

Type 2 diabetes raises serum sclerostin levels and disturbs the relation between sclerostin and bone mineral density: a call for caution with antisclerostin therapy in osteoporosis

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Background

Sclerostin is an osteocyte-secreted protein that negatively regulates osteoblasts. Wnt signaling may be crucial in the pathogenesis of impaired bone quality in type 2 diabetes mellitus (T2DM). The possibility that currently studied antisclerostin bone-forming agents could be useful to T2DM patients with osteoporosis needs further investigations.

Aim

The aim of this study was to investigate the relationship between serum sclerostin and bone mineral density in T2DM patients, in comparison with nondiabetic individuals.

Patients and Methods

This study was conducted on 21 T2DM patients and 22 nondiabetic individuals. All participants were 60 years or older. They underwent history taking, clinical examination, routine lab investigations, and glycated hemoglobin assessment. Serum sclerostin was measured by ELISA. Bone mineral density (BMD) was measured at the left femoral neck and lumbar spine.

Results

Serum sclerostin level was significantly higher in T2DM patients compared with nondiabetic individuals. Male participants showed significantly higher sclerostin levels among the nondiabetic individuals, whereas this difference was not significant among T2DM patients. The Bone mineral density (BMD) and *t*-values of T2DM patients and the nondiabetic group were not significantly different. We found a significant positive correlation between sclerostin level and lumbar spine BMD among nondiabetic individuals, whereas among T2DM patients, this correlation was not significant. Sclerostin levels did not show a significant difference between diabetic osteoporotic and diabetic nonosteoporotic patients.

Conclusion

Patients with T2DM have raised sclerostin levels that, unlike those in nondiabetic individuals, are not correlated with BMD. This pathological condition that is specific to diabetes necessitates further study, careful assessment of the role of antisclerostin therapy, and probable dose adjustment for osteoporosis in T2DM patients.

Keywords:

bone mineral density, elderly, osteoporosis, sclerostin, type 2 diabetes

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Introduction

Sclerostin is a glycoprotein secreted by osteocytes, which is a potent inhibitor of osteoblastogenesis [1]. Sclerostin, after secretion by osteocytes, travels through osteocyte canaliculi to the bone surface at which it binds to coreceptors low-density lipoprotein receptor-related protein (LRP5 and LRP6) and thereby reduces osteoblastogenesis and bone formation [2].

Studies on mice with a targeted deletion of the sclerostin gene have shown manifestations that provide evidence for a critical role of sclerostin as an inhibitor of bone formation and suggest the need for pharmacologic agents that target sclerostin to increase bone mass and bone strength [3]. Humanized monoclonal antibodies to sclerostin cause enhanced Wnt signaling and an increase in bone mass in rodents and nonhuman primates [4].

Sclerostin has been shown to be almost entirely restricted to late osteoblasts and osteocytes [5], which makes it suitable as a therapeutic target of choice with limited extraskeletal side effects [6]. Recently, the first human, phase I, randomized, double-blind, placebo-controlled clinical trial testing a humanized monoclonal sclerostin antibody in healthy men and postmenopausal women was reported [7]. Bone formation markers increased within 1 month after administration of a single sclerostin dose to levels similar to those after daily injections of parathormone (PTH) for 6 months, and markers of bone resorption decreased. More recently, Amgen/UCB reported in a press release (<http://www.amgen.com>) some of the results from the phase II study comparing the sclerostin antibody with placebo for the treatment of postmenopausal osteoporosis in ~400 postmenopausal women with low bone mineral density (BMD). At

12 months, BMD significantly increased in the lumbar spine in the sclerostin treatment group compared with the placebo treatment group.

The relationship between T2DM and osteoporosis has been widely investigated, yet it remains controversial. Evidence of decreased bone resorption, increased bone resorption, decreased bone formation and increased bone formation has been reported [8]. Various studies have found either normal, reduced, or increased BMD in type 2 diabetes mellitus (T2DM) patients in comparison with healthy controls [9]. This confusing effect of diabetes on bone could be mediated through several factors, some of which may have contradictory effects [10]. These multiple factors include obesity, changes in insulin levels, higher concentrations of advanced glycation end products in collagen, increased urinary excretion coupled with lower intestinal absorption of calcium, inappropriate homeostatic response of parathyroid hormone secretion, complex alterations of vitamin D regulation, reduced renal function, lower insulin-like growth factor-I levels, Microangiopathy and inflammation [11].

The role of sclerostin in bone metabolism in T2DM patients and the possibility that antisclerostin agents could be useful in the future to T2DM patients with osteoporosis need to be investigated. This is even more important in the elderly population, which has a higher incidence of osteoporosis associated with multiple comorbidities, requiring individualization of the management plan according to each case.

Objective

The aim of this study was to investigate the relationship between serum sclerostin level and bone mineral density in T2DM patients, in comparison with nondiabetic individuals.

