# Circulating Levels of Sclerostin Are Increased in Patients with Type 2 Diabetes Mellitus

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**Context:** Diabetes mellitus is a risk factor for osteoporotic fractures. Sclerostin is an inhibitor of bone formation. However, there are no data about sclerostin levels in type 2 diabetes mellitus (T2DM).

**Objectives:** The aims were to evaluate serum sclerostin in T2DM patients and to analyze its relationship with bone metabolism.

**Design, Setting, and Patients:** This was a cross-sectional study. We compared serum sclerostin in the T2DM group (n = 74) and control group (n = 50), and we analyzed its relationship with calciotropic hormones, bone turnover markers, bone mineral density (BMD), and morphometric vertebral fractures.

**Results:** Sclerostin levels were significantly higher in T2DM patients than control subjects ($P < 0.001$) and in T2DM males than in T2DM females ($P < 0.001$). Serum sclerostin was positively correlated with age in males T2DM ($P = 0.031$). In linear regression analysis, gender, study group, and age were predictive of sclerostin levels ($P < 0.05$). Sclerostin concentrations were positively associated with duration of T2DM ($P = 0.064$) and glycated hemoglobin ($P = 0.074$) independently of age in T2DM patients. Sclerostin was inversely related to bone turnover markers ($P < 0.05$) and positively related to lumbar spine, femoral neck, and total hip BMD ($P < 0.05$) in the T2DM group. Sclerostin was significantly lower in osteoporotic than nonosteoporotic patients with T2DM ($P = 0.048$).

**Conclusions:** Circulating sclerostin is increased in T2DM independently of gender and age. Serum sclerostin is also correlated with duration of T2DM, glycated hemoglobin, bone turnover markers, and BMD in T2DM patients. Additional studies are needed to evaluate the role of sclerostin on bone metabolism in this population. **(*J Clin Endocrinol Metab* 97: 234–241, 2012)**

Diabetes mellitus and osteoporosis are diseases with an increasing prevalence in the aging population and a substantial morbidity and mortality. The relationship between both medical conditions is complex and remains controversial, although it has been investigated extensively. Type 2 diabetes mellitus (T2DM) has been associated with an increased risk of fractures at any skeletal site because of the poorer quality of the bone, even when with greater bone mineral density (BMD) (1, 2). This association is due to detrimental effects of impaired glucose me-

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Abbreviations: BALP, Bone alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; CTX, carboxyl-terminal cross-linked telopeptide of type I collagen; DXA, dual-energy x-ray absorptiometry; FN, femoral neck; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; iPTH, intact PTH; LRP, lipoprotein receptor-related protein; LS, lumbar spine; T2DM, type 2 diabetes mellitus; TH, total hip; TRAP5b, tartrate-resistant acid phosphatase 5b.

tabolism on bone health (3) as well as to an increased risk of falls, frequently reported in diabetic patients (4). Moreover, some complications of diabetes may also contribute to fracture risk (5, 6).

The discovery of the Wnt signaling pathway and its relevance in bone homeostasis has contributed to a better knowledge of the cellular and molecular mechanisms of bone remodeling (7). The Wnt family includes more than 15 proteins that play an important role in organ development and in the regulation of various adult tissues such as bone. Activation of this pathway results in an expansion of osteoprogenitor cells as well as reduced apoptosis of osteoblast, leading to anabolic effects on bone (8). The binding of the Wnt ligands to a coreceptor complex composed of seven-transmembrane domain-spanning frizzled receptor and low-density lipoprotein receptor-related protein (LRP)-5 or -6 stabilizes cytoplasmic $\beta$-catenin protein, which translocates into the nucleus and activates the transcription of target genes, namely *Runx-2* and osteoprotegerin (9, 10). One of the major regulators of the Wnt pathway is the product of the *SOST* gene, sclerostin, which is expressed almost exclusively in osteocytes. It is a secreted Wnt antagonist that acts on bone mass by competitive binding to LRP-5 (11, 12).

The role of the Wnt signaling pathway may be crucial in the pathogenesis of impaired bone quality observed in diabetes mellitus. Data regarding this pathway in diabetes mellitus are limited to animal models and have focused on the analysis of gene expression or concentration of the major proteins in the bone environment (13, 14). However, to our knowledge, no studies had been conducted in humans and more specifically in T2DM.

