# Differences between Measurements of Bone Mineral Densities by Quantitative Ultrasound and Dual-Energy X-Ray Absorptiometry in Type 2 Diabetic Postmenopausal Women

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**Context:** Quantitative ultrasound (QUS) may be more helpful than dual-energy X-ray absorptiometry (DXA) in detecting bone deficits in patients with type 2 diabetes mellitus (T2DM).

**Objective:** The objective of the study was to compare differences in bone mass measurement by DXA and QUS in T2DM and nondiabetic postmenopausal women.

**Design, Setting, and Participants:** This clinical investigation was a cross-sectional study in 76 patients with T2DM and 86 nondiabetic postmenopausal women.

**Main Outcome Measures:** The primary outcomes were speed of sound (SOS) at the radius, phalanx, and tibia measured by QUS and bone mineral density (BMD) at the lumbar spine (LS), femoral neck (FN), and total hip (TH) measured by DXA.

**Results:** BMDs in T2DM patients were higher (LS, $1.06 \pm 0.12$ *vs.* $0.90 \pm 0.23$ g/cm$^2$; FN, $0.80 \pm 0.13$ *vs.* $0.74 \pm 0.12$ g/cm$^2$; TH, $0.87 \pm 0.14$ *vs.* $0.80 \pm 0.13$ g/cm$^2$, respectively, $P < 0.001$), whereas SOSs were lower than those in nondiabetics (radius, $4044 \pm 178$ *vs.* $4129 \pm 182$ m/sec; phalanx, $3902 \pm 207$ *vs.* $3999 \pm 214$ m/sec, respectively, $P < 0.001$). The positive relationships between SOS and BMD ($r = 0.26–0.75$, $P < 0.05$) in nondiabetics were not observed in women with T2DM. T2DM impacted negatively on SOSs (radius, $\beta = -0.223$, $P < 0.01$; phalanx, $\beta = -0.219$, $P < 0.01$) but positively on BMDs (LS, $\beta = 0.314$, $P < 0.001$; FN, $\beta = 0.173$, $P < 0.05$; TH, $\beta = 0.203$, $P < 0.01$).

**Conclusions:** Differences in bone mass as measured by DXA and QUS in postmenopausal T2DM and nondiabetic women do not change in parallel. QUS can provide useful information in the skeletal assessment of patients with T2DM. **(*J Clin Endocrinol Metab* 93: 1670–1675, 2008)**

Skeletal health in patients with type 2 diabetes mellitus (T2DM) is an area of interest and controversy (1–7). Many clinical and epidemiological studies have demonstrated that T2DM is associated with increased bone mineral density (BMD) as measured by dual-energy x-ray absorptiometry (DXA) (1–4). However, BMD values are generally higher in T2DM women, as are rates of bone loss and fracture risk, compared with those without diabetes (2). T2DM itself has been found to be an independent factor for fractures involving the hip, humerus, ankle, and foot, even after adjustments for age, body mass index (BMI), baseline BMD, and other comorbidities (3, 4). The paradox of a higher BMD but an increased fracture risk has been confirmed in many studies (1, 4, 5) and suggests other indices of bone quality may be important in these patients. For example, decreased bone turnover has been shown in T2DM postmenopausal women (6) and in diabetic rats, lower bone formation, and decreased bone turnover have been demonstrated (7). In T2DM patients, impaired bone quality may result from the deterioration of micro-

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Abbreviations: AGE, Advanced glycation end-products; BMD, bone mineral density; BMI, body mass index; CTR, control; DXA, dual-energy X-ray absorptiometry; FN, femoral neck; $HbA_{1c}$, hemoglobin; LS, lumbar spine; QUS, quantitative ultrasound; SOS, speed of sound; T2DM, type 2 diabetes mellitus; TH, total hip; YSM, years since menopause.

architecture rather than a decrease in bone mass. Consequently, the contradictory nature of the relationship between BMD and fracture risk in T2DM suggests that methods other than DXA may be more effective for detecting bone deficits in these patients.

Quantitative ultrasound (QUS) has been proposed as a possible alternative or adjunct to x-ray-based methods for assessing osteoporosis and fracture risk (8). Ultrasound velocity measured by QUS correlates with some mechanical properties of cortical bone as well as bone density (9). It has even been suggested that QUS may identify aspects of bone quality not captured by DXA, such as bone microarchitecture or material properties (*e.g.* bone elasticity) (9, 10). As a result, there is interest in using QUS as an instrument for diagnosis, fracture risk assessment, and monitoring with or without treatment (8). The advantages of QUS include its lack of radiation, portability and ease of operation.

