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Osteoporos Int. Author manuscript; available in PMC 2013 June 24.

Published in final edited form as:
Osteoporos Int. 2012 February ; 23(2): 635–641. doi:10.1007/s00198-011-1595-0.

Bone structure and turnover in type 2 diabetes mellitus

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Abstract

Summary—We compared skeletal parameters in type 2 diabetic (T2DM) and non-diabetic postmenopausal women. Bone structure by dual energy x-ray absorptiometry (DXA) and HR-pQCT was not different, although procollagen type 1 amino-terminal propeptide (P1NP) and osteocalcin levels were lower in T2DM.

Introduction—T2DM is associated with increased fracture risk, but, paradoxically, with higher cross-sectional bone density (BMD) as measured by DXA. We sought explanations to this puzzle by investigating detailed structural and biochemical skeletal parameters in T2DM.

Methods—Cross-sectional comparison of 25 postmenopausal T2DM women and 25 matched controls using DXA, high-resolution peripheral quantitative computed tomography (HR-pQCT) and biochemical bone turnover markers.

Results—BMD by DXA did not differ between T2DM and controls. HR-pQCT assessment also did not differ, with the exception of cortical area at the tibia, which tended to be lower in the diabetics (difference of 12±6 [mean ± SD] mm, p=0.06). P1NP and osteocalcin levels were lower in T2DM as compared to controls (P1NP, 34.3±16 vs. 57.3±28 ng/ml; p=0.005; osteocalcin, 4.5±2 vs. 6.2±2 nmol/L; p=0.001).

Conclusions—Postmenopausal women with T2DM had lower levels of bone formation markers as compared to controls. Aside from a possible decrease in cortical bone area at a weight-bearing site, bone structure was not altered in T2DM. Lower bone turnover may be a skeletal parameter that is present in T2DM.

Keywords

Bone quality; HR-pQCT; Osteocalcin; P1NP; Type 2 diabetes mellitus

Introduction

At a time when classical complications of type 2 diabetes mellitus (T2DM) are becoming less common due to tight glucose control, the skeleton is emerging as a target organ for disease complications. This seems counterintuitive, as T2DM is typically associated with features that should protect the skeleton, such as greater body weight and higher bone mineral density (BMD) [1–3]. These factors lead to an expectation of lower fracture risk in T2DM in comparison to age- and sex-matched controls. However, fracture risk is actually

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Conflicts of interest None.

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increased up to 1.7-fold despite the higher BMD in T2DM [4–6]. Fractures occur more frequently at the hip, spine, and peripheral skeletal sites [3, 5, 7, 8].

Why fractures are increased in patients with T2DM is not clear. An obvious explanation would be that complications of diabetes, such as neuropathy and retinopathy, result in more frequent falls that could lead to more fractures. However, such explanations have not been found to be causative [3, 9]. It is also plausible that previous studies documenting fracture risk in T2DM were confounded by medication use such as thiazolidinediones, which are known to have adverse effects on bone [10]. In this study, we considered the possibility that impairments of bone structure or metabolism may contribute to the increased fracture risk in T2DM. Although BMD by dual energy X-ray absorptiometry (DXA) is typically normal or even above normal, detailed volumetric densitometric and microarchitectural assessments by peripheral computed tomography in T2DM have yielded conflicting results [11–13]. Similarly, the characterization of bone formation in T2DM is unclear. Numerous studies have documented an association between low osteocalcin levels and T2DM [14–19]. However, whether decreases in other markers of bone formation, such as procollagen type 1 amino-terminal propeptide (P1NP), are present in T2DM has not been reported.

In this study, using structural and dynamic analyses, we examined the association between T2DM, bone structure as measured by DXA and HR-pQCT, and bone remodeling as measured by biochemical markers of bone turnover, in a group of postmenopausal women.

