025
Legs aBMD[h]	−0.01 (−0.04–0.04)	0.832	−0.03 (−0.01–0.10)	0.428	0.08 (0.03–0.12)	0.001	0.10 (0.03–0.21)	0.012
HR-pQCT - radius								
Volumetric bone mineral density (vBMD) measures								
Total (Tt.BMD), mg HA/cm3	24.42 (7.76–41.08)	0.004	75.6 (34.95–116.28)	<0.001	50.1 (32.64–67.59)	<0.001	101.8 (66.14–137.51)	<0.001
Cortical (Ct.BMD), mg HA/cm3	32.80 (16.01–49.59)	<0.001	76.58 (35.22–117.94)	<0.001	30.04 (12.42–47.65)	<0.001	65.00 (28.71–101.29)	<0.001
Trabecular (Tb.BMD), mg HA/cm3	9.22 (−2.17–20.63)	0.112	32.61 (−4.54–60.68)	0.123	29.78 (17.82–41.74)	<0.001	53.35 (28.72–77.98)	<0.001
Cortical (Ct.) measures								
Cortical area[a] (Ct.Ar), mm2	6.97 (2.55–11.38)	0.002	17.32 (6.45–28.19)	0.002	12.21 (7.58–16.84)	<0.001	21.15 (11.61–30.69)	<0.001
Cortical thickness[b] (Ct.Th), mm	0.06 (0.02–0.11)	0.003	0.19 (0.08–0.30)	<0.001	0.12 (0.06–0.16)	<0.001	0.23 (0.14–0.33)	<0.001
Cortical porosity[c] (Ct.Po), %	−0.019 (−0.014 to −0.004)	<0.001	−0.015 (−0.027--0.004)	0.008	−0.002 (−0.006–0.003)	0.562	−0.004 (−0.014–0.005)	0.455
Trabecular (Tb.) measures								
Thickness (Tb.Th), mm	−0.79 (−20.51–22.10)	0.932	−0.90 (−53.91–52.10)	0.933	2.17 (−20.18–24.52)	0.849	−18.08 (−64.60–28.4)	0.222
Number[d] (Tb.N), mm^{-1}	0.02 (−0.08–0.12)	0.701	−0.02 (−0.27–0.21)	0.832	0.24 (0.13–0.35)	<0.001	0.25 (0.03–0.47)	0.024
Separation[e] (Tb.Sp), mm	0.01 (−0.03–0.05)	0.682	−0.04 (−0.15–0.07)	0.459	−0.08 (−0.12–0.03)	<0.001	−0.12 (−0.21–0.02)	0.010
Finite-element analysis (FEA) measures								
Stiffness[f] $*10^3$, N/mm	1.06 (0.37–1.75)	0.003	2.64 (0.98–4.40)	0.002	1.73 (1.07–2.52)	<0.001	3.11 (1.62–4.61)	<0.001
Failure load[g] (FL) $*10^{-7}$, N	0.47 (0.14–0.80)	0.005	1.24 (0.42–2.52)	0.003	0.85 (0.50–1.19)	<0.001	1.44 (0.72–2.15)	<0.001
HR-pQCT – Tibia								
Volumetric bone mineral density (vBMD) measures								
Total (Tt.BMD), mg HA/cm3	20.66 (6.17–35.15)	0.003	30.59 (2.25–66.44)	0.048	37.61 (22.40–52.83)	<0.001	58.21 (26.75–89.66)	<0.001
Cortical (Ct.BMD), mg HA/cm3	36.88 (11.08–94.14)	<0.001	57.77 (6.37–109.18)	0.028	25.67 (12.71–101.72)	0.021	58.39 (13.28–103.50)	0.011
Trabecular (Tb.BMD), mg HA/cm3	10.82 (−2.41–20.80)	0.074	17.47 (−7.00–41.95)	0.161	22.87 (12.39–33.34)	<0.001	36.64 (15.16–58.12)	0.001
Cortical (Ct.) measures								
Cortical area[a] (Ct.Ar), mm2	10.82 (−1.63–20.01)	0.061	21.49 (−1.79 - 44.79)	0.070	23.90 (14.25–33.55)	<0.001	31.76 (11.31–52.20)	0.002
Cortical thickness[b] (Ct.Th), mm	0.04 (−0.01–0.11)	0.157	0.02 (−0.11–0.15)	0.579	0.16 (0.08–0.23)	<0.001	0.17 (0.02–0.31)	0.021
Cortical porosity[c] (Ct.Po), %	−0.016 (−0.026–0.005)	0.053	−0.032 (−0.056–0.008)	0.109	−0.004 (−0.015–0.006)	0.378	−0.021 (−0.041–0.001)	0.051
Trabecular (Tb.) measures								
Thickness (Tb.Th), mm	0.03 (−38.93–38.99)	0.999	49.74 (−45.29–144.77)	0.332	−9.60 (−31.29–50.50)	0.645	−3.62 (−79.77–87.01)	0.932
Number[d] (Tb.N), mm^{-1}	−0.05 (−0.09–0.11)	0.515	−0.13 (−0.34–0.08)	0.223	0.16 (0.07 0.26)	<0.001	0.10 (−0.08–0.28)	0.289
Separation[e] (Tb.Sp), mm	0.014 (−0.038–0.010)	0.254	0.018 (0.045–0.043)	0.512	−0.054 (−0.081 to −0.028)	<0.001	−0.050(−0.098--0.002)	0.039
Finite-element analysis (FEA) measures								
Stiffness[f] $*10^3$, N/mm	2.08 (0.65–3.52)	0.005	4.13 (0.45–6.28)	0.023	4.02 (2.51–5.52)	<0.001	6.04 (2.79–8.97)	<0.001
Failure load[g] (FL) $*10^{-7}$, N	2.66 (0.36–3.99)	0.023	3.88 (0.77–4.11)	0.044	4.21 (1.19–5.23)	<0.001	6.01 (1.29–7.91)	0.034

