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Authors

Schwartz, Ann V
Vittinghoff, Eric
Margolis, Karen L
et al.

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Intensive Glycemic Control and Thiazolidinedione Use: Effects on Cortical and Trabecular Bone at the Radius and Tibia

Ann V. Schwartz,
University of California, 185 Berry St., Suite 5700, San Francisco, CA 94107, USA

Eric Vittinghoff,
University of California, 185 Berry St., Suite 5700, San Francisco, CA 94107, USA

Karen L. Margolis,
HealthPartners Research Foundation, Minneapolis, MN, USA

Lesley M. Scibora,
University of Minnesota, Minneapolis, MN, USA

Lisa Palermo,
University of California, 185 Berry St., Suite 5700, San Francisco, CA 94107, USA

Walter T. Ambrosius,
Wake Forest School of Medicine, Winston-Salem, NC, USA

Trisha F. Hue, and
University of California, 185 Berry St., Suite 5700, San Francisco, CA 94107, USA

Kristine E. Ensrud
VA Medical Center, University of Minnesota, Minneapolis, MN, USA

Ann V. Schwartz: aschwartz@psg.ucsf.edu

Abstract

Factors that contribute to bone fragility in type 2 diabetes are not well understood. We assessed the effects of intensive glycemic control, thiazolidinediones (TZDs), and A_{1C} levels on bone geometry and strength at the radius and tibia. In a substudy of the Action to Control Cardiovascular Risk in Diabetes trial, peripheral quantitative computed tomographic (pQCT) scans of the radius and tibia were obtained 2 years after randomization on 73 participants (intensive $n = 35$, standard $n = 38$). TZD use and A_{1C} levels were measured every 4 months during the trial. Effects of intervention assignment, TZD use, and A_{1C} on pQCT parameters were assessed in linear regression models. Intensive, compared with standard, glycemic control was associated with 1.3 % lower cortical volumetric BMD at the tibia in men ($p = 0.02$) but not with other pQCT parameters. In women, but not men, each additional year of TZD use was associated with an 11 % lower polar strength strain index (SSIp) at the radius ($p = 0.04$) and tibia ($p = 0.002$) in models adjusted for A_{1C} levels. In women, each additional 1 % increase in A_{1C} was associated with an 18 % lower SSIp at the ultradistal radius ($p = 0.04$) in models adjusted for TZD use. There was no consistent evidence of an effect of intensive, compared with standard, glycemic control on bone strength at the radius or tibia. In women, TZD use may reduce bone strength at these sites. Higher A_{1C} may also be associated with lower bone strength at the radius, but not tibia, in women.

Correspondence to: Ann V. Schwartz, aschwartz@psg.ucsf.edu.

All other authors have stated that they have no conflict of interest.

Keywords

Diabetes mellitus; Hemoglobin A_{1C}; Thiazolidinedione; Peripheral quantitative computed tomography

Introduction

Type 2 diabetes is associated with higher bone density but, paradoxically, with increased fracture risk. The reasons for this increased risk and the best approaches to fracture prevention in patients with diabetes are not clearly understood. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, intensive glycemic control did not reduce fracture risk compared with standard control [1]. There was also no difference in bone loss as measured by dual-energy X-ray absorptiometry (DXA) in the two trial groups. However, the intensive therapy was characterized by greater use of thiazolidinediones (TZDs), known to increase fracture risk in women and possibly in men [2–7]. TZDs have also been shown to increase bone loss at the hip and spine in short-term trials based on DXA [2], but studies of the effects at peripheral skeletal sites are not available. Reports on the relationship between A_{1C} and bone density by DXA at the hip and spine are conflicting [8, 9]. A meta-analysis of A_{1C} and forearm BMD by DXA reported a trend toward lower BMD with higher A_{1C}, but the result, based on only four studies, was not statistically significant [9]. Information is not available on the effects of glycemic control on the separate compartments of cortical and trabecular bone.

To better understand the effect of the intensive glycemic control intervention on bone and to assess the separate effects of TZD use and improved A_{1C}, we used data from peripheral quantitative computed tomographic (pQCT) scans of the radius and tibia obtained on a subset of ACCORD participants. pQCT scans provide volumetric and geometric parameters that cannot be obtained from DXA scans, allowing separate assessment of trabecular and cortical bone and of estimated strength.

Subjects and Methods

ACCORD Trial Design and Participants

The ACCORD trial has been described previously [10]. Briefly, inclusion criteria for participants included type 2 diabetes, an A_{1C} of 7.5–11 %, age 40–79 years with a history of cardiovascular disease (CVD) or 55–79 years with subclinical evidence of CVD or significant risk factors for CVD. Exclusion criteria included frequent serious hypoglycemia, body mass index of 45 kg/m^2 or more, serumcreatinine above 1.5 mg/dL (132.6 lmol/L), or other serious illness. The trial included 77 clinical sites in the United States and Canada.