Methods

Subjects

The patients and controls were consecutively recruited from the Internal Medicine Clinics at Columbia University Medical Center. All were over age 40 years, and postmenopausal as defined by more than 1 year of amenorrhea and FSH above 30 mIU/ml, or FSH above 20 mIU/ml and estradiol below 30 pg/ml, or age above 55 years regardless of FSH and estrogen. Patients and controls were excluded with metabolic bone disease, multiple myeloma, cancer, serum creatinine above 1.5 mg/dl, celiac or inflammatory bowel disease, current glucocorticoid or anticonvulsant use, current hormone replacement therapy, and current or past treatment of osteoporosis. Thiazolidinediones were also an exclusion criterion in view of data implicating them in abnormal bone metabolism [10]. The patients and controls were recruited from the same population; the controls were representative of the local population. Diabetes mellitus was defined as the presence of a fasting plasma glucose> 126 mg/dl and use of an antiglycemic medication. To exclude subjects with type 1 diabetes mellitus, diabetics were excluded with a history of ketoacidosis, age of onset of diabetes prior to 25 years, body mass index (BMI)<21 kg/m^2 and use of insulin without a concomitant oral hypoglycemic agent. Postmenopausal women with T2DM and postmenopausal controls without T2DM were matched for age and race. Twenty-five pairs (n=50) underwent imaging studies and had measurements of biochemical markers of bone turnover.

The study was approved by the Institutional Review Board of Columbia University Medical Center. All subjects gave written informed consent.

Protocol

BMD by DXA—BMD of the lumbar spine, femoral neck, and distal 1/3 radius was measured by DXA. Short-term in vivo precision error (root-mean-square standard deviation) was 0.026 g/cm^2 for L1–L4 (1.1%); 0.041 g/cm^2 for the femoral neck (2.4%) and 0.033 g/cm^2 (1.8%) for the forearm.

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HR-pQCT—HR-pQCT was performed in a subset of the T2DM subjects (n=14) and matched controls (n=14) on the XtremeCT (Scanco Medical AG, Switzerland). The 14 in each group were chosen because they were consecutively enrolled after the installation of our HR-pQCT instrument; the other participants were enrolled prior to the arrival of the machine. The nondominant distal radius and tibia were immobilized in a carbon fiber shell. The first slice was 9.5 and 22.5 mm proximal to the reference line at the radius and tibia, respectively. A stack of 110 parallel CT slices was acquired at the distal end of both sites using an effective energy of 40 keV, slice thickness of 82 μm, image matrix size 1,024×1,024, nominal voxel size of 82 μm. Attenuation data were converted to equivalent hydroxyapatite densities. The analysis methods were as previously described [20–23].

Biochemical markers of turnover—Biochemistries were measured by automated techniques. Bone-specific alkaline phosphatase activity (BAP) was measured by immunoassay [24] (Metra BAP, Quidel Corp, San Diego, CA, USA). Inter-assay and intra-assay variabilities are 7.6% and 3.9%, respectively (normal range 14.2–42.7 U/L in postmenopausal women). Osteocalcin was measured by ELISA N-mid Osteocalcin [25] (IDS Ltd., Scottsdale, AZ, USA). The inter-assay and intra-assay variability is 2.7% and 1.8%, respectively (normal range 12.8–55.0 ng/mL in postmenopausal women). P1NP was measured by RIA (IDS Ltd., Fountain Hills, AZ, USA). Inter-assay and intra-assay variabilities are 8.3 and 6.5%, respectively (normal range 16–96 pg/mL for postmenopausal women). Serum C-terminal telopeptides of Type I collagen (CTX) was measured by ELISA (IDS Ltd.). The inter-assay and intra-assay variabilities are 9.7% and 1.7%, respectively (normal range: 0.142–1.351 ng/L for postmenopausal women). Serum N-telopeptide (NTX) was measured by ELISA (Inverness Medical, Princeton, NJ, USA). The inter-assay and intra-assay variabilities are 6.9% and 4.6%, respectively (normal range: 6.2–19.0 nM BCE for premenopausal women).

