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Sex-specific differences in progressive glucose intolerance and hip geometry: the Baltimore Longitudinal Study of Aging

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Abstract

Summary—Fracture risk is increased in type 2 diabetes mellitus (T2DM). The effect of pre-diabetes and T2DM on bone macroarchitecture and strength has not been well investigated. In this study, we show that in women only, both pre-diabetes and T2DM are associated with decreased hip bending strength and mineralization which might lead to skeletal weakness.

Introduction—Older men and women with T2DM are at increased risk for fracture despite normal bone mineral density (BMD). The discordance between bone quantity and skeletal fragility has driven investigation into additional determinants of fracture resistance in T2DM. Additionally,

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Conflicts of interest

None.

the effect of pre-diabetes on bone strength has not been well described. The aim of this study was to determine differences in bone macroarchitecture and strength, measured by hip geometry, in persons with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and T2DM.

Methods—We performed cross-sectional analyses of older (age >55 years) men ($n=472$) and women ($n=473$) participating in the Baltimore Longitudinal Study of Aging (BLSA) classified as NGT, IGT, or T2DM based on oral glucose tolerance testing. Bone strength measures included the hip geometry parameters of section modulus (Z), cross-sectional area (CSA), and buckling ratio (BR). Sex-stratified analyses were conducted using adjusted stepwise regression models.

Results—In women, IGT and T2DM were negatively associated with hip geometry parameters including mineralization in cross section (CSA, $\beta -0.076$ and -0.073 , respectively; both $p<0.05$) and hip bending strength (Z , $\beta -0.097$ and -0.09 , respectively; both $p<0.05$); conversely, IGT and T2DM were associated with improved compressive strength (BR, $\beta -0.31$ and -0.29 , respectively; both $p<0.05$). There was no significant association between glycemic status and hip geometry in men.

Conclusions—In women only, both IGT and T2DM were inversely associated with bone macroarchitecture and measures of bone mineralization and bending strength. The same association between worsening glycemic status and bone strength was not observed in men. These data suggest a differential effect of sex on hip geometry with evolving glucose intolerance.

Keywords

Bone architecture; Bone quality; Hip geometry; Type 2 diabetes

Introduction

With the population rapidly aging, the prevalence of osteoporosis and incidence of fracture are rising, bringing significant morbidity, loss of independence, and death [1–3]. Type 2 diabetes mellitus (T2DM) is also a disease with rising incidence and prevalence in the elderly associated with complex end-organ damage leading to substantial disability and mortality [4, 5]. Over the last decade, the skeleton has been added to the list of organ systems compromised by glucose intolerance. Multiple studies have demonstrated an association between T2DM and increased risk of fracture in the peripheral skeleton, spine, and hip [6–11]. Paradoxically, while those with T2DM are at increased risk of fracture, they show normal to high bone mineral density, as measured by dual X-ray absorptiometry (DXA). The discordance between the quantity of bone measured with DXA and the rate of fracture has led to growing research into additional approaches to assess skeletal strength in T2DM which might explain the paradox. One such novel measure is hip geometry which integrates the biomechanical properties of bone and its resistance to external loading and fracture [12–18].

The precise pathophysiology by which T2DM may increase skeletal fragility has not been established. Several mechanisms have been proposed, many of which focus on the complications and end-organ damage of long-standing T2DM. Diabetic nephropathy, retinopathy, neuropathies, and microvascular disease can contribute to increased fall risk and/or impaired bone mineralization and remodeling [19]. However, fracture risk may also

be increased in early, non-insulin-requiring diabetes before the onset or detection of multiorgan disease [8]. With the progression of impaired glucose tolerance, hyperglycemia, and insulin resistance, detrimental changes in bone microarchitecture, macroarchitecture, and material and biomechanical parameters of bone strength may occur without apparent loss of bone quantity estimated by BMD from DXA. It is also possible that diminished bone strength may be present before a formal diagnosis of T2DM has been made. Limited data are available comparing skeletal parameters across categories of glycemic status, specifically, normal glucose tolerance, impaired glucose tolerance, and type 2 diabetes mellitus.