ACCORD was a double two-by-two factorial, parallel treatment trial. All eligible participants (n = 10,251) were randomly assigned to the intensive or standard glycemia group, with A_{1C} goals of <6 and 7.0–7.9 %, respectively. Participants were also assigned to either the blood pressure or lipid trial, based on eligibility. During the trial, ACCORD achieved a median A_{1C} of 6.4 and 7.5 % in the intensive and standard glycemia groups, respectively. Participants in both arms of the trial received individualized therapeutic plans that increased the number and dose of diabetes medications (metformin, sulfonylureas, TZDs, insulin, and other medications) as needed to achieve the specified A_{1C} goal for that arm [11]. The intensive glycemia intervention protocol was stopped in February 2008 because of higher all-cause mortality in those assigned to this treatment strategy [11]. All participants were transferred to the standard glycemia therapy. The trial concluded in June 2009.

pQCT Ancillary Study

At five clinical sites in the Minneapolis area, pQCT scans of the radius and tibia were obtained on a subgroup of consenting participants ($n = 73$) at the 2-year visit. The scans were obtained within 3 months of the close of the intensive glycemia arm. Sixteen participants were scanned before the close (average 18 days, range 1–30 days), and 57 participants were scanned after the close (average 46 days, range 4–90 days). Institutional review boards at participating institutions approved the protocol for the pQCT ancillary study, and written informed consent was obtained from all participants.

pQCT (XCT-3000; Stratec, Pforzheim, Germany) was used to obtain slices (2.3 ± 0.2 mm) at the 4, 33, and 66 % sites of the left tibia and the 4 and 33 % sites of the non-dominant radius. Scans were obtained using a 0.5 mm voxel size and a scan speed of 30 mm/s. Slices were taken as a percentage of the limb length from the distal end of the relevant bone. Anatomic reference lines for the tibia (distal edge of the tibial plafond) and the radius (distal radius joint surface) were determined by acquisition of a 30-mm planar scout view of the joint line. Quality assurance was performed by daily scanning of a manufacturer-provided anthropometric phantom.

Image data were analyzed according to the manufacturer's specifications. Scans at the 4 % (radius and tibia) sites include predominantly trabecular bone, while scans at the 33 % (radius and tibia) and 66 % (tibia) sites include predominantly cortical bone. At the ultradistal trabecular (4 %) sites, Contour mode 2 (169 mg/cm^3) and Peel mode 1 (45 % area) were used. Ultradistal sites were assessed for total and trabecular bone cross-sectional area (mm^2) and volumetric density (mg/mm^3). As an index of bone compressive strength, bone strength index (BSI, mg/mm to the fourth) was calculated as (ToA × ToD^2)/1,000,000, where ToA is total bone area and Tod is total bone density. At the predominantly cortical radius (33 %) and tibia (33 and 66 %) sites, whole-bone properties were determined using Contour mode 2 (169 mg/cm^3) and cortical bone properties, using Cort mode 1 (710 mg/cm^3). A threshold of 280 mg/cm^3 was used to determine the polar strength strain index (SSIp). Predominantly cortical site variables included cross-sectional area (mm^2), cortical area (mm^2), cortical thickness (mm), endosteal and periosteal diameter (mm), cortical bone mineral content (BMC, mg/mm), and cortical bone volumetric density (mg/mm^3). Section modulus (mm^3) and SSIp (mm^3) were calculated as estimates of bone strength [12]. Section modulus is a measure of bone strength based on only bone geometry [13], and SSIp is a "density-weighted" section modulus value, which incorporates cortical density into the strength measure.

TZD Use in ACCORD

Rosiglitazone was included in the original treatment algorithm for the intensive and standard glycemia therapy groups, and pioglitazone was added in the fall of 2007. Participants attended clinic visits every 2–4 months. For each clinic visit, staff recorded the participant's use of diabetes medications, including TZDs, at visit entry and the prescribed medications at visit exit. Doses of oral medications were not systematically recorded. During the ACCORD trial, 92 % of the intensive glycemia group and 58 % of the standard glycemia group were prescribed a TZD [11]. "Cumulative days of TZD use" from baseline to the pQCT scans was calculated for each participant, using data from ACCORD visits starting with the first visit after randomization and continuing to the last visit before the scans. "Time since last TZD use" was calculated as the number of days from the last reported TZD use to the pQCT scans.

Average A_{1C} in ACCORD

During the trial, blood was drawn at the 4-month clinic visit for central assays of A_{1C}. The average A_{1C} during ACCORD was calculated for each participant at the time of the pQCT scans. Using an algorithm from the main trial [14], the average A_{1C} was calculated as the mean of all 4-month A_{1C} values after the baseline measurement through the clinic visit just preceding the scans.

Statistical Analyses

Linear regression models were used to assess the effects of assignment to the intensive glycemic control group compared to the standard control group on pQCT outcomes. As required for the ACCORD primary analyses, we adjusted for the presence of CVD at baseline, assignment to either the blood-pressure trial or the lipid trial, and randomized treatment assignments in the blood-pressure and lipid trials.

The associations of cumulative TZD use and average A_{1C} during ACCORD with pQCT outcomes were estimated using linear models with adjustment for baseline TZD use, baseline A_{1C}, and age. Regression effects are presented as the difference in the average value of each pQCT outcome per unit change in TZD use or average A_{1C}, as a percent of the mean of that outcome. Because TZD use is more clearly associated with increased fracture risk in women, these models were estimated separately for men and women.

Statistical significance was set at $p < 0.05$ and was not adjusted for multiple comparisons. These are hypothesis-generating analyses, designed to identify areas for future research. Given this objective and the small sample size, we focused on limiting the risk of Type II errors and have interpreted the results accordingly. Analyses were performed in SAS 9.2 (SAS Institute, Cary, NC).

Results

At ACCORD randomization, the 73 participants in the pQCT substudy included 48 men and 25 women (Table 1). Among these participants, 35 were randomized to the intensive and 38 to the standard glycemic control intervention. Average age was 62.1 years, and average A_{1C} at baseline was 8.1 %. From baseline to the pQCT scan, use of osteoporosis or hormone therapy was reported by three participants and use of oral steroids, by one participant.