In this context, the objectives of our study were to evaluate serum sclerostin levels in a cohort of T2DM patients and to analyze its relationships with bone turnover markers, BMD, and morphometric vertebral fractures. In addition, we compared serum sclerostin levels of T2DM with a control group of healthy subjects.

## Subjects and Methods

### Study population

Our study was a cross-sectional one that included a T2DM group and a control group. T2DM group included 74 patients with diagnosis of diabetes according to American Diabetes Association criteria (15). From January 2006 to December 2007 we consecutively recruited patients who had been referred to our outpatient clinic from community clinics for treatment of diabetes. The control group included 50 age-matched subjects who were consecutively recruited from the general community in the same period of time.

All participants were recruited according to the following criteria: Caucasian, free-living, ages from 35–65 yr, and normal values for blood count, renal creatinine, hepatic function, calcium. and phosphorus. Exclusion criteria were chronic diseases apart from T2DM in a specific group, known diseases affecting bone (Paget's disease, rheumatoid arthritis, hyperparathyroidism, hypercortisolism, malignant tumors, renal bone disease, chronic liver disease, and posttransplantation bone disease) and previous or current treatment with drugs affecting bone metabolism (calcium supplements, vitamin D preparations, selective estrogen receptor modulators, calcitonin, estrogens therapy, antiresorptive therapy, thiazides, steroids, glucocorticoids, or anticonvulsants).

The study was approved by the ethical review board of our hospital and was done conforming to the ethics guidelines for research in humans. All the participants in the study provided written informed consent.

### Clinical evaluation

Anthropometric data collected was body mass index (BMI) calculated by the Quetelet formula (weight in kilograms divided by the square of height in meters). Physical activity was collected through a specific questionnaire in which study subjects considered it on a scale from 0 (none) to 10 (sport more than an hour four times per week). Based on the results, the study sample was divided into two groups: sedentary ($<5$ on the scale) and no sedentary ($\geq 5$ on the scale).

### Serum measurements

Samples of venous blood were taken in the morning after fasting overnight. Sera were stored at −80 C until examination. Fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), calcium, phosphorus, and creatinine were measured using standard automated laboratory techniques. Glomerular filtration rate was estimated by Cockcroft-Gault equation.

Calciotropic hormones measurement included serum intact PTH (iPTH) (two-site immunoassay for iPTH; Roche Diagnostics SL, Barcelona, Spain; intra- and interassay variability of 3%) and 25-hydroxyvitamin D RIA (DiaSorin, Stillwater, MN). Bone turnover markers were measured as follows: total osteocalcin by RIA (DiaSorin; intra- and interassay variability of 5.3 and 8.6%, respectively); bone alkaline phosphatase (BALP) by an ELISA (Tandem-R Ostase; Hybritech Europe, Liege, Belgium; intra- and interassay variability of 4.2 and 7.2%, respectively); serum carboxyl-terminal cross-linked telopeptide of type I collagen (CTX) by enzyme immunoassay (Elecsys [$\beta$] CrossLaps; Roche Diagnostics; intra- and interassay variability of 4.2 and 5.1%, respectively), and tartrate-resistant acid phosphatase 5b (TRAP5b) by bone TRAP assay (IDS Ltd., Bensheim, Germany; intra- and interassay variability of 4.7 and 9%, respectively).

Serum sclerostin was measured using quantitative sandwich ELISA developed by Biomedica (Vienna, Austria). In our laboratory, two samples of known concentrations were tested six times to assess intraassay variability (4%), and two samples of known concentrations were tested in three assays to assess interassay variability (3%). Sclerostin measurements are reported throughout in picomoles per liter, and lower limit of detection was less than 10 pmol/liter.

### Bone density measurement and vertebral fractures assessment

BMD at lumbar spine (LS) L2–L4, femoral neck (FN), and total hip (TH) was performed in all patients by dual-energy x-ray

absorptiometry (DXA) using Hologic QDR 4500 densitometer (Waltham, MA; variation coefficient <1%). All BMD measurements were done by the same experienced operator. We used the World Health Organization criteria for osteoporosis (16).