To study the association between impaired glucose homeostasis and bone strength, we investigated men and women participants of the Baltimore Longitudinal Study of Aging (BLSA). In this cohort, glycemic status has been well characterized with fasting glucose levels and hemoglobin A1c (HbA1c). In addition, oral glucose tolerance testing (OGTT), a more sensitive measure than fasting plasma glucose for identifying pre-diabetic or diabetic status in the elderly, is also available for most participants [5]. We examined the relationship between glycemic status, measured using OGTT and defined as normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and T2DM, and bone mineral density (BMD), as measured by DXA. Uniquely, we examined the association between glycemic status and hip geometry as measured by hip structural analysis (HSA), a well-accepted parameter of bone macroarchitecture and surrogate measure of bone strength [17, 18]. We hypothesized that, consistent with past studies, persons with IGT and T2DM would have normal to higher BMD than individuals with NGT; however, we additionally hypothesized that both IGT and T2DM would be associated with poor bone macroarchitecture and strength, as measured by hip geometry. The relationship between OGTT-determined glycemic status in older men and women and hip geometry has not yet been investigated in the literature.

Research design and methods

Study population

Since 1958, the Intramural Research Program of the National Institute on Aging (NIA), National Institutes of Health, has been conducting a longitudinal cohort study to delineate the physiological, functional, and anatomical features of aging. Known as the BLSA, this cohort is comprised of community-dwelling women and men aged 20 years and older, who undergo evaluations at age-specified time intervals of 1 to 4 years. In addition to laboratory testing, imaging studies that include DXA of the spine and hip are conducted on all participants. Evaluation at each time point also includes specific characterization of glycemic status through OGTT on all participants not already on insulin or oral medications for diabetes. For this investigation, data from men and women over age 55 years ($n=945$) seen between 2006 and 2010 were used when all core variables of interest (OGTT in subjects not already on diabetes medications, proximal femur BMD from DXA) were available [20]. All additional social, anthropometric, and biochemical data obtained from that same study visit were used for analyses. Medications were coded based on WHO ATC codes. Participants with self-reported type 1 diabetes at the time of BLSA entry were excluded. All participants provided written informed consent to the research protocol. All

protocols were approved by the Intramural Research Program of the National Institute on Aging and the Institutional Review Board of the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Definition of glycemic status and oral glucose tolerance testing

Participant allocation to NGT, IGT, and T2DM groups was determined using the American Diabetes Association (ADA) classification scheme based on OGTT [20, 21]. For OGTT within the BLSA protocol, participants fasted for 10 h overnight and consumed 75 g of glucose solution the next morning. Participants treated with glucocorticoids within 3 months of their study visit were excluded from OGTT. Blood samples were collected over the course of 2 h and included times zero (fasting) and 120 min [20]. Using a glucose oxidase analyzer (Beckman Instruments, Brea, CA, from 2006 to 2009; YSI Incorporated, Yellow Springs, OH, from 2009 onwards), plasma glucose was measured at all time points. The two analyzers gave nearly identical results and no conversion factors were necessary. For this study, 120-min glucose levels were used to categorize participant diabetic status. BLSA participants 55 years or older were divided into one of three ADA-defined categories based on 2-h OGTT: NGT (glucose ≤ 7.8 mmol/L), IGT (glucose 7.8–11.0 mmol/L), and T2DM (glucose ≥ 11.1 mmol/L) [21]. After BLSA participants were classified as NGT, IGT, or T2DM based on OGTT, the ADA's categories for T2DM and increased risk for diabetes based on HbA1c and fasting plasma glucose were considered [21]. The NGT cohort was reassessed for individuals with $5.7\% < \text{HbA1c} < 6.5\%$ or $5.6 \text{ mmol/L} < \text{fasting glucose} < 7.0 \text{ mmol/L}$, and no NGT participants were moved to the IGT cohort. Further, the IGT cohort was assessed for individuals with $\text{HbA1c} \geq 6.5\%$ or fasting glucose $\geq 7.0 \text{ mmol/L}$. No subjects required reclassification into the T2DM cohort. All BLSA participants on oral diabetes medications and/or insulin at the time of their study visit were classified as having T2DM.