Intensive Glycemic Control

There were no statistically significant differences in pQCT parameters among women, comparing those assigned to intensive and standard glycemic control (Table 2). In men, cortical volumetric BMD (vBMD) at the 33 % tibia was lower in those randomized to intensive glycemic control (−1.3 %, $p = 0.045$), but none of the other parameters were statistically different (Table 3).

TZD Use

Between randomization and the pQCT scans, 52 participants used rosiglitazone and three of these participants also used pioglitazone. Among those who used a TZD, mean use from randomization to the pQCT scans was 655 days. In models for women, adjusted for average A_{1C} during ACCORD prior to the pQCT scans, greater cumulative TZD use was associated with several indicators of lower bone strength. SSIp was lower at all sites, but the differences were statistically significant only at the 33 % radius and 66 % tibia (Table 4). Other indicators of bone strength that were reduced with greater TZD use were as follows: at 33 % radius, lower total BMC, cortical BMC, and cortical bone area; at 33 % tibia, lower total bone area and periosteal diameter; at 66 % tibia, lower total bone area, periosteal

diameter, and section modulus. Other parameters were not statistically different by TZD use (Table 4). Among men ($n = 48$), none of the pQCT parameters differed ($p < 0.05$) by cumulative TZD use in adjusted models.

Average A_{1C}

The median value for average A_{1C} in ACCORD before the pQCT scan was 6.4 % in the intensive and 7.4 % in the standard glycemia therapy group. In models adjusted for cumulative TZD use during ACCORD prior to the pQCT scans, average A_{1C} in women was associated with deficits in several pQCT parameters for the radius at pQCT-V1: at the 33 % radius, total vBMD, cortical BMC, cortical bone area, cortical thickness, and endosteal diameter; at the 4 % radius, SSIp (Table 5). There were no statistically significant associations between average A_{1C} and pQCT parameters at the tibia in women. In men, there were no statistically significant associations with average A_{1C} at either site.

Discussion

Intensive glycemic control in ACCORD was not associated with consistent differences in bone density or strength, measured near the close of the intensive glycemia group after about 2 years of the intervention. These null findings for intensive glycemic control are consistent with our previous report that intensive control was not associated with increased fracture risk or with bone loss by DXA in ACCORD [15]. However, participants in the intensive glycemic control group had more TZD use, with potential negative effects on bone, which may have blunted any positive effect of improved A_{1C} levels. When we explored this hypothesis in observational analyses, we found evidence that TZD use in women may be associated with deficits in bone strength and geometry at the radius and tibia, while lower average A_{1C} levels in women may be associated with improved parameters at the radius. Our observational results suggest that, at least in women, the combination of greater TZD use with lower A_{1C} levels in the intensive glycemic control group may have resulted in little net effect on bone and may account for the lack of difference in bone parameters between the two treatment groups. This is the first report on TZD and A_{1C} effects on bone measured with pQCT.

We found evidence that TZD use in women was associated with reduced strength at the radius and tibia, particularly at the highly cortical sites (33 % radius, 33 and 66 % tibia). Differences with TZD use were not evident for trabecular or cortical vBMD but were seen in SSIp, a derived measure of bone strength that takes into account bone geometry and cortical density. SSIp has been shown to predict failure load in cadaveric studies [16], to discriminate between those with and without vertebral fracture [17], and to predict incident nonvertebral fractures [18].

Reduced strength with longer duration of TZD use was evident in models adjusted for achieved A_{1C} levels during ACCORD. In other words, among women with a similar A_{1C} level, those with greater TZD use tended to have reduced bone strength. These results suggest that TZD use may have a positive effect on bone strength by improving A_{1C} levels but may also have a negative effect on bone through other pathways. Rodent models indicate that one other pathway may be through peroxisome proliferator—activated receptor—gamma activation, causing decreased osteoblastogenesis and increased marrow adipogenesis [19].

Previous studies have not examined the effect of TZDs on bone density or strength in the peripheral skeleton. However, trials and observational studies have provided evidence of more rapid bone loss at the hip and spine in women, using DXA [20–24] and, in one trial, QCT of the hip and spine [25]. The QCT results indicated that rosiglitazone, compared with

metformin, was associated with greater losses of trabecular bone at the hip and spine over 12 months. Losses in cortical bone, measured at the hip, were not statistically different. In rodent models, increased loss of trabecular bone and whole-bone density has been reported with rosiglitazone [19] and pioglitazone treatment [26]. Recently, studies in rodents have also reported deficits in cortical bone with TZDs, including increased cortical porosity [27] and reduced cortical thickness [28, 29]. Consistent with our finding of reduced bone strength at the radius and tibia with TZD use, reports from trials and observational studies indicate that women have an increased risk of fractures with TZD use [2–7, 30, 31]. Clinical trials have demonstrated an increased risk of peripheral fractures in particular with TZD use. Trials lacked adequate numbers of hip and spine fractures to assess risks, but observational studies indicate that TZD use also increases fracture risk at these sites [3, 4, 7, 30, 31].

We did not find any consistent pattern of increased bone loss with TZD use in men. In the only trial that has examined the effect of TZD use on bone in men, an 80-week randomized trial comparing rosiglitazone plus metformin with metformin alone, addition of rosiglitazone was associated with increased bone loss at the total hip in men [24]. Previous observational studies have been inconsistent regarding effects on bone density in men [20, 32]. In clinical trials reporting fracture events TZD use has not been associated with increased risk in men [2], but some observational studies have reported increased fracture risk with TZD use in men [3–7].