The aim of this study was to compare data obtained by DXA and QUS in T2DM and nondiabetic postmenopausal women. In addition, we investigated the influence of T2DM on QUS parameters.

## Patients and Methods

### Study participants

We studied 76 postmenopausal women with T2DM (age range 46–83 yr, mean 64.1 ± 9.3 yr) with a mean BMI of 24.2 ± 3.8 kg/m$^2$ who were consecutively enrolled as inpatients at our clinical center. We defined the participants as having T2DM according to the following criteria: 1) confirmation of a diagnosis of T2DM and/or use of oral antidiabetic medications or insulin from patients' medical records; 2) symptoms of diabetes including polyuria, polydipsia and unexplained weight loss plus random plasma glucose 200 mg/dl or greater (11.1 mmol/liter); or 3) a fasting plasma glucose 126 mg/dl or greater (7.0 mmol/liter) or a 2-h postload glucose 200 mg/dl or greater (11.1 mmol/liter) during an oral glucose tolerance test [American Diabetes Association (1997) criteria] (11). We used the reported age at diagnosis to define diabetes duration. Glycosylated hemoglobin ($HbA_{1c}$) levels were measured on the day of the study. The clinical characteristics of the postmenopausal women with T2DM are presented in Table 1. Eighty-six nondiabetic postmenopausal women were recruited as a control (CTR) group. Potential control subjects were excluded if they had a history or evidence of any metabolic bone diseases (osteoporosis, hyper- or hypoparathyroidism, Paget's disease, osteomalacia, renal osteodystrophy, or osteogenesis imperfecta), a history of cancer, severe renal impairment (Cockcroft-Gault-glomerular filtration rate < 30 ml/min), or abnormal liver function, severe malabsorption, obesity (BMI > 30 kg/m$^2$) and prior use of any bisphosphonates, fluoride, or calcitonin. Additional exclusion criteria for CTRs were Cushing's syndrome, hyperthyroidism, and hypothyroidism. Participants were informed about the purpose and procedures of the study and provided written consent before any data were obtained. The study was approved by the Ethics Committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine.

Baseline characteristics including age, years since menopause, duration of diabetes, and the use of therapy (oral antidiabetic agents only and/or insulin) were recorded.

**TABLE 1.** Clinical characteristics of 76 postmenopausal women with T2DM

| Characteristics | |
|---|---|
| $HbA_{1c}$ (%) | 9.0 ± 2.2 |
| Duration of the diabetes (yr) | 10.1 ± 7.3 |
| Carotid or lower extremity atherosclerosis (n) | 51/63 |
| Peripheral neuropathy (n) | 33/68 |
| Retinopathy (n) | 18/67 |
| Microalbuminuria (n) | 29/73 |
| Oral antidiabetics (n) | 41/76 |
| Insulin (n) | 35/76 |

### BMD measurements

Lumbar spine (LS; L2-L4) BMD , femoral neck (FN) BMD, and total hip (TH) BMD were measured by DXA using the DXA system (Lunar Prodigy; GE Healthcare, Madison WI). Results are expressed as absolute values in grams per square centimeter.

### QUS measurements

Ultrasound data were obtained using the Sunlight Omnisense 7000P device (Sunlight Medical Ltd., Petach Tikva, Israel) equipped with probes specifically designed for the measurement of axial speed of sound (SOS; meters per second) along the surface of bone. Measurements of SOS were obtained at the distal third of the radius, proximal phalanx of the third finger, and at the midshaft of the tibia on the patient's nondominant side. Quality control measurements of the Omnisense instrument were acquired daily using an SOS verification phantom provided by the manufacturer. From repeated consecutive measurements in 10 nondiabetic individuals, the precision of the QUS measurements was 1.0% (radius), 0.8% (phalanx), and 0.6% (tibia).

### Statistical analyses

All statistical analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL). Data are expressed as mean (SD). Two-tailed student's *t* test was used to compare mean values between patients with T2DM and nondiabetic controls. The difference between groups was adjusted for age and BMI. The correlation between DXA values and multisite SOS measurements was analyzed by Pearson's correlation coefficient. Independent factors including T2DM, age, years since menopause (YSM) and BMI, and dependent factors including BMD at the LS, FN, and TH as well as SOS measurements at $SOS_R$, $SOS_P$, and $SOS_T$ were included in the multiple stepwise regression analysis. In the T2DM group, factors substantially influencing the DXA BMD and SOS measurements were identified by multiple stepwise regression analysis. These factors consisted of age, YSM, duration of diabetes, and $HbA_{1c}$levels. $P < 0.05$ was considered statistically significant.