Anthropometrics and skeletal measures

Height, weight, and waist circumference were measured in all participants. BMI was determined as kilograms per square meter. Total body DXA was performed using the Lunar Prodigy Advance (General Electric, Waukesha, WI) and analyzed with GE enCore software version 10.51.006 software (General Electric). BMD was calculated as grams per square centimeter at the lumbar spine (L1–L4), femoral neck, and hip. Established hip structure analysis (HSA) equations developed by Beck and colleagues were employed to calculate hip geometry parameters [18, 22]. Using information from DXA on BMD and area at the femoral neck region, the cross-sectional area (CSA, average mineral density with soft tissue spaces removed) was estimated. Subsequent derivation of the estimated endosteal diameter, trabecular porosity, and cross-sectional moment of inertia from CSA enabled determination of the hip section modulus (Z, a measure of resistance to bending). Higher values of both CSA and Z indicate greater hip mineralization in cross section and higher bending strength, respectively. Cortical thickness was estimated from an annulus model of the femoral neck with a fixed fraction of measured mass at the cortex. The propensity of cortical buckling under compressive loads, or the buckling ratio (BR) of the hip, was estimated from femoral neck width and mean cortical thickness. Lower BR is favorable in HSA, signifying a decreased likelihood of hip compression in response to external loading.

Statistical analysis

After ensuring normal distribution of all variables of interest, the means and standard deviations were calculated. For the initial assessment, the entire cohort was evaluated, followed by the population divided by sex when significant differences in anthropometric and skeletal measures between male and female participants were detected. Subsequent sex-stratified subgroup analyses were employed to characterize baseline characteristics across diabetic category (NGT, IGT, and T2DM) using chi-squared tests for categorical variables and ANOVA for continuous variables. Stepwise regression models were constructed to assess associations between predictor variables (T2DM and IGT) and bone quantity (DXA) and strength (hip geometry) outcomes. All models were initially adjusted for age, BMI, race, smoking status, calcium and vitamin D supplementation, multivitamin (MVI) use, creatinine clearance by MDRD, serum calcium and vitamin D, and femoral neck BMD (when a hip geometry measure was the outcome of interest). These sex-stratified stepwise regression models were then adjusted for the variables noted above in addition to diabetes medications (metformin, insulin, thiazolidinediones (TZDs), DPP-4 inhibitors, exenatide, alpha-glucosidase inhibitors, sulfonylureas). Models were further adjusted for use of osteoporosis medications (bisphosphonates, teriparatide, raloxifene/tamoxifen, calcitonin, calcium, and D supplements), and models for sensitivity analysis were run separately, excluding individuals on osteoporosis medication. Other medications including estrogen, testosterone, thiazide diuretics, proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs), anti-epileptics, and corticosteroids (inhaled, topical, and oral) were also entered into stepwise models in the full cohort as well as by sex.

Results

Anthropometrics, biochemical parameters, and the BLSA

Men and women BLSA participants differed significantly across many demographic, anthropometric, and biochemical indices. In the full sample ($n=945$, data not shown), men ($n=472$) were significantly older than women ($n=473$), with a mean age of 68.1 ± 10.8 years versus 65.2 ± 10.5 years. In the full sample, men were also heavier than women with a mean BMI of 27.6 ± 4.1 kg/m² versus 26.9 ± 5.4 kg/m². In sex-stratified analyses (Table 1), age did not differ by diabetes category amongst women or men with NGT, IGT, or T2DM. In both men and women, those with NGT had a significantly lower BMI than those with IGT or T2DM. The population was 50 % white; 42–50 % of women and men were past or present smokers at the time of analysis. Women had higher 25-hydroxy vitamin D levels than men and were also more likely to be taking vitamin D supplementation (36 % women, 20 % men). Similarly, women were also more likely to be taking calcium supplementation (45 % women, 25 % men). Use of pharmacologic treatment for osteoporosis (bisphosphonates, calcitonin, raloxifene, tamoxifen, teriparatide) at the time of assessment was more common in women (22 % women, 5 % men), but osteoporosis medication and calcium/vitamin D supplementation use did not differ by diabetes category in either sex.