We found evidence of deficits in cortical bone at the radius with higher A_{1C} in women. Previous studies of glycemic control and peripheral bone density are limited. In a meta-analysis, Ma et al. [9] found no statistically significant association between A_{1C} and forearm BMD by DXA in type 2 diabetes. For spine and hip BMD, however, this meta-analysis reported a positive association between A_{1C} levels and BMD. On the other hand, a meta-analysis by Vestergaard [8] found no relationship between A_{1C} and hip or spine BMD. In a longitudinal study of the effects of improved glycemic control on bone, patients with initial poor control (mean A_{1C} 11.6 %) had improvements in spine and hip BMC, measured by DXA, after 1 year of adequate control [33].

Hyperglycemia may contribute to bone fragility through effects on bone cells. In rodent models, hyperglycemia is associated with reduced differentiation of osteoblasts and increased marrow fat, suggesting that stem cell lineage may favor adipogenesis over osteoblastogenesis with high glucose levels [34]. Consistent with this hypothesis, Baum et al. [35] reported that A_{1C} levels are positively correlated with vertebral marrow fat in women with type 2 diabetes. Higher A_{1C} levels are positively correlated with sclerostin, a product of osteocytes that inhibits bone formation [36], in patients with type 2 diabetes [37]. Osteocyte function is crucial for bone to respond to mechanical loading signals with appropriate increases in size and density [38]. Hyperglycemia may also affect bone through increases in microangiopathy, peripheral neuropathy, and decreased renal function, factors that are associated with lower bone density [39–41].

These findings raise the possibility that lower A_{1C} levels may contribute to skeletal health in diabetes, possibly through maintenance of osteocyte and osteoblast function. In ACCORD, lower A_{1C} levels were achieved with a high rate of TZD use, in both the standard and intensive control groups [11]. The negative effects of TZDs on bone, particularly in women, may have offset any gains from lowering A_{1C} in the intensive glycemia treatment group, resulting in a lack of differences in bone parameters between the intensive and standard glycemia groups. Additional research is needed to ascertain whether improved glycemic control achieved without use of TZDs has a positive effect on bone health.

The randomized trial design of ACCORD provides an optimal setting for comparing the effects of intensive and standard glycemic control on bone parameters. However, pQCT scans were obtained about 2 years after randomization. Measurements at baseline would have provided more power to detect a difference by treatment group. Because of randomization, baseline characteristics in ACCORD, including pQCT parameters, will generally be similar across treatment assignments. The baseline factors that we considered were similarly distributed across treatment arms in the pQCT subgroup (Table 1). However, baseline differences in pQCT parameters are possible due to chance in this randomized design.

The comparison of the effects of intensive and standard glycemic control is necessarily limited to the ACCORD algorithms for achieving control, an approach that included substantial TZD use. Another limitation is the small number of participants included in this substudy. Along with the lack of a baseline measurement, this reduced the power of the study to detect effects of intensive glycemic control on pQCT parameters, limiting our ability to interpret negative findings. This study also included multiple comparisons, increasing the possibility of Type I errors. Our examination of the contributions of A_{1C} levels and TZD use to bone parameters is an observational cross-sectional analysis subject to potential confounding. Thus, our results for the effects of TZD use and A_{1C} levels must be considered hypothesis-generating, requiring cautious interpretation and confirmation in other settings.

In conclusion, 2 years of intensive, compared with standard, glycemia therapy among patients with type 2 diabetes in the ACCORD trial had little effect on bone strength or geometry at the radius and tibia. In women, TZD use may have detrimental effects on bone strength, particularly cortical bone, at peripheral skeletal sites. Although intensive glycemic control was not associated with differences in bone strength, higher A_{1C} levels may be associated with lower bone strength at the radius in women independently of TZD use. These preliminary findings need to be tested in larger studies.

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References

1. Schwartz AV, Margolis KL, Sellmeyer DE, Vittinghoff E, Ambrosius WT, Bonds DE, Josse RG, Schnall AM, Simmons DL, Hue TF, Palermo L, Hamilton BP, Green JB, Atkinson HH, O'Connor PJ, Force RW, Bauer DC. Intensive glycemic control is not associated with fractures or falls in the ACCORD randomized trial. Diabetes Care. 2012; 35:1525–1531. [PubMed: 22723583]
2. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. CMAJ. 2009; 180:32–39. [PubMed: 19073651]
3. Douglas IJ, Evans SJ, Pocock S, Smeeth L. The risk of fractures associated with thiazolidinediones: a self-controlled case-series study. PLoS Med. 2009; 6:e1000154. [PubMed: 19787025]