## Results

### Comparison of DXA and QUS values between T2DM and nondiabetic postmenopausal women

There was no significant difference in age, BMI, and YSM between the T2DM and CTR groups ($P > 0.05$) (Table 2). In the T2DM group, BMD values at the LS, FN, and TH were significantly higher than those in nondiabetic women. (LS, 1.06 ± 0.12 *vs.* 0.90 ± 0.23 g/cm$^2$; FN, 0.80 ± 0.13 *vs.* 0.74 ± 0.12 g/cm$^2$; TH, 0.87 ± 0.14 *vs.* 0.80 ± 0.13 g/cm$^2$, $P < 0.001$) (Fig. 1A),

**TABLE 2.** Comparison of age, BMI, and years since menopause between patients with T2DM and nondiabetic controls

| | n | Age (yr) | BMI (kg/m$^2$) | YSM (yr) |
|---|---|---|---|---|
| T2DM | 76 | 64.1 ± 9.3 | 24.2 ± 3.8 | 15.0 ± 9.8 |
| Nondiabetic CTRs | 86 | 66.5 ± 6.5 | 24.1 ± 4.1 | 16.9 ± 6.5 |
| *P* value | | NS | NS | NS |

NS, Not significant.

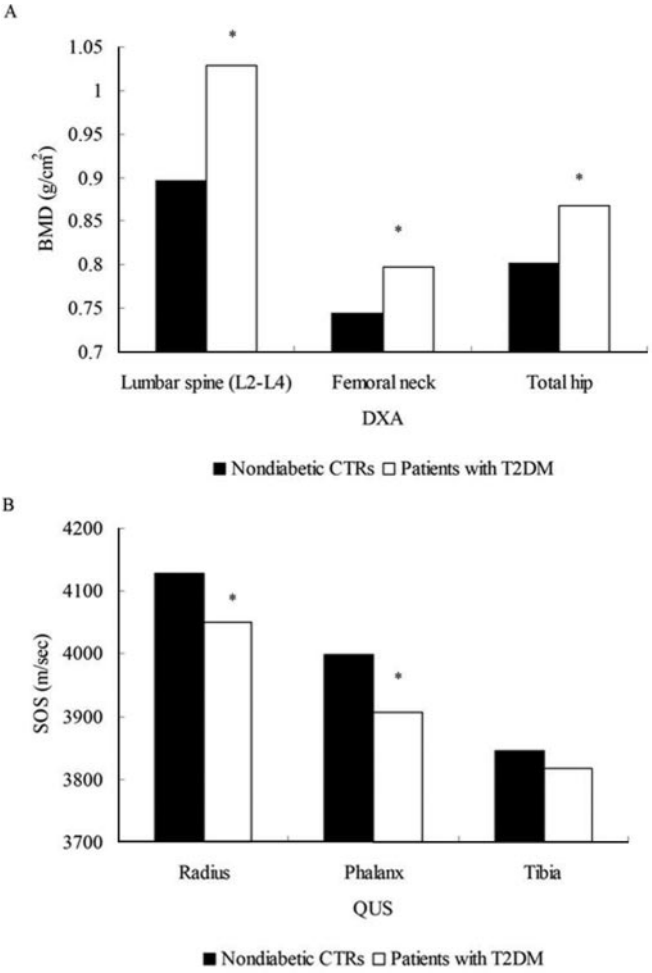


**FIG. 1.** Comparison of DXA BMD (A) and qualitative ultrasound speed of sound (B) measurements between patients with T2DM and nondiabetic controls. *, $P < 0.001$, compared with nondiabetic controls.

whereas SOS measurements at the radius and phalanx were significantly lower than those in the nondiabetic control group (radius, 4044 ± 178 *vs.* 4129 ± 182 m/sec; phalanx, 3902 ± 207 *vs.* 3999 ± 214 m/sec, $P < 0.001$). The SOS value at the tibia was also lower in the T2DM group but did not reach statistical significance (3815 ± 148 *vs.* 3845 ± 139 m/sec, $P > 0.05$) (Fig. 1B).

