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Serum sclerostin concentration reflects bone turnover and glycation in men with type 2 diabetes mellitus

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Abstract

Objective: The risk of fracture is higher in people with than without diabetes. Because bone mineral density is not a good predictive marker of bone strength in people with diabetes, another surrogate is needed. Sclerostin is an inhibitor of bone formation and is secreted mainly by osteocytes. This study was performed to clarify how the serum sclerostin concentration reflects bone turnover in patients with type 2 diabetes.

Methods: We measured the serum sclerostin concentration and other bone turnover markers in 49 patients with type 2 diabetes (26 men and 23 postmenopausal women). The osteo-sono assessment index was measured using ultrasonography at the calcaneus.

Results: In men, the serum sclerostin concentration was significantly correlated with age, homocysteine, and pentosidine, reflecting an accumulation of advanced glycation end products in the bone. The multiple regression analysis showed that the serum pentosidine concentration was associated with the serum sclerostin concentration in men with type 2 diabetes. In contrast, sclerostin was not significantly correlated with pentosidine or other bone turnover markers in women with type 2 diabetes.

Conclusions: The serum sclerostin concentration seems to increase in accordance with the accumulation of advanced glycation end products in patients with type 2 diabetes and might reflect the bone quality in men with diabetes.

Keywords: Sclerostin, Type 2 diabetes, Bone turnover, Osteoporosis

Introduction

People with type 1 and 2 diabetes have an increased risk of fracture.[1,2] In people without diabetes, decreased bone mineral density (BMD) is an essential predictive factor for osteoporosis-associated fracture; however, an increased incidence of hip fracture has been shown in people with type 2 diabetes despite a higher BMD at the femoral neck.[2] Moreover, the prevalence of vertebral fracture is not always associated with BMD in patients with diabetes.[3] These observations indicate that BMD is insufficient to assess the bone strength in patients with diabetes and that another surrogate marker is needed to predict osteoporotic fracture.

Bone quality has been proposed as another bone strength factor,[4] and the usefulness of various biological markers that reflect bone quality has been reported. Advanced glycation end products (AGEs), which form with aging and chronic hyperglycemia, have been associated with complications of diabetes[5,6] and can accumulate in the bone matrix.[7,8] Saito et al.[9] reported that pentosidine, an AGE, increases with age and forms pathological cross-links in the bone, contributing to decreased bone quality in the diabetic rat. Yamamoto et al.[10] and Schwartz et al.[11] reported that the serum and urine concentrations of pentosidine are correlated with vertebral fracture in patients with diabetes. Furthermore, the concentration of endogenous secretory receptors for AGEs, which neutralize and inhibit the biological action of AGEs, is reportedly associated with the prevalence of vertebral fractures.[12] These observations suggest that AGEs play important roles in the bone fragility of patients with diabetes.

Sclerostin is secreted from osteocytes and inhibits Wnt/β-catenin signaling in bone metabolism.[13] Sclerostin is a product of *SOST*, and suppression of its biological function in association with *SOST* abnormalities causes sclerosteosis[14,15] and van Buchem disease.[16,17] Suppression of sclerostin is represented by a marked increase in bone mass. Sclerostin may be involved in bone metabolism changes caused by estrogen deficiency[18] or immobilization.[19] The serum sclerostin concentration is reportedly increased in patients with diabetes[20,21]; however, its exact mechanism in bone fragility has not yet been elucidated.

In this study, we measured the serum sclerostin concentration and analyzed its relationships with other clinical parameters in patients with type 2 diabetes to explore the role of sclerostin in bone fragility in patients with type 2 diabetes.

Methods

Patients

In total, 49 patients with type 2 diabetes (26 men, 23 women)

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at the Fujita Health University Hospital were recruited for this study from March to July 2009. The mean age of the patients was 66.0±11.6 years. Patients who had sustained a fragility fracture within 3 months of the study or who had an estimated glomerular filtration rate of ≤30 mL/min were excluded from the study. Patients who had taken steroids or hormone replacement therapy were also excluded. None of the patients took drugs for bone metabolic disorders (vitamin D derivatives, bisphosphonate, selective estrogen receptor modulators, or teriparatide). This descriptive study was approved by the Review Board for Epidemiology and Clinical Studies of Fujita Health University (#08-175) and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from each participant.