4. Hsiao FY, Mullins CD. The association between thiazolidinediones and hospitalisation for fracture in type 2 diabetic patients: a Taiwanese population-based nested case-control study. Diabetologia. 2010; 53:489–496. [PubMed: 19943156]
5. Dormuth CR, Carney G, Carleton B, Bassett K, Wright JM. Thiazolidinediones and fractures in men and women. Arch Intern Med. 2009; 169:1395–1402. [PubMed: 19667303]
6. Aubert RE, Herrera V, Chen W, Haffner SM, Pendergrass M. Rosiglitazone and pioglitazone increase fracture risk in women and men with type 2 diabetes. Diabetes Obes Metab. 2010; 12:716–721. [PubMed: 20590749]
7. Colhoun HM, Livingstone SJ, Looker HC, Morris AD, Wild SH, Lindsay RS, Reed C, Donnan PT, Guthrie B, Leese GP, McKnight J, Pearson DW, Pearson E, Petrie JR, Philip S, Sattar N, Sullivan FM, McKeigue P. Hospitalised hip fracture risk with rosiglitazone and pioglitazone use compared with other glucose-lowering drugs. Diabetologia. 2012; 55:2929–2937. [PubMed: 22945303]
8. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis. Osteoporos Int. 2007; 18:427–444. [PubMed: 17068657]
9. Ma L, Oei L, Jiang L, Estrada K, Chen H, Wang Z, Yu Q, Zillikens MC, Gao X, Rivadeneira F. Association between bone mineral density and type 2 diabetes mellitus: a meta-analysis of observational studies. Eur J Epidemiol. 2012; 27:319–332. [PubMed: 22451239]
10. Buse JB, Bigger JT, Byington RP, Cooper LS, Cushman WC, Friedewald WT, Genuth S, Gerstein HC, Ginsberg HN, Goff DC Jr, Grimm RH Jr, Margolis KL, Probstfield JL, Simons-Morton DG, Sullivan MD. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. Am J Cardiol. 2007; 99:21i–33i.
11. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008; 358:2545–2559. [PubMed: 18539917]
12. Ferretti JL, Capozza RF, Zanchetta JR. Mechanical validation of a tomographic (pQCT) index for noninvasive estimation of rat femur bending strength. Bone. 1996; 18:97–102. [PubMed: 8833202]
13. Liu D, Manske SL, Kontulainen SA, Tang C, Guy P, Oxland TR, McKay HA. Tibial geometry is associated with failure load ex vivo: a MRI, pQCT and DXA study. Osteoporos Int. 2007; 18:991–997. [PubMed: 17268944]
14. Riddle MC, Ambrosius WT, Brillon DJ, Buse JB, Byington RP, Cohen RM, Goff DC Jr, Malozowski S, Margolis KL, Probstfield JL, Schnall A, Seaquist ER. Action to Control Cardiovascular Risk in Diabetes I. Epidemiologic relationships between A_{1C} and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. Diabetes Care. 2010; 33:983–990. [PubMed: 20427682]
15. Schwartz AV, Vittinghoff E, Margolis KL, Ambrosius WT, Bonds DE, Josse RG, Sellmeyer DE, Schnall AM, Simmons DL, Palermo L, Force RW, Green JB, O'Connor PJ, Bauer DC. Intensive glycemic control and fracture risk. Diabetes. 2011; 60:A372.
16. Muller ME, Webber CE, Bouxsein ML. Predicting the failure load of the distal radius. Osteoporos Int. 2003; 14:345–352. [PubMed: 12730737]
17. Gorai I, Nonaka K, Kishimoto H, Sakata H, Fujii Y, Fujita T. Cut-off values determined for vertebral fracture by peripheral quantitative computed tomography in Japanese women. Osteoporos Int. 2001; 12:741–748. [PubMed: 11605740]
18. Sheu Y, Zmuda JM, Boudreau RM, Petit MA, Ensrud KE, Bauer DC, Gordon CL, Orwoll ES, Cauley JA. Bone strength measured by peripheral quantitative computed tomography and the risk of nonvertebral fractures: the Osteoporotic Fractures in Men (MrOS) study. J Bone Miner Res. 2011; 26:63–71. [PubMed: 20593412]
19. Rzonca SO, Suva LJ, Gaddy D, Montague DC, Lecka-Czernik B. Bone is a target for the antidiabetic compound rosiglitazone. Endocrinology. 2004; 145:401–406. [PubMed: 14500573]
20. Schwartz AV, Sellmeyer DE, Vittinghoff E, Palermo L, Lecka-Czernik B, Feingold KR, Strotmeyer ES, Resnick HE, Carbone L, Beamer BA, Park SW, Lane NE, Harris TB, Cummings SR. Thiazolidinedione use and bone loss in older diabetic adults. J Clin Endocrinol Metab. 2006; 91:3349–3354. [PubMed: 16608888]