### Correlation analysis of DXA with QUS in T2DM and nondiabetic subjects

In nondiabetic CTRs, there was a moderate and significantly positive relationship between SOS and BMD measurements (r = 0.26–0.75, $P < 0.05$). However, such a relationship was diminished and even eliminated in women with T2DM. Only the SOS measurement at the phalanx had a positive association with BMDs (r = 0.41–0.50, $P < 0.05$) but with weakened coefficiency. The SOS measurement at the radius was only correlated with FN-BMD (r = 0.27, $P < 0.05$), and no correlation was found between tibial SOS and BMDs (r = 0.05–0.16, $P > 0.05$) (Table 3).

### Multiple stepwise regression analysis of factors contributing to the QUS and DXA measurements

In all patients, the results showed the negative impact of T2DM on SOS measurements at the radius and phalanx (radius, $R^2 = 0.05$, $\beta = -0.223$, $P < 0.01$; phalanx, $R^2 = 0.048$, $\beta = -0.219$, $P < 0.01$). When BMD at the LS, FN, and TH were used as independent factors, the multiple stepwise regression analysis showed the positive impact of T2DM on BMDs (LS, $R^2 = 0.234$, $\beta = 0.314$, $P < 0.001$; FN, $R^2 = 0.177$, $\beta = 0.173$, $P < 0.05$; TH, $R^2 = 0.204$, $\beta = 0.203$, $P < 0.01$). BMI also had a positive impact on BMDs (LS, $\beta = 0.173$, $P < 0.01$; FN, $\beta = 0.165$, $P < 0.01$; TH, $\beta = 0.306$, $P < 0.001$). However, YSM exerted a negative effect on BMDs (LS, $\beta = -0.6$, $P < 0.05$; FN, $\beta = -0.335$, $P < 0.001$; TH, $\beta = -0.252$, $P < 0.01$).

In patients with T2DM, the effects of duration of diabetes, age, YSM, BMI, and $HbA_{1c}$ levels on SOS and BMD measurements were evaluated. Multiple stepwise regression analysis revealed that a longer duration of diabetes was significantly associated with lower SOS measurements at the radius ($R^2 = 0.088$, $\beta = -0.297$, $P < 0.05$).

YSM was the only parameter affecting BMD values (LS, $R^2 = 0.053$, $\beta = -0.704$, $P < 0.01$; FN, $R^2 = 0.1163$, $\beta = -0.403$, $P < 0.001$; TH, $R^2 = 0.073$, $\beta = -0.271$, $P < 0.05$). Other factors such as age, BMI, diabetes duration, and $HbA_{1c}$ levels were all excluded from the regression model.

## Discussion

This is the first study to compare the differences in bone mass measured by DXA and QUS among patients with T2DM and nondiabetic controls. We found that in patients with T2DM, BMD measured by DXA was significantly higher at the LS, FN, and TH, whereas the ultrasound SOS measurements were significantly lower at the radius and phalanx, compared with nondiabetic controls. The SOS value at the tibia was also lower (but not significantly) in the T2DM group. These results may help to explain the increased risk of fractures in patients with T2DM that have been reported in the literature despite increased BMD as measured by DXA (1–6).

**TABLE 3.** Correlation coefficients of DXA BMD and QUS SOS between postmenopausal patients with T2DM and nondiabetic controls

| | T2DM | | | Nondiabetic CTRs | | |
|---|---|---|---|---|---|---|
| | Radial SOS | Phalangeal SOS | Tibial SOS | Radial SOS | Phalangeal SOS | Tibial SOS |
| LS (L2-L4) BMD | 0.15 (NS) | 0.41 ($P < 0.05$) | 0.05 (NS) | 0.26 ($P < 0.05$) | 0.51 ($P < 0.05$) | 0.40 ($P < 0.05$) |
| FN BMD | 0.27 ($P < 0.05$) | 0.50 ($P < 0.05$) | 0.16 (NS) | 0.35 ($P < 0.05$) | 0.75 ($P < 0.05$) | 0.29 ($P < 0.05$) |
| TH BMD | 0.20 (NS) | 0.46 ($P < 0.05$) | 0.11 (NS) | 0.30 ($P < 0.05$) | 0.61 ($P < 0.05$) | 0.30 ($P < 0.05$) |

NS, Not significant.