Standardized spinal x-rays were taken for morphometric analysis of all participants of the study and interpreted according to the algorithm developed by McCloskey *et al.* (17).

### Statistical analysis

Data for continuous variables are presented as mean ± SD. Data for categorical variables are presented as numbers and/or percentages. Kolmogorov-Smirnov test was used to test the normality of distribution of continuous variables. Associations between continuous variables were described by Pearson's or Spearman's correlation coefficients. Comparisons of categorical variables among groups were performed using $\chi^2$ test or Fisher's test. Comparisons of continuous variables among groups were performed using unpaired Student's *t* test or Mann-Whitney *U* test. Linear regression models were used to determine the influence of independent variables on serum sclerostin levels (dependent variable). Statistical significance was set at $P < 0.05$ (two-tailed). Statistical analysis was performed with specific software, SPSS version 15.0.

## Results

### Baseline characteristics of the study population

Table 1 shows the clinical characteristics and biochemical and DXA parameters of the study population.

T2DM and control groups were comparable in most of baseline characteristics. As expected by the inclusion criteria, mean FPG and HbA1c were significantly higher in the T2DM group than in the control group ($P < 0.001$). Serum iPTH levels were lower in T2DM patients than in controls ($P = 0.002$). Bone resorption markers were also lower in T2DM patients than in controls ($P < 0.05$). There was a significant difference in physical activity between T2DM patients and control subjects ($P = 0.04$).

### Serum sclerostin in T2DM patients and controls

Sclerostin levels were significantly higher than control subjects in T2DM males plus females (54.58 ± 24.98 *vs.* 42.1 ± 16.23 pmol/liter, $P < 0.001$) and in T2DM males (63.15 ± 27.03 *vs.* 46.77 ± 18.31 pmol/liter, $P = 0.005$) but were not statistically significantly increased in T2DM females (43.92 ± 17.28 *vs.* 37.8 ± 12.95 pmol/liter, $P = 0.138$).

We found that serum sclerostin concentrations were significantly higher in males than in females, both in the T2DM group (63.15 ± 27.03 *vs.* 43.92 ± 17.28 pmol/liter, $P < 0.001$) and control group (46.77 ± 18.31 *vs.* 37.8 ± 12.95 pmol/liter, $P = 0.048$) (Fig. 1).

In T2DM males and control subjects, sclerostin levels were positively correlated with age (r = 0.338, $P = 0.031$; and r = 0.451, $P < 0.001$, respectively), but there was no relationship in T2DM females (r = 0.223; $P = 0.213$). In contrast, a significant relationship between serum sclerostin, BMI, and physical activity was not found.

When linear regression analysis was done to determine the independent variables that explain serum sclerostin levels, gender ($\beta = 0.320$; $P < 0.001$), study group ($\beta = 0.225$; $P = 0.006$), and age ($\beta = 0.185$; $P = 0.025$) remained significant.

In T2DM patients, sclerostin concentrations were positively associated with duration of T2DM ($\beta = 0.223$; $P = 0.064$) and HbA1c ($\beta = 0.211$; $P = 0.074$) independently