21. Grey A, Bolland M, Gamble G, Wattie D, Horne A, Davidson J, Reid IR. The peroxisome-proliferator-activated receptorgamma agonist rosiglitazone decreases bone formation and bone mineral density in healthy postmenopausal women: a randomized, controlled trial. J Clin Endocrinol Metab. 2007; 92:1305–1310. [PubMed: 17264176]
22. Glintborg D, Andersen M, Hagen C, Heickendorff L, Hermann AP. Association of pioglitazone treatment with decreased bone mineral density in obese premenopausal patients with polycystic ovary syndrome: a randomized, placebo-controlled trial. J Clin Endocrinol Metab. 2008; 93:1696–1701. [PubMed: 18285411]
23. Berberoglu Z, Yazici AC, Demirag NG. Effects of rosiglitazone on bone mineral density and remodelling parameters in postmenopausal diabetic women: a 2-year follow-up study. Clin Endocrinol (Oxf). 2010; 73:305–312. [PubMed: 20148906]
24. Borges JL, Bilezikian JP, Jones-Leone AR, Acusta AP, Ambery PD, Nino AJ, Grosse M, Fitzpatrick LA, Cobitz AR. A randomized, parallel group, double-blind, multicentre study comparing the efficacy and safety of Avandamet (rosiglitazone/metformin) and metformin on long-term glycaemic control and bone mineral density after 80 weeks of treatment in drug-naive type 2 diabetes mellitus patients. Diabetes Obes Metab. 2011; 13:1036–1046. [PubMed: 21682834]
25. Bilezikian JP, Eastell R, Nino AJ, Northcutt AR, Kravitz B, Paul G, Cobitz AR, Josse RG, Fitzpatrick LA. Rosiglitazone reduced BMD in women with type 2 diabetes and the effect was attenuated after switching to metformin. J Bone Miner Res. 2011; 26:S68–S69.
26. Syversen U, Stunes AK, Gustafsson BI, Obrant KJ, Nordsletten L, Berge R, Thommesen L, Reseland JE. Different skeletal effects of the peroxisome proliferator activated receptor (PPAR)alpha agonist fenofibrate and the PPARgamma agonist pioglitazone. BMC Endocr Disord. 2009; 9:10. [PubMed: 19331671]
27. Sardone LD, Renlund R, Willett TL, Fantus IG, Grynpas MD. Effect of rosiglitazone on bone quality in a rat model of insulin resistance and osteoporosis. Diabetes. 2011; 60:3271–3278. [PubMed: 21998400]
28. Stunes AK, Westbroek I, Gustafsson BI, Fossmark R, Waarsing JH, Eriksen EF, Petzold C, Reseland JE, Syversen U. The peroxisome proliferator–activated receptor (PPAR) alpha agonist fenofibrate maintains bone mass, while the PPAR gamma agonist pioglitazone exaggerates bone loss, in ovariectomized rats. BMC Endocr Disord. 2011; 11:11. [PubMed: 21615901]
29. Broulik PD, Sefc L, Haluzik M. Effect of PPAR-gamma agonist rosiglitazone on bone mineral density and serum adipokines in C57BL/6 male mice. Folia Biol (Praha). 2011; 57:133–138. [PubMed: 21978754]
30. Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, Meier CR. Use of thiazolidinediones and fracture risk. Arch Intern Med. 2008; 168:820–825. [PubMed: 18443256]
31. Kanazawa I, Yamaguchi T, Yamamoto M, Sugimoto T. Relationship between treatments with insulin and oral hypoglycemic agents versus the presence of vertebral fractures in type 2 diabetes mellitus. J Bone Miner Metab. 2010; 28:554–560. [PubMed: 20177722]
32. Yaturu S, Bryant B, Jain SK. Thiazolidinediones treatment decreases bone mineral density in type 2 diabetic men. Diabetes Care. 2007; 30:1574–1576. [PubMed: 17363747]
33. Gregorio F, Cristallini S, Santeusanio F, Filipponi P, Fumelli P. Osteopenia associated with non-insulin-dependent diabetes mellitus: what are the causes? Diabetes Res Clin Pract. 1994; 23:43–54. [PubMed: 8013262]
34. McCabe LR. Understanding the pathology and mechanisms of type I diabetic bone loss. J Cell Biochem. 2007; 102:1343–1357. [PubMed: 17975793]
35. Baum T, Yap SP, Karampinos DC, Nardo L, Kuo D, Burghardt AJ, Masharani UB, Schwartz AV, Li X, Link TM. Does vertebral bone marrow fat content correlate with abdominal adipose tissue, lumbar spine bone mineral density, and blood biomarkers in women with type 2 diabetes mellitus? J Magn Reson Imaging. 2012; 35:117–124. [PubMed: 22190287]
36. Bonewald LF, Johnson ML. Osteocytes, mechanosensing and Wnt signaling. Bone. 2008; 42:606–615. [PubMed: 18280232]

37. Garcia-Martin A, Rozas-Moreno P, Reyes-Garcia R, Morales-Santana S, Garcia-Fontana B, Garcia-Salcedo JA, Munoz-Torres M. Circulating levels of sclerostin are increased in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2012; 97:234–241. [PubMed: 22031520]

38. Noble BS, Reeve J. Osteocyte function, osteocyte death and bone fracture resistance. Mol Cell Endocrinol. 2000; 159:7–13. [PubMed: 10687847]

39. Vogt MT, Cauley JA, Kuller LH, Nevitt MC. Bone mineral density and blood flow to the lower extremities: the study of osteoporotic fractures. J Bone Miner Res. 1997; 12:283–289. [PubMed: 9041062]

40. Strotmeyer ES, Cauley JA, Schwartz AV, de Rekeneire N, Resnick HE, Zmuda JM, Shorr RI, Tylavsky FA, Vinik AI, Harris TB, Newman AB. Reduced peripheral nerve function is related to lower hip BMD and calcaneal QUS in older white and black adults: the health, aging, and body composition study. J Bone Miner Res. 2006; 21:1803–1810. [PubMed: 17002569]

41. Ishani A, Paudel M, Taylor BC, Barrett-Connor E, Jamal S, Canales M, Steffes M, Fink HA, Orwoll E, Cummings SR, Ensrud KE. Renal function and rate of hip bone loss in older men: the Osteoporotic fractures in men study. Osteoporos Int. 2008; 19:1549–1556. [PubMed: 18392664]

Table 1

Baseline characteristics of ACCORD participants in the pQCT substudy

Characteristic	Women		Men	
Glycemic control group:	**Intensive**	**Standard**	**Intensive**	**Standard**
n	11	14	24	24
Race/ethnicity				
White	11 (100.0)	14 (100.0)	23 (95.8)	21 (87.5)
African-American	0 (0.0)	0 (0.0)	1 (4.2)	2 (8.3)
Native American	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)
Age (years)	61.1 ± 4.4	60.4 ± 5.2	62.6 ± 7.2	63.3 ± 6.9
Duration of diabetes (years)	8.4 ± 8.9	10.9 ± 7.2	9.0 ± 4.9	9.9 ± 8.7
Prevalent CVD	2 (18.2)	3 (21.4)	10 (41.7)	9 (37.5)
TZD use	1 (9.1)	3 (21.4)	7 (29.2)	4 (16.7)
HbA_{1c} (%)	8.2 ± 0.9	8.4 ± 1.3	8.1 ± 0.9	8.0 ± 1.1