Statistical analysis—Data are expressed as mean ± SD. Differences between diabetics and controls were assessed with independent T tests. Bone turnover markers were additionally analyzed with nonparametric statistical tests (Wilcoxon signed-ranks test). Linear regression was used to assess the relationship between diabetes status and biochemical and structural parameters, after controlling for age, race, and BMI. Adjustments were made for these variables because of the possibility that bone parameters may be differentially affected by them in diabetics as compared to controls. A value of $p<0.05$ was considered significant. All statistical analyses were performed using SPSS for Windows (version 11.0; SPSS, Chicago, IL, USA).

Results

Study population

The participation rate of both the patients and controls was 80%. None of the diabetic subjects had a history of ketoacidosis. Eight of the 25 diabetics (32%) were on insulin; each of the insulin users was also using an oral hypoglycemic agent. The mean age of onset of diabetes was 54.6±10 years; the mean BMI was in the obesity range (Table 1). The T2DM subjects and controls were matched by age (within 5 years) and race (African American or Hispanic and non-Hispanic white) and did not differ by years since menopause, BMI, or biochemistries (Table 1). Duration of diabetes ranged from 1 to 30 years (median, 7 years).

BMD by DXA

Areal BMD by DXA did not differ between T2DM and controls (Table 2), with measurements being close to normal in both populations. There were no significant differences in BMD, T-score, or Z-score between diabetics and controls when only African

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American women were included, or when only Hispanic white and non-Hispanic white women were included.

HR-pQCT

The HR-pQCT sub-groups of T2DM and controls did not differ from the overall groups of T2DM and controls in terms of age, race, BMI, fasting plasma glucose, and DXA values. HR-pQCT at the radius and tibia revealed no differences in total, trabecular, or cortical volumetric BMD (Table 3). Similarly, there were no differences in bone size, cortical thickness, trabecular bone volume, or trabecular microarchitecture, including trabecular number, thickness, and separation. After controlling for age, race, and BMI, cortical area tended to be lower in the diabetics at the tibia, with a decrease in the diabetics of 12±6 mm (p=0.06).

Biochemical markers of bone turnover

P1NP levels were significantly lower in T2DM as compared to controls (T2DM, 34.3±16 ng/ml vs. controls, 57.3± 28 ng/ml; p=0.005), as were osteocalcin levels (T2DM, 4.5± 2 nmol/L vs. controls, 6.2±2 nmol/L; p=0.001). BAP levels were not different (T2DM, 31.4±12 U/L vs. controls, 27.5±11 U/L; p=0.3), nor were serum CTX (T2DM, 0.37± 0.2 ng/ml vs. controls, 0.45±0.2 ng/ml; p=0.3) or serum NTX (T2DM, 14.1±3 nmol/BCE/L vs. controls 16.6± 7 nmol/BCE/L; p=0.1) levels. The bone turnover markers were also assessed with the nonparametric Wilcoxon signed ranks test; osteocalcin was significantly lower in diabetics (p=0.009), as was P1NP (p=0.005). BAP was not different (p=0.17), nor was NTX (p=0.29) or CTX (p=0.3). The analyses were also performed within groups of race. African American diabetic women had lower P1NP and osteocalcin levels than African American controls (34.7± 11 vs. 62.5±29 ng/ml, p=0.02 and 4.5±1.3 vs. 6.7± 2.5 nmol/L, p=0.02, respectively). The Hispanic white and non-Hispanic white diabetic women also had lower P1NP and osteocalcin levels than the Hispanic white and non-Hispanic white controls, but these did not reach statistical significance (P1NP, 34.0±20 vs. 52.6±28 ng/ml, p=0.11; osteocalcin, 4.5±1.9 vs. 5.7±1.6 nmol/L, p=0.15).