**TABLE 1.** Characteristics of study population

| | T2DM group (n = 74) | Control group (n = 50) | *P* value |
|---|---|---|---|
| Age (yr) | 57.7 ± 6.5 | 56.4 ± 6 | 0.232 |
| Male/female (n) | 41/33 | 24/26 | 0.418 |
| Height (m) | 1.6 ± 0.1 | 1.6 ± 0.1 | 0.167 |
| Weight (kg) | 82 ± 16.2 | 78.4 ± 13.7 | 0.197 |
| BMI (kg/m$^2$) | 31.2 ± 5.8 | 29.2 ± 6 | 0.064 |
| Sedentary (%) | 52.7 | 34 | 0.04 |
| Diabetes duration (yr) | 13.5 ± 7.5 | | |
| Serum parameters | | | |
| FPG (mg/dl) | 176.1 ± 63.2 | 89.9 ± 10.7 | <0.001 |
| HbA1c (%) | 8.1 ± 1.9 | 4.9 ± 0.4 | <0.001 |
| Creatinine (mg/dl) | 0.9 ± 0.19 | 0.87 ± 0.17 | 0.304 |
| GFR(ml/min/1.73 m$^2$) | 93.5 ± 27.2 | 92.9 ± 20.4 | 0.907 |
| Calcium (mg/dl) | 9.6 ± 0.5 | 9.4 ± 0.4 | 0.093 |
| Phosphorus (mg/dl) | 3.7 ± 0.6 | 3.5 ± 0.5 | 0.102 |
| iPTH (pg/ml) | 38.8 ± 18.1 | 49.9 ± 19.5 | 0.002 |
| 25(OH)D (ng/ml) | 17.1 ± 10.5 | 19.8 ± 9.9 | 0.159 |
| OC (ng/ml) | 1.49 ± 1.27 | 1.5 ± 1.26 | 0.939 |
| BALP (μg/liter) | 14.91 ± 6.57 | 13.48 ± 6.8 | 0.253 |
| CTX (ng/ml) | 0.212 ± 0.13 | 0.349 ± 0.154 | <0.001 |
| TRAP5b (UI/liter) | 1.38 ± 1 | 1.86 ± 0.84 | 0.008 |
| Sclerostin (pmol/liter) | 54.56 ± 24.98 | 42.11 ± 16.23 | 0.001 |
| DXA parameters: | | | |
| BMD LS (g/cm$^2$) | 0.953 ± 0.138 | 0.997 ± 0.148 | 0.107 |
| BMD FN (g/cm$^2$) | 0.823 ± 0.128 | 0.812 ± 0.112 | 0.62 |
| BMD TH (g/cm$^2$) | 0.909 ± 0.141 | 0.905 ± 0.122 | 0.848 |
| T-score LS | −1.3 ± 1.3 | −0.9 ± 1.3 | 0.094 |
| T-score FN | −0.56 ± 1 | −0.60 ± 0.92 | 0.803 |
| T-score TH | −0.58 ± 1 | −0.57 ± 0.87 | 0.965 |
| Osteoporosis (%) | 21.9 | 10.2 | 0.1 |
| Morphometric VF (%) | 26.5 | | |

Data for continuous variables are presented as mean ± SD. Data for categorical variables are presented as numbers and/or percentages. GFR, Glomerular filtration rate; OC, osteocalcin; 25(OH)D, 25-hydroxyvitamin D; VF, vertebral fractures.

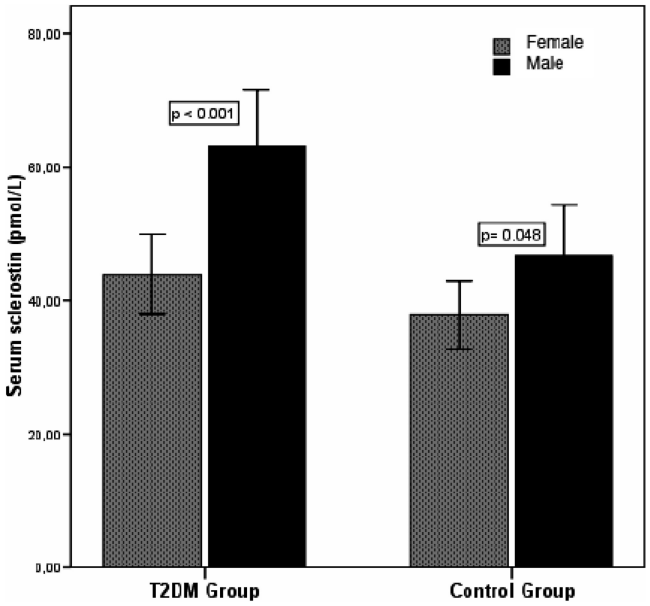


**FIG. 1.** Serum sclerostin levels in T2DM group and control group according to gender.

of age (Fig. 2). A significant relationship between serum sclerostin and diabetes complications was not found.

### Serum sclerostin levels, calciotropic hormones, and bone turnover markers

There was an inverse association between sclerostin concentrations and PTH levels ($\beta = -0.185$; $P = 0.033$) in the entire cohort and T2DM group ($\beta = -0.204$; $P = 0.087$), independently of age and creatinine.