Values are expressed as mean ± SD or *n* (%). Baseline of the ACCORD trial, approximately 2 years before the pQCT scans

Table 2

Peripheral QCT bone parameters in women (n = 25) by glycemia treatment group, measured approximately 2 years after randomization in the ACCORD trial

	Radius				Tibia					
	33 %		4 %		66 %		33 %		4 %	
	Int	Std	Int	Std	Int	Std	Int	Std	Int	Std
Total bone										
vBMD (mg/cm^3)	988 (118)	928 (140)	374 (86)	350 (87)	598 (147)	625 (126)	860 (109)	853 (98)	303 (51)	297 (62)
BMC (mg/mm)	94 (15)	92 (18)	92 (13)	89 (15)	320 (52)	339 (49)	287 (31)	302 (31)	265 (33)	279 (44)
Bone area (mm^2)	97 (17)	100 (18)	254 (52)	264 (55)	549 (76)	555 (97)	336 (29)	357 (48)	888 (134)	964 (186)
Cortical bone										
vBMD (mg/cm^3)	1,176 (37)	1,158 (42)			1,076 (48)	1,085 (26)	1,159 (34)	1,144 (18)		
BMC (mg/mm)	92 (15)	88 (18)			267 (66)	291 (53)	278 (43)	284 (30)		
Area (mm^2)	78 (11)	76 (15)			246 (52)	268 (45)	239 (34)	248 (28)		
Thickness (mm)	3 (0.6)	3 (0.7)			4 (1)	4 (1)	5 (1)	5 (0.7)		
Periosteal diameter (mm)	35 (3)	35 (3)			83 (6)	83 (7)	65 (3)	67 (5)	105 (8)	110 (10)
Endosteal diameter (mm)	14 (6)	18 (5)			61 (12)	59 (11)	36 (7)	36 (7)		
Strength indices										
SSIp (mm^3)	213 (44)	228 (48)	330 (75)	318 (71)	2,098 (225)	2,257 (430)	1,476 (326)	1,461 (261)	1,409 (299)	1,514 (502)
Section modulus (mm^3)	208 (40)	220 (48)			2,019 (282)	2,225 (424)	1,429 (311)	1,463 (271)		
Trabecular bone										
vBMD (mg/cm^3)			210 (55)	192 (50)					236 (35)	236 (49)
BMC (mg/mm)			23 (5)	22 (5)					94 (18)	100 (17)
Area (mm^2)			114 (24)	119 (25)					399 (60)	434 (84)
Compressive BSI (mg^2/mm^4)			35 (9)	32 (13)					81 (19)	84 (26)

Mean (SD). p>0.10 for all comparisons between intensive and standard groups

Int intensive glycemia treatment group, *Std* standard glycemia treatment group, SSI_p polar strength strain index, *BSI* bone strength index

Table 3

Peripheral QCT bone parameters in men (n = 48) by glycemia treatment group, measured approximately 2 years after randomization in the ACCORD trial

	Radius				**Tibia**					
	33 %		**4 %**		**66 %**		**33 %**		**4 %**	
	Int	**Std**	**Int**	**Std**	**Int**	**Std**	**Int**	**Std**	**Int**	**Std**
Total bone										
vBMD (mg/cm^3)	964 (118)	982 (78)	351 (66)	375 (66)	639 (79)	651 (69)	897 (66)	921 (52)	321 (45)	324 (30)
BMC (mg/mm)	148 (34)	145 (17)	153 (34)	154 (21)	475 (58)	482 (56)	415 (47)	428 (53)	398 (67)	407 (51)
Bone area (mm^2)	161 (76)	148 (20)	447 (116)	421 (87)	751 (106)	746 (96)	464 (52)	467 (66)	1,262 (253)	1,264 (169)
Cortical bone										
vBMD (mg/cm^3)	1,165 (64)	1,180 (31)			1,083 (31)	1,092 (31)	**1,147 (20)** *	**1,164 (28)**		
BMC (mg/mm)	139 (25)	139 (17)			412 (59)	418 (60)	394 (48)	410 (52)		
Area (mm^2)	119 (21)	118 (14)			380 (49)	383 (52)	343 (41)	353 (48)		
Thickness (mm)	4 (0.6)	4 (0.5)			5 (0.7)	5 (0.6)	6 (0.7)	6 (0.6)		
Periosteal diameter (mm)	44 (8)	43 (3)			97 (7)	97 (6)	76 (4)	76 (5)	125 (13)	126 (8)
Endosteal diameter (mm)	21 (11)	19 (4)			68 (9)	67 (7)	39 (5)	38 (5)		
Strength indices										
SSIp (mm^3)	435 (160)	411 (69)	606 (180)	616 (120)	3,614 (607)	3,628 (697)	2,208 (371)	2,275 (448)	2,737 (730)	2,902 (533)
Section modulus (mm^3)	402 (117)	393 (69)			3,653 (612)	3,642 (755)	2,189 (389)	2,241 (489)		
Trabecular bone										
vBMD (mg/cm^3)			212 (62)	214 (32)					242 (32)	241 (31)
BMC (mg/mm)			43 (18)	40 (10)					138 (32)	138 (27)
Area (mm^2)			201 (52)	189 (39)					568 (114)	569 (76)
Compressive BSI (mg^2/mm^4)			54 (19)	58 (13)					128 (31)	132 (23)