Diabetes status and treatment

Overall, 15.7 % of participants had T2DM and 21.5 % had IGT. Prevalence of T2DM and IGT varied by sex, with 20 % of women having IGT and 13 % T2DM compared to 22 and

18 %, respectively, of men. In those with treated T2DM, 77 % of women and 90 % of men were on oral medications (metformin, TZDs, sulfonylureas, alpha-glucosidase inhibitors, DPP-4 inhibitors, sitagliptin). Only 15 % of participants were on TZDs alone or in combination with other medications for diabetes. An additional 4 % of women and 14 % of men were taking insulin alone or in combination with oral medication at the time of assessment. Both men and women with T2DM had significantly higher mean HbA1c than individuals with NGT or IGT (Table 1). In women with T2DM, 75 % had a HbA1c ≥ 7 %, compared with 73 % of men. Only 1 % of women and 1 % of men with T2DM had a HbA1c ≥ 10 %.

Skeletal outcomes

Amongst all study participants ($n=945$), men had significantly greater bone density and better hip geometry at all sites evaluated compared to women. This finding was independent of glycemic status (NGT, IGT, and T2DM; Table 1). Thus, after excluding participants taking osteoporosis medications (Table 2), men and women were considered separately in sex-stratified analyses. In models adjusted for the demographic, anthropometric, biochemical, and medication variables noted above, T2DM status was positively associated with total hip BMD in men but not in women. Glycemic status had no association with BMD, or bone quantity, at any other site in either sex. Both IGT and T2DM were associated with compromised bone macroarchitecture, however, but in a sex-specific manner. In women, both IGT and T2DM were inversely associated with Z and CSA, two parameters of bone strength. This association persisted after multiple adjustments. The relationship between glucose intolerance and impaired resistance to bending (Z) and diminished mineralization in cross section (CSA) was not present in men. In women only, IGT and T2DM were also inversely associated with hip BR, indicating that worsening glycemic status may be associated with favorable resistance to compression. These associations between glucose status and skeletal outcomes remained after adding diabetes and osteoporosis medications, hormone replacement, steroids, and other medications to the multivariate models (Table 2).

Discussion

Our analysis examined differences in hip geometry, a measure of bone strength, across three categories of glycemic status (NGT, IGT, and T2DM) determined by OGTT, highlighting an intriguing sex difference in how evolving glucose intolerance, as defined by IGT and T2DM, may contribute to impairments in hip geometry and macroarchitecture. In women only, parameters of bone strength (ascertained via calculation of CSA and Z) were adversely associated with both IGT and T2DM; that is, worsening glycemic status manifested by both the “pre-diabetic” state and frank T2DM predicted lower CSA and Z. The same was not observed in men. At the same time, both IGT and T2DM were associated with favorable hip compressive strength (BR) in women only. These findings add an important contribution to a growing body of knowledge aimed at explaining the pathophysiology by which T2DM may promote skeletal failure differently in men and women and indicate that adverse skeletal effects may begin in the early stages of glucose impairment.

When the vulnerability of the diabetic skeleton first came to light, the clinical complications of long-standing T2DM were implicated first. Loss of vision due to retinopathy and deteriorated sensitivity due to neuropathy may increase fall risk, while diabetic nephropathy contributes to impaired calcium and vitamin D handling, secondary hyperparathyroidism, and renal osteodystrophy [23]. However, diabetic complications do not fully explain the observed increased fracture risk in T2DM. Longitudinal studies controlling for falls, renal failure, and calcitropic hormones still demonstrate increased fracture risk in T2DM [6–9]. Furthermore, there is some evidence that bone changes that reduce mechanical resistance may accumulate *before* T2DM is overt and accompanied by clinically detectable end-organ complications [24]. For example, in the Study of Osteoporotic Fractures, older, postmenopausal women with non-insulin-requiring diabetes had an increased risk of hip fracture (relative risk (RR) 1.82) compared to healthy controls independent of BMD [8]. In smaller cohorts, other investigators have reported similarly increased fracture risk in men and women with either T2DM for less than 5 years or disease management on oral medications alone [25–28]. These studies, consistent with our findings in the BLSA cohort, indicate that even in early stages of glucose intolerance, diabetic women with normal BMD exhibit signs of skeletal compromise.