Biochemical measurements

Data were obtained from each patient using plasma or serum collected at one ambulatory visit. Glycated hemoglobin (HbA1c) was measured using automated techniques at the central laboratory of our hospital. The serum 25-hydroxyvitamin D (25-OHD) concentration was measured using a chemiluminescent immunoassay (DiaSorin, Inc., Stillwater, MN, USA). Intact parathyroid hormone (iPTH) was measured using a two-site immunoradiometric assay (IRMA) (Nichols Diagnostics Institute, San Clemente, CA, USA). Serum type I collagen N-terminal telopeptide (NTx) and bone-specific alkaline phosphatase (BAP) were measured by enzyme-linked immunosorbent assay (ELISA) (Osteomark NTx; Alere Inc., Waltham, MA, USA) and an enzyme immune assay (Osteolinks BAP; DS Pharma Biomedical Co., Ltd., Osaka, Japan), respectively. Serum procollagen type 1 N-terminal propeptide (P1NP) was measured by a radio-immunoassay. Serum osteocalcin was measured with an IRMA (BGP IRMA; Mitsubishi Chemical Medience Co., Tokyo, Japan). Serum pentosidine and homocysteine were measured by ELISA (FSK pentosidine; Fushimi Pharmaceutical Co., Ltd., Marugame, Japan) and high-performance liquid chromatography (YMC Co., Ltd., Kyoto, Japan). Sclerostin was measured using an ELISA kit purchased from Biomedica Laboratory (Wien, Austria), with an intra-assay coefficient of variation less than 7%.

Quantitative ultrasound assessment of the calcaneus

To assess the bone strength, quantitative ultrasound of the right calcaneus was performed using an AOS-100 system (ALOKA, Tokyo, Japan) according to the manufacturer's instructions.[22] This method involves measurement of the average speed of sound in the patient's right calcaneus from the propagation delay time of ultrasound pulses as well as the transmission index of ultrasound from the transmission waveform. Finally, it calculates the osteo-sono assessment index as the T-score and Z-score.

Statistical analysis

All analyses were performed using JMP 13.0.0 statistical software (SAS Inc., Cary, NC, USA). An unpaired t-test was used to compare the serum sclerostin concentration between subgroups. Single regression analysis was used to examine the correlation between sclerostin and other parameters. Given the skewed distribution of sclerostin and some other parameters, Spearman's rank-order correlation was also used to analyze the data. Multiple regression analysis was examined using the serum sclerostin concentration as a dependent variable with all independent variables entered in the models. A p value of <0.05 was considered statistically significant.

Results

Patients' background parameters

Table 1 shows the background data of 26 men and 23 postmenopausal women with type 2 diabetes. All patients were taking medication for diabetes. The HbA1c concentration was 7.0±0.8% in men and 7.8±1.5% in postmenopausal women. None of the patients had a history of clinical fracture. The osteo-sono assessment index assessed by quantitative ultrasound was not lower than average in terms of the absolute value (T-score) or age-matched value (Z-score), and it was not associated with the serum sclerostin concentration in patients with type 2 diabetes (Tables 2 and 3).

Table 1 Background data and clinical parameters of men and postmenopausal women with type 2 diabetes

	Men	Women
n	26	23
Age (years)	63.7±13.3	68.5±8.9
HbA1c (%, NGSP)	7.0±0.8	7.8±1.5
iPTH (pg/mL)	29.8±15.4	30.0±14.5
25-OHD (ng/mL)	26.9±7.7	23.0±6.9
BAP (IU/L)	20.7±6.7	24.2±5.5
P1NP (µg/L)	40.8±17.0	51.6±18.1
Osteocalcin (ng/L)	3.34±1.67	4.70±1.97
NTx (nmol BCE/L)	10.6±3.9	12.5±4.9
Homocysteine (µmol/L)	13.0±4.8	9.4±6.3
Pentosidine (µg/mL)	0.05±0.03	0.06±0.08
Sclerostin (pmol/L)	30.5±19.0	25.3±23.6
OSI (T-score)	−0.44±1.72	−1.40±0.99
OSI (Z-score)	0.29±1.68	0.07±1.01

Data are expressed as mean±standard deviation. HbA1c: glycated hemoglobin, iPTH: intact parathyroid hormone, 25-OHD: 25-hydroxyvitamin D, BAP: bone-specific alkaline phosphatase, PINP: type 1 procollagen N-propeptide, NTx: N-terminal telopeptide of type I collagen, BCE: bone collagen equivalents, OSI: osteo-sono assessment index.

Table 2 Single regression analysis of associations between sclerostin and clinical parameters in patients with type 2 diabetes

	Men		Women	
	r	p	r	p
Age	0.439	0.022	0.069	0.761
HbA1c	0.216	0.280	−0.011	0.961
iPTH	0.363	0.063	0.211	0.346
25-OHD	−0.113	0.576	0.120	0.594
BAP	−0.020	0.920	−0.058	0.797
P1NP	−0.062	0.759	−0.123	0.584
Osteocalcin	0.567	0.003	0.052	0.824
NTx	0.454	0.017	0.183	0.415
Homocysteine	0.548	0.003	0.307	0.164
Pentosidine	0.831	<0.0001	0.934	<0.001
OSI (T-score)	−0.097	0.630	−0.060	0.806
OSI (Z-score)	0.051	0.800	−0.037	0.880

HbA1c: glycated hemoglobin, iPTH: intact parathyroid hormone, 25-OHD: 25-hydroxyvitamin D, BAP: bone-specific alkaline phosphatase, PINP: type 1 procollagen N-propeptide, NTx: N-terminal telopeptide of type I collagen; OSI: osteo-sono assessment index.