Multiple regression analysis performed in the total study population showed that T2DM and BMI were positively related to BMD measured by DXA. It has been suggested that the often observed increase in BMI in diabetics tends to be protective and decreases the risk of fractures by increasing BMD (5). However, further analysis conducted in our T2DM group showed that BMI is not a determinant of BMD, indicating that higher BMD in T2DM is independent of BMI. Indeed, several studies have demonstrated that increased BMD in the FN and LS in patients with T2DM persists, even after adjustments for age, weight, and/or BMI (6, 12). Thus, the increased BMD cannot simply be attributed to the greater BMI of T2DM patients. In fact, in our study the mean BMIs of T2DM and CTR groups was similar.

Unlike previous studies that reported a weak negative correlation between diabetic duration and BMD (13), our data found no such association, which is in accordance with the results from Vestergaard's metaanalysis performed in diabetic patients (14). It is well recognized that the onset of T2DM begins nearly 5–10 yr before the diagnosis of the disorder. Indeed, the term, time since diagnosis, may be more appropriate than the term, duration of diabetes, as suggested by Hofbauer *et al.* (15). As a consequence, it is very difficult to accurately estimate the impact of real diabetic duration on BMD. Interestingly, an increased BMD has been observed around the time of diagnosis of T2DM (5).

Although hyperglycemia may itself be associated with several adverse effects on bone, the effects of glycemic control on BMD are controversial. Majima *et al.* (16) reported a negative correlation between FN and distal radius BMD and the mean $HbA_{1c}$ level. In addition, Gregorio *et al.* (17) observed that the decline in BMD in poorly controlled diabetic patients increased with improvement of metabolic control. However, in one of the most recent metaanalyses of bone metabolism in diabetes, $HbA_{1c}$ levels were not linked to BMD (14). Similarly, no relationship between $HbA_{1c}$ and BMD was found in our study. It may be that the effects of metabolic control, such as fasting glucose or $HbA_{1c}$, are reflected by bone turnover markers but not BMD (18, 19).

Because more fractures are seen in patients with chronic diabetic complications (such as retinopathy and cataracts) (3, 5), the importance of glycemic control in these patients is still paramount, despite the finding that $HbA_{1c}$ levels do not appear to be directly linked to BMD.

It is important to note that even with higher BMD, patients with T2DM experienced higher rates of fractures, compared with nondiabetic controls (1–5). For example, in a large-scale prospective study, it was shown that after a mean follow-up of 7 yr, there was a higher rate of fracture among women with T2DM (3). Yamamoto *et al.* (20) also reported that lumbar BMD was not significantly associated with the presence of vertebral fractures in patients with T2DM. These results indicate that BMD may not be sensitive enough to evaluate and predict fracture risk in patients with T2DM and that BMD measurement by DXA may not be the best standard for assessing bone quality in these patients (20).

However, QUS is a possible candidate for providing more direct information relating to fracture risk in these patients (9, 10). In our study, the ultrasound parameter SOS was lower in patients with T2DM than in CTRs. The reduction in SOS measurements in T2DM patients was further confirmed by the multiple regression analysis in all study participants. We found that T2DM, independent of age, YSM, and BMI, is associated with a negative impact on SOS, opposite to its positive impact on BMD as measured by DXA. We also observed that the consistently positive correlations between SOS and BMD seen in nondiabetic CTRs were diminished and even eliminated in the T2DM group. These results clearly demonstrate that in patients with T2DM, BMD does not change in parallel with the SOS measurement. The finding of a significant association between BMD and vertebral fracture risk in nondiabetic individuals but not T2DM subjects (20) further supports the idea that BMD may not capture essential elements of fracture risk in the T2DM population.

Fractures in patients with T2DM commonly occur at nonvertebral sites, such as the hip, humerus, tibia, fibula, patella, and foot (3, 4). QUS devices are more accessible for measuring peripheral cortical bones, and this makes the QUS measurement more helpful for assessing bone status, especially in T2DM. After comparing BMD measurements at sites with a different cortical/cancellous bone ratio, Christensen and Svendsen (21) reported that the BMD at the distal radius was the lowest, followed by the total femur and LS. Selective cortical bone loss was also demonstrated in another study (16) and from bone biopsy samples in patients with T2DM (22). Other studies have confirmed the potential sensitivity of QUS at the radius to changes in cortical bone (23, 24) and showed that the transmission of QUS at three sites was sensitive enough to detect the material properties of cortical bone. Taken together, it is reasonable to suggest that QUS is more helpful than DXA in the evaluation of fracture risk among patients with T2DM.