In the total sample, sclerostin levels were negatively correlated with CTX ($r = -0.388$; $P < 0.001$) and TRAP5b ($r = -0.305$; $P < 0.001$). In the T2DM group, sclerostin concentrations were negatively correlated with BALP ($r = -0.277$; $P = 0.021$), CTX ($r = -0.363$; $P = 0.002$), and TRAP5b ($r = -0.276$; $P = 0.02$) (Fig. 3).

### Serum sclerostin levels, BMD, and morphometric vertebral fractures

Both in T2DM patients and control subjects, unadjusted and age-adjusted LS, FN, and TH BMD and T-score were positively related to serum sclerostin (Table 2).

In T2DM osteoporotic patients, sclerostin levels were 44.03 ± 19.41 pmol/liter, significantly lower compared with T2DM nonosteoporotic patients (56.95 ± 25.98 pmol/liter, $P = 0.048$). Also, in control subjects, sclerostin levels were lower in osteoporotic patients, but differences were not significant (33.25 ± 11.66 *vs.* 42.82 ± 16.55 pmol/liter, $P = 0.176$). In contrast, a significant relationship with morphometric vertebral fractures was not found in T2DM patients.

## Discussion

Our results show higher serum sclerostin in T2DM patients compared with control subjects independently of gender and age. Sclerostin levels are negatively correlated with bone turnover markers and positively related to duration of T2DM, HbA1c, and BMD in T2DM patients. Also, we found lower sclerostin concentrations in T2DM with osteoporosis than in T2DM without osteoporosis. These findings suggest that the Wnt signaling pathway is impaired in T2DM, and this dysfunction can affect bone quality in this population.

In a recent study investigating the disturbances in the Wnt signaling pathway induced by type 1 diabetes mellitus in mice, down-regulation of sclerostin, increased osteo-

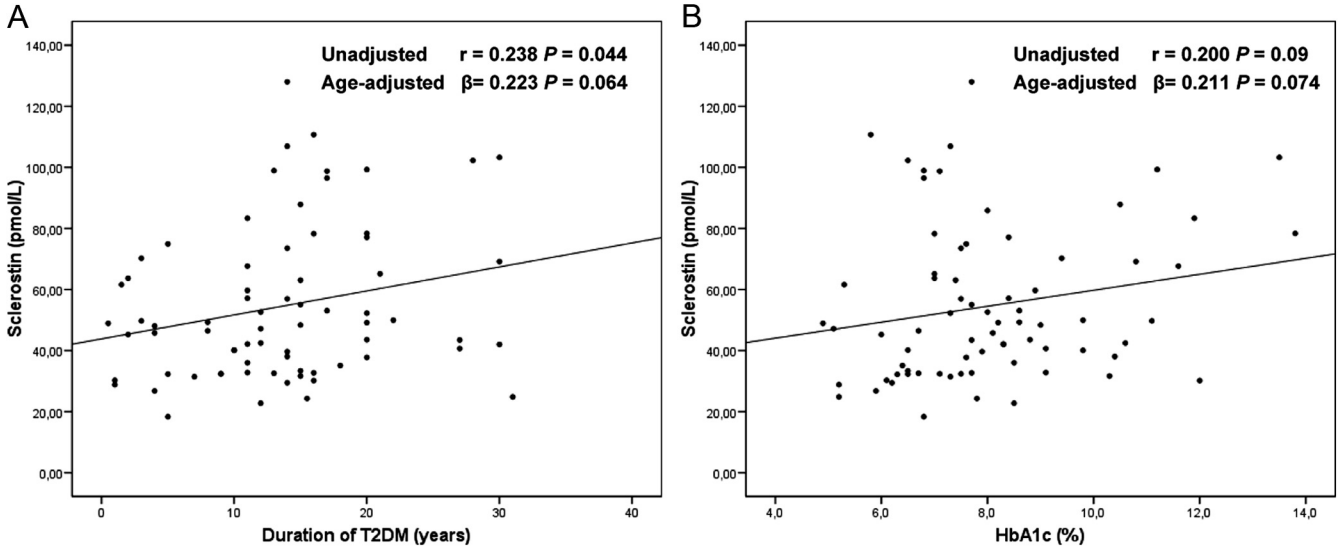


**FIG. 2.** Scatter plot showing the correlation (Pearson's test) between serum sclerostin and duration of T2DM (A) and HbA1c (B) in T2DM patients.