Abbreviations: T1D: Type 1 diabetes, T2D: Type 2 diabetes, SD: Standard deviation, HA: Hydroxyapatite. HR-pQCT: high resolution peripheral quantitative computed tomography, TUG: Timed Up and GO test, VPT: Vibration perception thresholds.

[a] Mean area occupied by cortical bone.

[b] Calculated directly.
[c] Calculated using void-voxel.
[d] Mean number of trabeculae per unit length.
[e] Mean distance between trabeculae.
[f] Whole bone stiffness.
[g] Estimated maximum load.
[h] Data derived from a whole body DXA scan.
[i] The model was adjusted for sex, age, BMI, diabetes duration, HbA1c, alcohol consumption, smoking, previous fractures, menopause, HGS, TUG and VPT, metformin and insulin use.

reported. The risks associated with the project are few, and the tests implied limited risks. The potential benefits in terms of well-being were considerable and estimated to outweigh the potential risks. The study was reported to the local ethical committee in the North Jutland Region (N-2019-0004). The study was conducted in compliance with Harmonized Tripartite Guideline for *Good Clinical Practice (*ICH GCP) and applicable regulatory requirements and in accordance with the Helsinki Declaration for biomedical research involving test participants [1,2]. Finally, the project was reported to the North Jutland Research department (ID-number of 2018–174).

Consent to participate

Consent for each participant was achieved.

Consent for publication

Consent for each participant was achieved.

Availability of data and material

All sensitive data were collected and secured in REDCap under "DIAFALL" in accordance with current legislation. Data was stored anonymized after the termination of the project. Physical data achieved doing the study was stored in locked desks with locked doors. Computer equipment was borrowed by the North Jutland Region and was password protected in accordance with current guidelines.

The data and study material are not available.

Code availability

The code is not available.

CRediT authorship contribution statement

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version.

Declaration of competing interest

Peter Vestergaard is head of research in the Steno Diabetes Center North Denmark, sponsored by the Novo Nordisk Foundation. Joop van den Bergh is involved in research that is sponsored by Amgen, Eli Lilly, and UCB. Morten Hasselstrøm Jensen is a former employee of Novo Nordisk and holds shares in Novo Nordisk. Nicklas H. Rasmussen holds shares in Novo Nordisk and lecture fees from Boehringer. Jakob Dal: unrestricted research grants and lecture fee from Pfizer and IPSEN. Annika Vestergaard Kvist declares that she has no conflict of interest.

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