In contrast to the lack of association between duration of diabetes and BMD observed in our study, the duration of diabetes was a negative determinant of SOS. The higher fracture rates in T2DM reported in the literature, together with the overall lower SOS measurements in patients with T2DM and the negative impact of T2DM on SOS reported in our study, may indicate that QUS is an useful tool in detecting the impaired bone quality in T2DM subjects.

The mechanisms of impaired bone quality in patients with T2DM are complex. The formation of advanced glycation endproducts (AGE) is one of the hypotheses. The nonenzymatic glycosylation of type I collagen matrix can alter osteoblastic growth and inhibit osteoblast differentiation. The accumulation of AGE on bone extracellular matrix could also contribute to the decrease in osteoblastic function (25).

In animal models, the bones of diabetic rats with a high content of pentosidine (one kind of glycation-induced nonenzymatic cross-links) showed impaired biomechanical properties on the three-point bending test (26). These findings indicated that diabetogenic overglycosylation may impair bone quality. In fact, the receptor for AGEs (RAGE) is expressed in all stages of osteoblastic development; the AGEs-induced biological effects observed in osteoblasts could be mediated by RAGE, with the involvement of the ERK signal transduction pathway (27). RAGE mRNA has also been found to be present on osteoclast-like cells (28). AGEs, mediating through RAGE, could stimulate the apoptosis of osteoblastic cells *in vitro* (29). $RAGE^{-/-}$ mice have a

significantly increased bone mass and bone biomechanical strength, and a decreased number of osteoclasts compared with wild-type mice. $RAGE^{-/-}$ mice could even maintain bone mass after ovariectomy, indicating that RAGE could act as a positive factor in regulating osteoclast formation.

In addition to bone quality, extraskeletal factors such as falls and poor vision and other chronic diabetic complications may also account for the higher fracture risks in patients with T2DM (14, 30). It has been reported that the incidence of falls in diabetic patients is 25%, compared with 15% in nondiabetic subjects (5). However, even after adjustment for age, body weight, a history of falls, poor vision, and other factors, the adjusted relative risk of any fractures in diabetic patients is still about 20% higher than that in the control group (3).

There are a number of limitations of this study. First, we do not have direct data on the incidence of fractures. Thus, it cannot be concluded that the differences in SOS measurements between the T2DM and CTR groups explain the higher fracture risk in patients with T2DM. However, the usefulness of QUS in discriminating individuals with or without fractures has been reported. For example, SOS measured at the radius clearly separated subjects with hip fracture from those without hip fracture (31). Similarly, in a recent community-based study, SOS at the phalanx was found to be significantly lower in postmenopausal women with a history of nonvertebral fracture (32). Other cross-sectional and prospective studies have reported an association between low SOS at the calcaneus and hip fracture (8, 33).

The other limitation of this study is that we did not measure other parameters of QUS, such as broadband ultrasound attenuation (BUA)/stiffness and quantitative ultrasound index (QUI), simply because of the inability to test these variables using our QUS device.

It has been suggested that BUA is more suitable for quantitative analysis of low-density trabecular bone (34). However, the device we used was specifically designed for measurement of sound velocity at skeletal sites such as the radius, phalanx, tibia, and metatarsals, thereby focusing on the properties of cortical bone. Sound velocity measured by this axial transmission device has enough capacity to detect bone deterioration in stiffness, strength, and toughness (10, 23). In one report, it was suggested that SOS measurements presented a greater adjusted odds ratio than stiffness index (SI; a composite parameter derived from BUA and SOS) and BUA for fractures (35).

Because QUS measures speed of sound at the surface of multiple skeletal sites, rather than using a distance technique such as DXA, the influence of obesity or body weight and fat distribution on the measurement results should be considered. Tromp *et al.* (36) found that, after adjustments for body weight, correlations of tibia and calcaneal QUS with BMD improved, suggesting the importance of correction for body weight for QUS parameters. However, in two large-scale studies conducted in healthy women, SOS and BUA did not appear to be as strongly influenced by total body mass or lean mass and fat mass, as did BMD (37, 38). Body adiposity accounted for less than 11% of the differences between the peripheral and central DXA measurements and QUS (39). It is well documented that ultrasound variables are influenced mainly by bone strength, as reflected by the cortical density near the surface and the cortical thickness (10, 40).

In conclusion, the present study compared differences in bone mass measurement using two different methods, namely DXA and QUS, in postmenopausal women with T2DM and nondiabetic controls. Our results indicated that QUS may have greater promise than DXA in detecting bone defects in patients with T2DM.

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