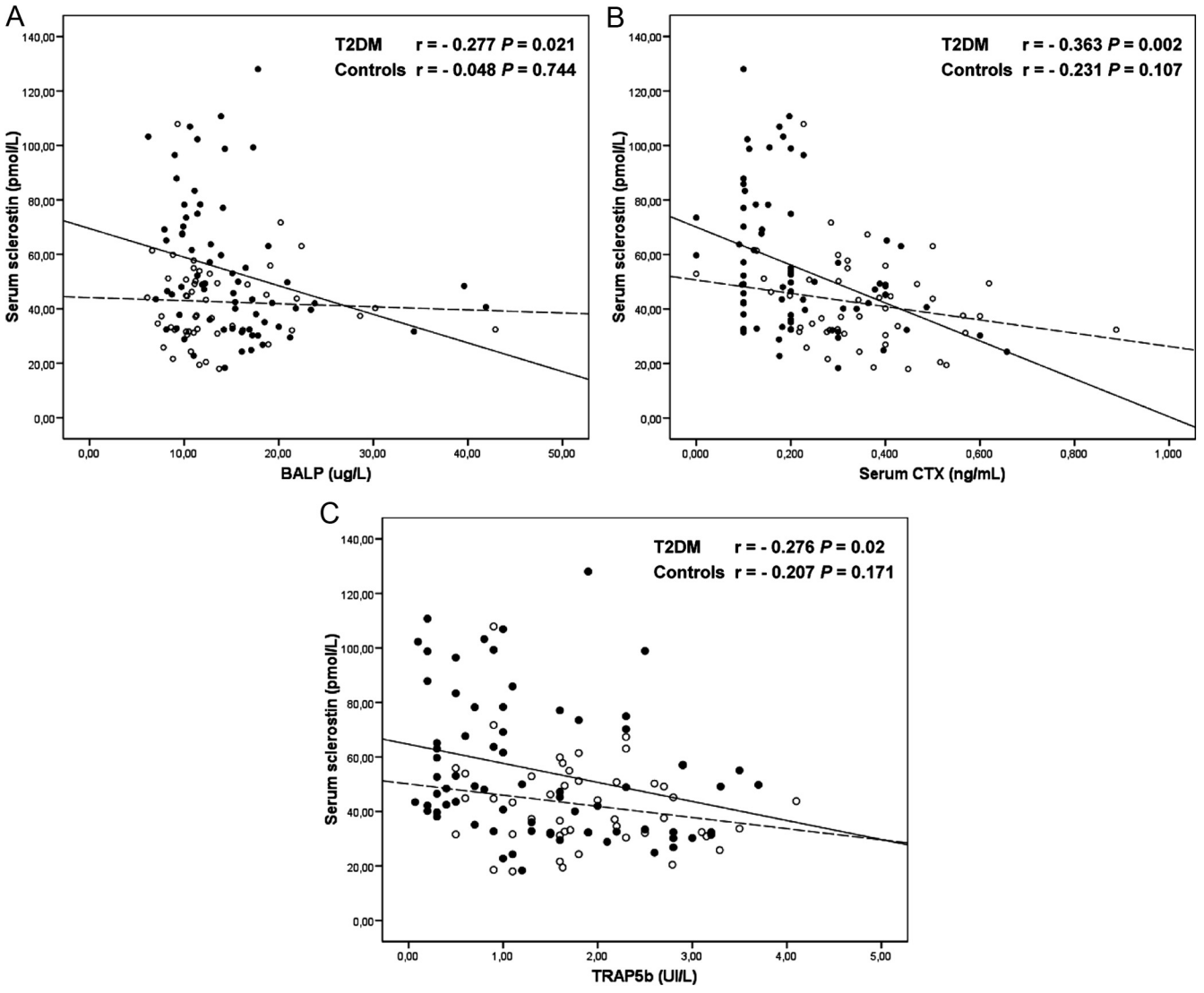


**FIG. 3.** Scatter plot showing the correlation (Pearson's test) between serum sclerostin levels and BALP (A), serum CTX (B), and TRAP5b (C) in T2DM patients (*closed circles* and *solid line*) and control subjects (*open circles* and *dashed line*).