The discordance between BMD and fracture risk in persons with diabetes has raised the logical suspicion that ongoing changes in glucose metabolism may affect bone quality and strength in T2DM. These macroarchitectural, microarchitectural, material, and biomechanical properties of bone are not assessed clinically but may underlie fracture risk in glucose-intolerant states. To examine the microarchitecture and material properties of diabetic bone, investigators have employed high-resolution peripheral quantitative computed tomography and micro finite element analysis to show greater intracortical pore volume, cortical porosity, and endocortical bone surface as well as increased stiffness, failure load, and cortical load fraction at peripheral sites in postmenopausal women with T2DM [29]. Using micro-indentation of the tibia and controlling for end-organ complications of T2DM, Farr et al. have demonstrated lower bone material strength in postmenopausal women with T2DM compared to non-diabetic controls [30]. Hip geometry can be estimated from DXA, an imaging test performed routinely in clinical settings. Geometry is a critical component of bone macroarchitecture, emphasizing the importance of biomechanics in fracture resistance. Differences in hip geometry have not been reported previously in either early or late stages of glucose intolerance. In this study, we demonstrate that *both* IGT and T2DM have an adverse association with hip geometry, as measured by CSA and Z in postmenopausal women. These outcomes persisted even when controlling for age, BMI, race, renal function, and calcium and vitamin D status and supplementation. Controlling for medication use, our findings also do not support the common hypothesis that the increased fracture risk seen in T2DM is explained by medication use (thiazolidinediones, PPIs, SSRIs, etc.) alone [31, 32].

Whether the IGT state is also associated with changes in bone that induce fragility has been only minimally investigated in women and even less so in men. The results of these studies are mixed. In The Rotterdam Study, fracture risk was limited to treated women with type 2 diabetes (hazard ratio (HR) 1.69) while those with impaired glucose tolerance (IGT) had a lower vertebral fracture risk (HR 0.80) [7]. Similarly, in the Health Aging and Body

Composition Study (Health ABC), T2DM was associated with elevated fracture risk (RR 1.64) in older men and women, while IGT had no significant effect on skeletal events [6]. At a minimum, these studies suggest a possible process by which, in the transition from IGT to T2DM, fracture risk increases despite maintenance of BMD. The data for the role of progressive glucose intolerance on bone macroarchitecture and strength is even more sparse. In fact, the few previously published hip geometry studies in T2DM have used self-report of diabetic status, medication use, fasting plasma glucose, and HbA1c measures to classify individuals along the diabetic spectrum [33, 34]. These criteria have limitations in that they do not necessarily capture those older individuals in whom the pre-diabetic state is marked by impaired response to a glucose load, or IGT. In NHANES, OGTT captured a greater percentage of elderly men and women with pre-diabetes when compared to fasting glucose levels [5]. HbA1c measures, though convenient and an accepted method of categorizing both diabetes and pre-diabetes, can be affected by physiology (hemolysis, hemoglobin variants, renal disease, etc.) as well as assay variation. Self-report of diabetes or the use of diabetes medications can muddle data with human error and inaccurate classification. Building on these studies, our findings strengthen the concept that hyperglycemia and insulin resistance are detrimental to bone strength in women even in the absence of a formal diagnosis of T2DM. Our findings are consistent with those obtained by Garg et al. who found that women with T2DM on insulin had lower Z compared to self-reported non-diabetic women and T2DM women managed on oral medications or diet alone after adjustment for lean mass [34]. Srikanthan et al. have also found that greater insulin resistance, as measured by HOMA-IR, was associated with diminished indices of femoral neck strength relative to load [35]. These findings, in part, support our own data demonstrating that both the “pre-diabetic” state and frank T2DM are inversely associated with qualitative measures of hip geometry. In contrast to our findings, however, the associations between measures of glucose metabolism and of bone strength were no longer significantly correlated when the analysis was adjusted for BMI. There also appeared to be no significant contribution of sex to these diabetes-bone strength associations.