The effect of diabetes on bone turnover markers, after controlling for BMI, age, and race, was also ascertained. With these adjustments, diabetes was still associated with a lower PINP by 23±8 ng/ml (p=0.008) and a lower osteocalcin by 1.6±0.6 nmol/L (p=0.009). Within the diabetic subjects, there was a trend towards an inverse relationship between P1NP and HgbA1c (r=−0.43, p=0.09).

Discussion

Recent observational studies have documented an increased fracture risk in T2DM, despite normal or increased BMD measurements by DXA, in comparison to controls [3–8]. This increased risk may be attributable at least in part to an increased risk of falling, as is intuitively expected, based on increased rates of peripheral neuropathy, postural hypotension, hypoglycemia, and vascular disease in diabetic populations. However, we sought to examine whether there are alterations in diabetic bone structure or metabolism that could potentially contribute to an increase in fracture risk.

Bone formation is known to be decreased in the setting of high glucose levels. In healthy individuals, ingestion of 75 g of glucose leads to a decrease in markers of both bone formation and resorption [26] and in vitro data show that exposure to high glucose levels impairs osteoblast function [27–29]. With regard to T2DM, it has been previously reported that bone formation is suppressed. In our study, we found that bone turnover in diabetics was in the lower part of the normal premenopausal range and significantly lower than in

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controls. Most of the studies investigating bone formation have described low osteocalcin levels in T2DM [14–19] and consistent with previous literature, we found lower osteocalcin levels in our diabetic subjects. In order to better characterize bone formation in T2DM, we additionally measured P1NP, a robust marker of bone formation. P1NP levels have been previously measured longitudinally [41] in diabetics on different treatment regimens [30], and were found in a combined population of diabetic and non-diabetic men to be inversely related to glucose levels and fat mass [31], but have not been studied before in diabetics as compared to controls. Our finding that P1NP levels were decreased supports the concept that biochemical indices of bone formation are lower in T2DM than in controls. The observation that our controls were in fact overweight and thus similar to the diabetics with regard to BMI strengthens our findings of low bone formation markers, since the difference between diabetics and controls cannot be simply attributable to a difference in BMI. Our observation of a trend towards an inverse relationship between P1NP and HgbA1c also suggests that there might be a "dose–response" effect; as glucose control worsens, the bone formation rate also falls.

We did not find that the bone formation marker BAP was similarly lower in T2DM. This discrepancy between osteocalcin and BAP has been found in other reports of T2DM [14, 19]. One possible explanation for the normal BAP may be that it is reflecting an abnormal degree of mineralization in diabetic bone [32], with higher BAP levels signaling a mineralization defect.

The lack of structural abnormalities by DXA in T2DM as compared to controls is consistent with other studies in which BMD by DXA is not decreased or is even increased in T2DM [1, 2, 11]. To investigate this issue in greater detail, we used HR-pQCT to assess skeletal structural parameters. This high-resolution technology distinguishes between cortical and trabecular bone and visualizes details of trabecular microarchitecture previously measureable only by bone biopsy [23, 33, 34]. Our finding that HR-pQCT measurements did not generally differ between T2DM and controls is consistent with a previous cross-sectional study by Melton et al. which found no difference in cortical volumetric BMD, bone cross-sectional area, and cortical thickness between T2DM and controls [11]. However, we did find that cortical area at the tibia tended to be lower in the diabetics, after controlling for age, race, and BMI. The smaller cortical area may suggest that at the weight-bearing site of the tibia, cortical bone is being distributed closer to the neutral axis, a geometrical change which can contribute to lower bone bending strength [35]. This finding is consistent with a recent report by Petit et al., in which older men with T2DM were found by conventional (non-high resolution) pQCT to have smaller skeletal cross- sectional area, as compared to controls [36]. These observations may explain how areal BMD is increased in T2DM: an equivalent amount of bone material within a smaller bone area would appear as a higher areal BMD when measured by DXA [2, 35]. Yet this smaller bone area and higher areal BMD can conceivably translate to a bone that may be more predisposed to fracture.