Associations between sclerostin and metabolic parameters in men with type 2 diabetes

Table 2 shows the associations between the serum sclerostin concentration and clinical parameters in men with type 2 diabetes ($n=26$). Sclerostin was significantly correlated with age ($p=0.022$). The concentrations of HbA1c, iPTH, 25-OHD, and bone formation parameters (BAP and P1NP) were not associated with the sclerostin concentration; however, the serum osteocalcin ($p=0.003$), NTx ($p=0.017$), homocysteine ($p=0.003$), and pentosidine concentrations ($p<0.001$) were significantly correlated with the sclerostin concentration. The multiple regression analysis showed that pentosidine was independently associated with the serum sclerostin concentration in men (data not shown). Because the data distribution was skewed with respect to the serum sclerostin and pentosidine concentrations (Fig. 1), we also analyzed the relationship between serum sclerostin and various clinical parameters, including pentosidine, by non-parametric methods (Table 3). We found that age, homocysteine, and pentosidine were related to serum sclerostin in men with type 2 diabetes.

Associations between sclerostin and metabolic parameters in postmenopausal women with type 2 diabetes

Table 2 shows the associations between the serum sclerostin

concentration and clinical parameters in postmenopausal women with type 2 diabetes ($n=23$). In contrast to men, the serum sclerostin concentration was only significantly associated with pentosidine. Furthermore, only one extremely high value was found for the sclerostin and pentosidine concentrations (Figure 1B), and the significant association between the two parameters disappeared in the non-parametric analysis (Table 3).

Discussion

In the present study, we showed that the concentration of serum sclerostin, which suppresses bone formation, is associated with that of serum pentosidine, an AGE with a high affinity for the bone matrix in patients with diabetes. Bone fragility in patients with diabetes might depend on both the bone volume and quality, including the bone microarchitecture and the content of the bone matrix proteins[4]; however, evaluation of bone quality in the clinical setting is difficult. To retain good bone quality, appropriate bone turnover should be maintained to replace the aged bone matrices. Two key factors suppress bone turnover in patients with diabetes. One is hyperglycemia, which suppresses PTH secretion from the parathyroid gland, and the other is AGEs, which directly suppress bone formation. A higher serum pentosidine concentration reflects, at least in part, the accumulation of AGEs in the bone matrix and is related to a higher fracture risk in the aged population.[9,11] In the present study, the serum sclerostin concentration was significantly correlated with the pentosidine concentration in patients with type 2 diabetes. Because the key role of sclerostin is inhibition of bone formation,[13] our results indicate that sclerostin suppresses bone formation in association with the accumulation of AGEs in patients with type 2 diabetes. Among the bone metabolic markers, osteocalcin is known to be suppressed by a high blood glucose concentration and recovers quickly after blood glucose normalization[23]; however, we have shown in the present study that sclerostin was not associated with HbA1c in men and postmenopausal women. These results suggest that current glycemic control does not directly affect sclerostin secretion. Antidiabetic drugs, including pioglitazone, which could affect bone metabolism,[24,25] were not associated with sclerostin; however, more long-term observations are needed to clarify the effects of chronic glycemic control and antidiabetic drugs on sclerostin.

In our male patients with diabetes, the serum sclerostin concentration was significantly associated with age, osteocalcin, and NTx, suggesting their relationship with high bone turnover in accordance with aging. As aforementioned, low bone turnover

Table 3 Association between serum sclerostin and other clinical parameters in patients with type 2 diabetes analyzed by Spearman's rank-order correlation

	Men ($n=26$)	Women ($n=23$)
	rS	rS
Age	0.514[a]	0.245
HbA1c	0.253	−0.069
iPTH	−0.127	−0.009
25-OHD	0.220	0.151
BAP	−0.045	0.016
P1NP	−0.224	−0.205
Osteocalcin	0.068	−0.032
NTx	0.127	−0.114
Homocysteine	0.404[a]	0.174
Pentosidine	0.483[a]	0.203
OSI (T-score)	0.128	−0.102
OSI (Z-score)	0.330	−0.038