cyte apoptosis, and lower total and nuclear β-catenin staining were found (13). On the other hand, Nuche-Berenguer *et al.* (14) demonstrated up-regulation of gene expression of *Dkk1* and *SOST* in T2DM rats and found *SOST* overexpression associated with increased mRNA levels of the activator *LRP5* in insulin-resistant rats. Serum levels of sclerostin in T2DM patients have not been previously analyzed. We found that sclerostin levels were significantly higher in the T2DM group than in control group independently of gender and sex. However, sclerostin levels were not statistically significantly increased in T2DM females. In our cohort, PTH levels were lower in T2DM patients compared with control subjects, and sclerostin levels were negatively associated with PTH in total sample. These finding are consistent with phosphocalcic balance alterations described in T2DM (18) and could explain in part the increase in sclerostin that we observed in T2DM. The reduced effect of PTH on bone might decrease inhibition of the *SOST* gene, which would stimulate the expression of sclerostin, an inverse situation to that described in patients with primary hyperparathyroidism (19). Furthermore, if sclerostin expression is decreased by mechanical loading of the skeleton, low physical activity, which is often found in patients with T2DM, might contribute to the elevation of sclerostin serum levels. This association has been noted before in immobilized patients (20). We also found that sclerostin concentrations were positively associated with duration of T2DM and HbA1c. Hyperglycemia has both a direct effect on bone cells and indirect effects through the formation of advanced glycation end-products that have been shown to reduce bone strength (3). Also, sclerostin glycosylation or glycation could explain the increase in sclerostin levels in T2DM, and this hypothesis is very stimulating to additional investigations.

The influence of age in sclerostin levels is being increasingly studied. Osteoblastic expression of each Wnt-related

**TABLE 2.** Unadjusted and age-adjusted correlation coefficients between serum sclerostin levels and DXA parameters

| | T2DM group | | Control group | |
|---|---|---|---|---|
| | Unadjusted r | Age-adjusted r | Unadjusted r | Age-adjusted r |
| BMD LS | | | | |
| r | 0.318 | 0.352 | 0.303 | 0.389 |
| *P* | 0.010 | 0.004 | 0.032 | 0.006 |
| BMD FN | | | | |
| r | 0.470 | 0.511 | 0.294 | 0.297 |
| *P* | <0.001 | <0.001 | 0.04 | 0.04 |
| BMD TH | | | | |
| r | 0.490 | 0.521 | 0.395 | 0.386 |
| *P* | <0.001 | <0.001 | 0.005 | 0.007 |
| T-score LS | | | | |
| r | 0.266 | 0.294 | 0.274 | 0.373 |
| *P* | 0.032 | 0.018 | 0.054 | 0.008 |
| T-score FN | | | | |
| r | 0.387 | 0.421 | 0.221 | 0.254 |
| *P* | 0.001 | <0.001 | 0.127 | 0.082 |
| T-score TH | | | | |
| r | 0.389 | 0.417 | 0.329 | 0.338 |
| *P* | 0.001 | <0.001 | 0.021 | 0.019 |

protein is regulated individually by aging (21). In our study, sclerostin levels were positively associated with age in T2DM males and control subjects. A large study had reported the increase of sclerostin serum levels with age (22). The authors postulated that sclerostin production by individual osteocytes is increased with aging, although they cannot exclude reduced clearance of the protein. In the same study, men had higher serum sclerostin levels than women. We also found this result in our study, both in T2DM patients and control subjects. The larger skeleton in men may explain gender differences in the production and release of sclerostin circulation, but recent data indicate that sclerostin concentrations are also regulated by estrogen (23, 24).

PTH has an inhibitory role in sclerostin production in humans as described by several authors (19, 23), and circulating sclerostin is reduced by intermittent PTH therapy (25). Sclerostin levels were negatively associated with PTH in our study, both in the entire cohort and in the T2DM group. Conceptually, high sclerostin serum levels would be indicative of decreased formation of bone markers. In our study, sclerostin levels were negatively related to both formation and resorption bone markers in T2DM patients. Our results are consistent with those reported by Mödder *et al.* (22) where BALP and serum CTX were inversely associated with sclerostin levels in elderly women. In patients with immobilization-induced bone loss, sclerostin levels were also negatively correlated with BALP, but the association with CTX was positive. However, there was no significant relationship between serum sclerostin and biochemical markers of bone turnover in other populations (19, 26, 27) as occurred in our control group. Therefore, the data about sclerostin and bone turnover markers are controversial, and no clear conclusions can be drawn.