Our finding of possibly lower tibial cortical area in diabetics is consistent with other recent reports. In the study of Petit et al., diabetic men had bone strength that was low relative to body weight at predominantly cortical sites [36]. Similarly, Burghardt et al. recently found increased cortical porosity at the radius, as measured by intra-cortical pore volume fraction via HR-pQCT, in 19 T2DM women [12]. An elevation in trabecular bone density at the tibia was also found by Burghardt et al., suggesting a redistribution of bone mass that may be associated with an impaired resistance to bending [12]. Taken together, these recent findings suggest that subtle structural skeletal abnormalities, especially in the cortical compartment, may be present in diabetic bone. These observations need to be confirmed in other studies, because the resolution constraints of HR-pQCT limit the smallest pore area that can be

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measured to 0.0067 mm^2, corresponding to a diameter of 82 μm [37], so that partial volume effects may limit ascertainment to only large cortical pores. Ultimately, definitive histomorphometric analyses will be necessary to characterize structural skeletal abnormalities in T2DM.

This study has a number of limitations. It is possible that diabetics with long-standing type 1 diabetes may have been inadvertantly included, although all of the diabetic subjects had clinical features consistent with type 2 diabetes. Specifically, none of the diabetic subjects had a history of ketoacidosis and those who did use insulin were additionally using an oral hypoglycemic agent, suggesting a clinical profile more consistent with insulin resistance, rather than deficiency. The mean age of onset of diabetes of 55 years, as well as the high BMI levels, was also clinically consistent with type 2 diabetes. An additional limitation is that the inclusion of diabetics who were taking different medications and especially those who were and were not taking insulin could have affected our results. Moreover, our small sample size may not have been adequate to detect alterations in the other biochemical markers of bone turnover, in addition to osteocalcin and P1NP. A larger sample size may have also revealed additional differences by HR-pQCT between T2DM and controls. Finally, we did not investigate bone material properties, which may be an important explanation for bone fragility in T2DM. Data suggest that accumulation of advanced glycation endproducts in bone collagen, such as pentosidine, contributes to the increased fracture risk of T2DM [38–40].

In conclusion, decreased bone formation markers were found in T2DM. Aside from a trend toward a decrease in tibial cortical area, bone structure was not altered in T2DM. Further investigation of skeletal parameters may shed light on the paradox of greater bone fragility in T2DM despite the presence of normal BMD.

Acknowledgments

Irving Institute for Clinical and Translational Research CTSA/CTO pilot award, NIH AR055968, NIH AI065200-05

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Table 1

Characteristics of patient population

±SD

	T2DM (n=25)	**Controls (n=25)**	***p* value**
Age (years)	63.4±7	60.4±14	NS
BMI (kg/m^2)	30.6±6	29.2±5	NS
Race	African American: 10	African American: 10	
	Hispanic and non-Hispanic white: 15	Hispanic and non-Hispanic white: 15	
Duration of T2DM	8.5±7 (range: 1–30 yrs)		
History of fracture (*n*)	1 spine	3 forearm, 1 ankle	
Serum estrone (pg/ml)	24.5±12	29.2±14	NS
Time since menopause (years)	16±9	16±7	NS
Serum calcium (mg/dl)	9.3±0.4	9.4±0.3	NS
PTH (pg/ml)	39.9±22	40.7±16	NS
Serum creatinine (mg/dl)	0.84±0.2	0.80±0.2	NS
GFR estimation by MDRD (mL/min/1.73 m^2)	72.6±21	85.3±46	NS
Total alkaline phosphatase activity (U/L)	86.1±22	72.5±24	NS
25-Hydroxyvitamin D (ng/ml)	21.1±10	24.6±16	NS
1,25-Dihydroxyvitamin D (pg/ml)	40.1±13	41.9±16	NS
Fasting plasma glucose (mg/dl)	139±81	84±12	0.001
Hgb A1c (%)	7.9±2		
Diabetes medications (*n*)	Insulin: 8		
	Sulfonylurea: 11		
	Metformin: 9		