Although we hypothesized that the progression of NGT to IGT to T2DM would prove detrimental to hip geometry in a non-discriminatory fashion, worsening glucose intolerance was adversely associated with skeletal parameters in women only. This finding, not previously reported in the literature, may stem in part from a lack of data on bone macroarchitecture and strength in men with T2DM. To date, men have been largely excluded from current investigations, almost all of which have focused on postmenopausal women. Nevertheless, there may be pertinent sex-based differences in bone metabolism in men and women with insulin resistance, hyperglycemia, and T2DM that require special attention in future studies. Specifically, the interplay between sex hormones and bone strength in states of glucose intolerance should be queried, as should sex-based differences in body composition, inflammation, bone remodeling, and other novel determinants of bone quantity, quality, and macroarchitecture. Furthermore, we hypothesized that all measures of hip geometry would be adversely associated with IGT and T2DM. In women, however, increasing glucose intolerance was associated with favorable declines in BR, or a decreased propensity to buckle under compression. This outcome has been previously described as a part of WHI-OS in which higher BMI in women was associated with lower BR, as well as in

our own work looking at the association between lean mass in T2DM on hip geometry measures [36, 37]. In the Rotterdam Study, men and women with inadequately controlled diabetes had narrower femoral necks and thicker cortices, leading to increased cortical stability and less susceptibility to buckling (decreased BR) when compared to those without diabetes [38]. Whether this parameter of hip geometry is adaptive or in direct response to systemic changes in T2DM is unclear.

There are limitations to this study. Analyses presented are cross sectional and may implicate important relationships between IGT, T2DM, and bone geometry, but cannot speak to causality. The BLSA is a well-characterized and large cohort; however, the population is relatively healthy and predominantly white, which may affect the generalizability of our findings. Along these same lines, the severity of diabetes in the men and women of the cohort was not marked. Of those with diabetes, only 14 % of men and 4 % of women were on insulin, and mean HgbA1c in even those with T2DM demonstrated fair control (mean HbA1c for diabetic men and women, 6.8 %). While we were able to control for renal function in multivariate models, our analyses could not fully account for additional diabetic complications such as neuropathy or microvascular disease which might also impair hip geometry differently across the categories of glycemic status. Whether similar relationships between IGT, T2DM, and bone strength and hip geometry would be observed in men and women with later-stage or more complicated disease requires investigation. We would argue, however, that the relative health of even those with T2DM in the BLSA cohort also strengthens our hypothesis that declines in bone strength and macroarchitecture with the progression of IGT to T2DM occur independently of end-organ diabetic complications. Finally, we acknowledge that hip geometry measures derived from femoral neck DXA represent an approximation of the three-dimensional (3D) properties of bone. Hip geometry parameters and femoral neck BMD can also be highly correlated, for which we made every effort to control in our models. Finally, we did not have access to more advanced imaging techniques within the BLSA to include peripheral quantitative computed tomography which may have provided greater insight into more precise 3D measures of bone quality and strength. We would expect that our findings will continue to motivate future studies employing advanced technologies to highlight possible differences in bone geometry amongst men and women with different degrees of glucose intolerance.

Our findings are novel in that bone strength, as measured by hip geometry, has yet to be described across the three categories of glycemic control specifically defined by the use of OGTT. This research has also revealed an unexpected sex difference in diabetic status and its association with impaired bone bending strength and mineralization in cross section, prompting the need for further research to understand the mechanisms by which glucose intolerance may lead to compromised bone macroarchitecture in women differently than in men. Most importantly, our findings further highlight the need for alternative methods to predict bone strength beyond conventional BMD measurements in states of glucose intolerance. This is especially significant in those with IGT, a population not studied previously, in whom early intervention could result in fracture prevention. By defining changes in bone quality and macroarchitecture in those with IGT and T2DM, we might identify how progressive glucose intolerance impairs bone strength and potentially allow for targeted interventions to prevent future mortality, disability, and frailty following fracture.