Bold values indicate p<0.05

Mean (SD)

Int intensive glycemia treatment group, *Std* standard glycemia treatment group, *SSIp* polar strength strain index, *BSI* bone strength index

* p<0.05 comparing intensive and standard groups. p>0.10 for all other comparisons between intensive and standard groups

Table 4

Difference (%) in bone parameters for each additional year of TZD use among women ($n = 25$) in the ACCORD trial

	Radius				Tibia					
	33 %		4 %		66 %		33 %		4 %	
	Difference[a]	*p*	Difference[a]	*p*	Difference[a]	*p*	Difference[a]	*p*	Difference[a]	*p*
Total bone										
vBMD (mg/cm^3)	−3.7	0.21	2.4	0.68	1.8	0.76	2.0	0.44	−3.0	0.51
BMC (mg/mm)	**−10.0**	**0.037**	−4.6	0.26	−6.3	0.10	−4.9	0.060	−6.5	0.095
Bone area (mm^2)	−6.4	0.12	−7.6	0.16	**−8.7**	**0.014**	**−6.6**	**0.009**	−2.4	0.54
Cortical bone										
vBMD (mg/cm^3)	−0.2	0.85			−0.1	0.88	0.9	0.14		
BMC (mg/mm)	**−9.8**	**0.049**			−6.3	0.24	−3.5	0.28		
Area (mm^2)	**−9.8**	**0.033**			−6.2	0.19	−4.4	0.16		
Thickness (mm)	−7.1	0.10			−1.7	0.79	0.9	0.86		
Periosteal diameter (mm)	−3.0	0.16			−4.2	**0.018**	−3.3	**0.009**	−1.3	0.52
Endosteal diameter (mm)	−1.1	0.85			−5.1	0.26	−5.6	0.15		
Strength indices										
SSIp (mm^3)	**−11.3**	**0.041**	−9.2	0.11	**−11.5**	**0.002**	−6.1	0.24	−14.0	0.060
Section modulus (mm^3)	−10.2	0.059			**−10.2**	**0.011**	−7.9	0.13		
Trabecular bone										
vBMD (mg/cm^3)			3.0	0.65					−2.4	0.60
BMC (mg/mm)			−3.7	0.49					−5.7	0.22
Area (mm^2)			−7.6	0.16					−2.4	0.54
Compressive BSI (mg^2/mm^4)			−0.4	0.97					−8.6	0.24

Bold values indicate $p<0.05$

TZD use from randomization to pQCT scan, approximately 2 years. Adjusted for age, baseline A_{1C}, baseline TZD use, average achieved A_{1C} (4 months after randomization to pQCT scan)

SSIp polar strength strain index, *BSI* bone strength index

[a]Difference in bone parameter, expressed as a percent of its mean value, for each additional year of TZD use

Table 5

Difference (%) in bone parameters for each 1 % increase in average A_{1C} among women ($n = 25$) in the ACCORD trial

	Radius				**Tibia**					
	33 %		**4 %**		**66 %**		**33 %**		**4 %**	
	Difference[a]	***p***	**Difference[a]**	***p***	**Difference[a]**	***p***	**Difference[a]**	***p***	**Difference[a]**	***p***
Total bone										
vBMD (mg/cm^3)	**−11.5**	**0.014**	−13.1	0.15	0.2	0.98	−0.6	0.87	−9.8	0.15
BMC (mg/mm)	−13.6	0.053	−12.1	0.056	−5.5	0.32	−4.7	0.20	−5.7	0.30
Bone area (mm^2)	−1.9	0.75	0.5	0.95	−6.0	0.22	−3.4	0.32	6.0	0.31
Cortical bone										
vBMD (mg/cm^3)	−2.1	0.14			−0.5	0.74	−0.2	0.80		
BMC (mg/mm)	**−16.3**	**0.028**			−5.6	0.48	−7.1	0.14		
Area (mm^2)	**−14.1**	**0.036**			−4.8	0.48	−6.8	0.14		
Thickness (mm)	**−19.4**	**0.005**			−1.9	0.85	−8.0	0.28		
Periosteal diameter (mm)	−0.7	0.82			−2.9	0.23	−1.8	0.27	2.8	0.35
Endosteal diameter (mm)	**23.9**	**0.009**			−3.4	0.61	−1.8	0.75		
Strength indices										
SSIp (mm^3)	−8.0	0.31	**−18.1**	**0.039**	−8.0	0.097	−10.1	0.18	−15.0	0.16
Section modulus (mm^3)	−7.0	0.36			−6.8	0.22	−11.1	0.14		
Trabecular bone										
vBMD (mg/cm^3)			−14.4	0.15					−7.9	0.24
BMC (mg/mm)			−13.5	0.10					−4.1	0.55
Area (mm^2)			0.5	0.95					6.0	0.31
Compressive BSI (mg^2/mm^4)			−20.5	0.12					−13.8	0.19

Bold values indicate $p<0.05$

Average A_{1C} from 4 months after randomization to pQCT scan, approximately 2 years after randomization. Adjusted for age, baseline A_{1C}, baseline TZD use, cumulative days of TZD use from baseline to pQCT scan

SSIp polar strength strain index, *BSI* bone strength index

[a] Difference in bone parameter, expressed as a percent of its mean value, for each 1 % increase in average A_{1C}