In our study, LS, FN, and TH BMD showed a positive correlation with sclerostin levels both in T2DM and control group. In addition, sclerostin levels were decreased in T2DM patients with osteoporosis compared with nonosteoporotic T2DM patients. This finding differs from previous data of sclerostin function derived from sclerosteosis (28) and Van Buchem's disease (29), murine sclerostin knockout models (30), and low BMD and bone volume in mice overexpressing sclerostin (31). Given that sclerostin inhibits osteoblastic activity, a negative correlation would be expected. According with our results, in hemodialysis patients (26), serum sclerostin levels correlated positively with BMD and some microarchitecture parameters. Another study (27) found that serum sclerostin was lower in women with postmenopausal osteoporosis and were positively correlated to LS BMD. On the other hand, Ardawi *et al.* (32) found significant negative correlations between serum sclerostin and BMD for both LS and FN in pre- and postmenopausal women, but these correlations disappeared after adjustment for age and BMI. A possible explanation could be that serum levels of sclerostin reflect osteocyte number. Mödder *et al.* (22) observed that serum sclerostin levels were inversely related to total-body bone mineral content in older individuals and postulated that this correlation could reflect changes occurring with aging in skeletal sclerostin production, *i.e.* an increase in the sclerostin production by individual osteocytes. Moreover, high sclerostin levels were associated with decreased bone formation, suggesting low bone turnover. Low bone turnover could slow bone loss and explain the positive relationship between serum sclerostin and BMD. In the T2DM group, we found no differences in sclerostin levels between patients who had morphometric vertebral fractures *vs.* those who did not, but the number of patients with vertebral fractures was too small.

It has to be pointed that sclerostin assays are relatively new. A study that compared two commercial ELISA for the measurement of sclerostin concentrations concluded that a standardization of sclerostin assays is necessary. However, these authors recognized also that the same assay should be used for comparing groups of patients (33). Bone marrow plasma and peripheral serum sclerostin levels were strongly correlated (25), which suggests the circulating levels may be a good index of osteocyte production. On the other hand, it is unknown whether hyperglycemia and possible glycation of sclerostin may in-

terfere with its measurement with currently available assays.

Our study has certain limitations. First, this study was not specifically designed to evaluate serum sclerostin levels; however, patients were meticulously characterized and clinical and biochemical data were extensively collected. Second, the sample size is relatively small and may affect the statistical power of our study. Furthermore, the directionality of our outcomes from the cross-sectional analyses cannot be determined with certainty. Another potential limitation could be that we did not measure Dickkopf-related protein 1, another Wnt antagonist. Results of circulating Dickkopf-related protein 1 on bone metabolism in human studies are less consistent with sclerostin, so in our opinion, it does not affect our results. Strengths of our study are the evaluation of serum sclerostin levels in T2DM for the first time and the exhaustive evaluation of bone metabolism including calciotropic hormones, bone turnover markers, BMD, and assessment of morphometric vertebral fractures.

The role of sclerostin in physiological and pathological processes opens a new area for the development of therapeutic strategies in metabolic bone diseases as monoclonal antibodies that inhibit sclerostin biological activity. Such antibodies have already been shown to increase BMD in animal studies (34, 35) and in a published clinical phase I study (36). Based on our results, we advocate that these new bone-forming agents could be useful in the future to T2DM patients with osteoporosis. However, this possibility needs to be further investigated.

In summary, we demonstrate that serum sclerostin is increased in T2DM, independently of gender and age, and is correlated with calciotropic hormones, bone turnover markers, and BMD. Also, serum sclerostin is associated with duration of T2DM and HbA1c in T2DM patients. We postulated that the Wnt signaling pathway is impaired in T2DM, which promotes the deterioration of osteoblastogenesis and increased bone fragility. Additional studies are needed to evaluate the role of sclerostin on bone metabolism and their relationship with glycemic control of this population.

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