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Table 1

BLSA cohort by diabetes status

Study outcomes	Diabetes categories			ANOVA results
	Normal glucose tolerance (women, <i>N</i> =317; men, <i>N</i> =285)	Impaired glucose tolerance (women, <i>N</i> =95; men, <i>N</i> =109)	Type 2 diabetes (women, <i>N</i> =63; men, <i>N</i> =85)	
	Mean	Mean	Mean	<i>p</i> value
Age (years)				
Women	63.81±12.84 ^a	67.46±11.98	68.89±10.16	0.002
Men	66.28±13.64 ^a	70.64±11.81	71.88±9.71	<0.001
BMI (kg/m ²)				
Women	26.05±4.96 ^a	28.16±6.28	29.72±5.34	<0.001
Men	26.76±3.51 ^a	28.49±4.41	29.21±5.02	<0.001
BMD total hip (g/cm ²)				
Women	0.95±0.13	0.96±0.15	1.00±0.15	0.14
Men	1.04±0.16	1.06±0.15	1.09±0.18	0.10
BMD femoral neck (g/cm ²)				
Women	0.90±0.13	0.92±0.15	0.92±0.15	0.42
Men	0.97±0.17	0.97±0.15	0.98±0.16	0.80
BMD spine, L1–L4 (g/cm ²)				
Women	1.19±0.19	1.20±0.20	1.20±0.22	0.53
Men	1.32±0.12	1.32±0.19	1.38±0.25	0.11
Section modulus (cm ³)				
Women	1.55±0.34	1.53±0.31	1.56±0.35	0.35
Men	2.27±0.53	2.37±0.85	2.29±0.57	0.42
Cross-sectional area (cm ²)				
Women	2.72±0.47	2.69±0.48	2.78±0.52	0.82
Men	3.41±0.64	3.48±0.69	3.46±0.68	0.77
Buckling ratio				
Women	9.79±1.82	9.49±1.67	9.36±1.73	0.11
Men	10.64±2.35	10.59±2.27	10.29±2.06	0.52
25-Hydroxy vit D (nmol/L)				
Women	83.37±32.45	82.62±29.21	78.87±33.70	0.68
Men	77.63±24.21 ^b	76.88±22.96	66.89±25.46 ^a	0.02
HbA1c (%)				
Women	5.66±0.33	5.81±0.39	6.75±0.92 ^a	<0.001
Men	5.61±0.39	5.78±0.34	6.71±1.12 ^a	<0.001
GFR (mL/min)				
Women	86.73±29.93	87.43±31.90	91.20±37.94	0.58
Men	80.26±26.28	80.75±27.74	75.04±30.50	0.26

Subjects on osteoporosis medications excluded from analyses; values are mean±standard deviation (SD)

BMI body mass index, *BMD* bone mineral density, *vit* vitamin, *HbA1c* hemoglobin A1c, *GFR* glomerular filtration rate, *MDRD* by Modification of Diet in Renal Disease Study equation

^aSignificantly different from all other groups

^bSignificantly different from type 2 diabetes

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Table 2

Multiple linear regression models showing the association of IGT and T2DM with BMD and hip geometry stratified by sex

Skeletal outcomes and glycemic category predictors	Men (n=472)			Women (n=473)		
	β	Standard error	p	β	Standard error	p
Bone mineral density of femoral neck (g/cm ²)						
IGT	0.0040	0.017	0.81	0.010	0.014	0.46
T2DM	0.014	0.019	0.47	0.021	0.017	0.22
Bone mineral density of total hip (g/cm ²)						
IGT	0.015	0.017	0.36	0.0048	0.014	0.74
T2DM	0.035	0.019	0.075	0.029	0.017	0.089
Bone mineral density L1-L4 (g/cm ²)						
IGT	-0.034	0.026	0.19	0.011	0.022	0.63
T2DM	0.0063	0.029	0.83	0.026	0.027	0.32
Section modulus (cm ³)						
IGT	0.017	0.063	0.79	-0.097	0.030	0.0011*
T2DM	-0.11	0.071	0.11	-0.090	0.036	0.013*
Cross-sectional area (cm ²)						
IGT	-0.0051	0.040	0.90	-0.076	0.025	0.0020*
T2DM	-0.076	0.045	0.092	-0.073	0.030	0.014*
Buckling ratio						
IGT	-0.12	0.14	0.41	-0.31	0.098	0.023*
T2DM	-0.36	0.26	0.083	-0.29	0.12	0.012*

All models in men and women adjusted for diabetes status, age, BMI, race, smoking, multivitamin use, calcium and D supplementation, serum creatinine, vitamin D and calcium, current and prior bisphosphonate use, and femoral neck BMD (hip geometry measures only)

IGT impaired glucose tolerance, T2DM type 2 diabetes mellitus, BMI body mass index, BMD bone mineral density

* p 0.05; NGT used as reference group