[a] $p<0.05$
HbA1c: glycated hemoglobin, iPTH: intact parathyroid hormone, 25-OHD: 25-hydroxyvitamin D, BAP: bone-specific alkaline phosphatase, PINP: type 1 procollagen N-propeptide, NTx: N-terminal telopeptide of type I collagen, OSI: osteo-sono assessment index.
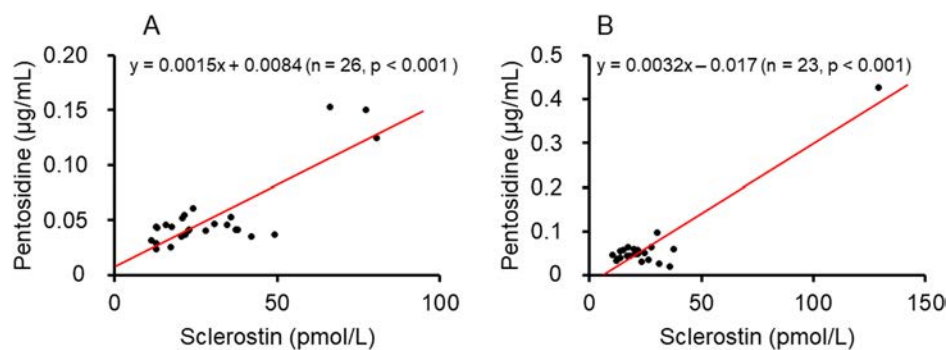

Figure 1 Scatter plot of the serum sclerostin and pentosidine concentrations in (A) men and (B) women with type 2 diabetes.

via suppression of bone formation is a typical pathological condition in patients with diabetes because the excessively high bone turnover results in bone mass reduction due to an imbalance between bone formation and resorption.[26] Mödder et al.[27] reported that tartrate-resistant acidic phosphatase 5b, a bone resorption marker, is correlated with sclerostin in men aged >60 years irrespective of the presence of diabetes. When we performed a multiple regression analysis including age, NTx, osteocalcin, pentosidine, and other parameters as independent variables, their significant relationship with the serum sclerostin concentration disappeared, except for pentosidine. These findings suggest that the association between sclerostin and bone resorption markers could be a nonspecific phenomenon of aging.

Serum sclerostin was not associated with any clinical parameters in postmenopausal women with type 2 diabetes. Sex-related differences in associations among sclerostin and bone metabolic markers have also been reported in other studies.[27] The reasons for this are unclear, but to the extent that the circulating sclerostin concentration might reflect the total-body bone mass, the larger skeleton in men may simply produce and release more sclerostin into the circulation.[27] In addition, the circulating sclerostin concentration is reduced by estradiol but not by testosterone, suggesting that the variation in the serum estradiol concentration could more strongly affect the sclerostin concentration in postmenopausal women than in men.[28] Bone fragility in postmenopausal women mainly depends on volumetric loss of bone caused by the rapid decline of estrogen.[26] Therefore, bone quality may contribute less to bone fragility in postmenopausal women with diabetes than in aged men with diabetes.

Bone fragility in patients with osteoporosis, especially in postmenopausal women, is often associated with bone volume loss with a high bone turnover.[26] Therefore, the current first-line treatment for osteoporosis is the use of antiresorptive agents such as bisphosphonates and selective estrogen receptor modulators.[29] In patients with diabetes, however, the suppression of bone formation is also a crucial factor for bone fragility. Although antiresorptive agents also effectively prevent osteoporotic fracture in patients with diabetes,[30] stimulation of bone formation could be another method with which to improve the bone quality in patients with diabetes. The biological function of sclerostin in suppressing bone formation is very strong.[13,31] Use of antibodies with sclerostin to attenuate its biological effects is a potential new treatment for osteoporosis[32] and will be available in the near future. When bone turnover recovers with antisclerostin antibody treatment, the "old bones" with pentosidine may be replaced with new bones. Because pentosidine is related to sclerostin secretion in patients with diabetes, it seems likely that pentosidine and sclerostin could be useful markers with which to assess the efficacy of antisclerostin antibodies in patients with diabetes. Further studies are required.

This study has several limitations. First, this cross-sectional study was performed in a single center. Second, the number of patients was too small to elucidate all possible associations among the parameters. Third, we did not examine bone biopsies to directly assess bone formation. Fourth, this study included a rather aged population, resulting in a diminishing age-dependent increase of the serum sclerostin concentration. Nevertheless, this study showed a significant association between sclerostin, a bone-derived hormonal factor, and pentosidine, an AGE with a high affinity for the bone matrix, in patients with type 2 diabetes.

Conclusion

The serum sclerostin concentration seems to increase in accordance with the accumulation of AGEs in patients with type 2 diabetes and might reflect the bone quality in men with diabetes.

Conflict of Interest

The authors declare no conflicts of interest for this study.

Acknowledgments

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