To convert estrone to picomoles per liter (pmol/L), multiply by 37; serum calcium to millimoles per liter (mmol/L), multiply by 0.25; PTH to nanograms per liter (ng/L), multiply by 1; creatinine to micromoles per liter (μmol/L), multiply by 88.4; 25-hydroxyvitamin D to nanomoles per liter (nmol/L), multiply by 2.496; 1,25-dihydroxyvitamn D to picomoles per liter (pmol/L), multiply by 2.6; plasma glucose to millimoles per liter (mmol/L), multiply by 0.0555

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Table 2

Bone mineral density by dual energy X-ray absorptiometry in T2DM and controls

±SD				
		T2 DM (*n*=25)	**Control (*n*=25)**	***p* value**
Lumbar spine	g/cm^2	0.939±0.1	0.944±0.2	NS
	Z-score	0.62±1.4	0.60±1.5	NS
	T-score	−1.02±1.3	−1.17±1.6	NS
Femoral neck	g/cm^2	0.734±0.1	0.787±0.2	NS
	Z-score	0.33±1.0	0.49±1.3	NS
	T-score	−1.20±1.1	−0.91±1.3	NS
1/3 Radius	g/cm^2	0.658±0.1	0.649±0.1	NS
	Z-score	1.03±1.3	0.92±0.9	NS
	T-score	−0.61±1.5	−0.74±1.1	NS

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Table 3

High resolution peripheral quantitative computed tomography in T2DM and controls

± SD

	T2DM (*N*=14)	**Controls (*N*=14)**	***p* value**
Age (years)	64±6	63±5	NS
BMI (kg/m^2)	31.7±8	30.0±8	NS
Race	African American: 7	African American: 7	
	Hispanic and non-Hispanic white: 7	Hispanic and non-Hispanic white: 7	
Fasting plasma glucose (mg/dl)	132±44	88±12	0.001
Hgb A1c (%)	8.2±2		
Radius			
Mean area (mm^2)	244±60	256±49	NS
Cortical area (mm^2)	51±11	49±15	NS
Trabecular area (mm^2)	189±60	201±48	NS
Total density (mgHA/cm^3)	310 ±87	284 ±75	NS
Ct density (mgHA/cm^3)	884 ±88	845±88	NS
Ct thickness (mm)	781±213	726±227	NS
Trabecular density (mgHA/cm^3)	126 ±42	121 ±35	NS
Trabecular bone volume (%)	9.7±3	10.1±3	NS
Trabecular number (1/mm)	1.7±0.4	1.6±0.4	NS
Trabecular thickness (mm)	60±11	62±8	NS
Trabecular separation (mm)	543 ±154	586±180	NS
SD of 1/trabecular number[a]	269±115	321 ±211	NS
Tibia			
Mean area (mm^2)	708±139	711±105	NS
Cortical area (mm^2)	94±22	105±23	NS
Trabecular area (mm^2)	584±138	571±106	NS
Total density (mgHA/cm^3)	243±58	251±49	NS
Ct density (mgHA/cm^3)	833±71	812 ±62	NS
Ct thickness (mm)	931 ±240	1009±202	NS
Trabecular bone volume (%)	11.2±4	11.6±3	NS
Trabecular density (mgHA/cm^3)	135±43	139±37	NS
Trabecular number (1/mm)	1.6±0.4	1.6±0.3	NS
Trabecular thickness (mm)	70±14	71±13	NS
Trabecular separation (mm)	588±154	558±96	NS
SD of 1/trabecular number[a]	280±97	290±113	NS

[a]SD of 1/trabecular number is a measure of trabecular network heterogeneity, or the irregularity of the trabecular spacing.