Patients and methods

This study included 43 elderly participants: 21 were diagnosed according to the American Diabetic Association [12] as type 2 diabetic patients and 22 were nondiabetic individuals. They attended the physical medicine, rheumatology and rehabilitation, and geriatric outpatient clinics of Ain Shams University Hospitals. Patients with a history of any other chronic disease known to affect bones, including Paget's disease, rheumatoid arthritis, hyperparathyroidism, hypercortisolism, malignant tumors, renal bone disease, end-stage liver or kidney disease, and post-transplantation bone disease, were excluded. Patients who had undergone previous

treatment or were under current treatment with drugs affecting bone metabolism, such as calcium supplements, vitamin D preparations, selective estrogen receptor modulators, calcitonin, estrogen, antiresorptive agents, thiazides, steroids, glucocorticoids, or anticonvulsants were also excluded. The protocol for the research met the criteria of the Ethics Committee of the Faculty of Medicine, Ain Shams University. Informed consent was obtained and patient anonymity has been preserved.

All participants underwent the following:

- (1) Full history taking with special emphasis on generalized bone pain, fall history, history of fractures, and drug history.
- (2) Thorough clinical examination, including weight, height, and Body Mass Index (BMI), and examination of the spine and bones for tenderness and deformities. Comprehensive musculoskeletal and geriatric assessments were also made, with special consideration to factors increasing the risk for osteoporosis.
- (3) Functional assessments on the basis of activities of daily living [13] and instrumental activities of daily living [14], fall risk assessment, and the Timed Up and Go Test [15].

Laboratory investigations

- (1) Complete blood count was determined by the Coulter count method and erythrocyte sedimentation rate by the Westergren method.
- (2) Fasting blood sugar, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, serum urea, and creatinine levels were evaluated.
- (3) Glycated hemoglobin, HbA1c, levels were determined.
- (4) Human sclerostin levels were assayed using a commercially available ELISA kit (Wuhan EIAab Science Co. Ltd. East Lake, China) according to the manufacturer's instructions.

Dual-energy X-ray absorptiometry

Bone mineral density was measured in grams per square centimeter by dual-energy X-ray absorptiometry at the left femoral neck and lumbar spine (L2–L4) using a Lunar DPX-L densitometer (Lunar Radiation Corp., Madison WI, USA). The WHO classification (normal, *t*-score -1.0 or above; osteoporosis, *t*-score -2.5 or below; osteopenia, *t*-score between -1.0 and -2.5) was used [16]. The lowest *t*-score of the lumbar spine or femoral neck was selected [17]. Dual-energy X-ray absorptiometry was performed in the Osteoporosis Unit of the Geriatrics and Gerontology Department, Faculty of Medicine, Ain Shams University.

Statistical analysis

Statistical analysis was carried out using SPSS statistical software package (V. 17, Echo soft Corp., USA, 2008). Data were expressed as mean \pm SD for quantitative measures. The following tests were performed:

- (1) Student's *t*-test to compare parametric data between two independent mean groups.
- (2) Wilcoxon's Rank Sum test to compare nonparametric data between two independent groups.
- (3) Ranked Spearman's correlation test to compare nonparametric data in terms of the association between two variables from each group.

Results

General and clinical characteristics of diabetic patients and nondiabetic participants are shown in Table 1.

On using the Pearson χ^2 test to compare the two groups, no significant differences were found as regards sex distribution, incidence of smoking, amount of exercise, presence of other comorbidities, number of participants with impaired activities of daily living and instrumental activities of daily living, history of falls, and number of osteoporotic patients among both groups.

Male participants showed significantly higher serum sclerostin levels compared with female participants among the nondiabetic participants (1200 ± 356.37 pg/ml in males, 667.5 ± 382.53 pg/ml in females, $P < 0.01$), whereas T2DM patients of both sexes did not show a significant difference in serum sclerostin levels (6700 ± 1753.57 pg/ml, 7000 ± 2130.37 pg/ml, $P > 0.05$), as shown in Fig. 1.

Serum sclerostin levels were significantly higher in T2DM patients when compared with nondiabetic individuals (7214.29 ± 5 pg/ml and 812.73 ± 440.09 pg/ml, respectively, $P < 0.001$; Fig. 2).

The mean BMD and *t*-values of T2DM patients and nondiabetic individuals at the lumbar spine L2–L4 (LS)

and femoral neck did not show a significant difference. Values are shown in Table 2. Among T2DM patients, nine (42.8%) were osteoporotic, whereas 12 (57.2%) were nonosteoporotic. Among the nondiabetic group, 11 (50%) proved to be osteoporotic, whereas 11 (50%) were nonosteoporotic.

Using the ranked Spearman's correlation test, we found a significant positive correlation between serum sclerostin level and lumbar spine L2–L4 BMD ($r = 0.4$, $P < 0.05$) among the nondiabetic individuals (Fig. 3), whereas among T2DM patients this correlation was not statistically significant ($r = -0.042$, $P = 0.856$). Serum sclerostin was not significantly correlated with age or BMI in both groups.

Upon further analysis of the results, we found the mean serum sclerostin level among diabetic osteoporotic patients to be 6857.14 ± 2173.98 pg/ml, whereas the mean among nondiabetic osteoporotic patients was 797.27 ± 464.07 pg/ml. The difference between the two groups was statistically significant ($z = -3.49$, $P < 0.01$). In contrast, serum sclerostin did not show a significant difference among diabetic osteoporotic and diabetic nonosteoporotic patients (6857.14 ± 2173.98 and 6958.33 ± 1982.4 pg/ml, respectively, $z = -0.299$, $P > 0.01$; Fig. 4).

Discussion

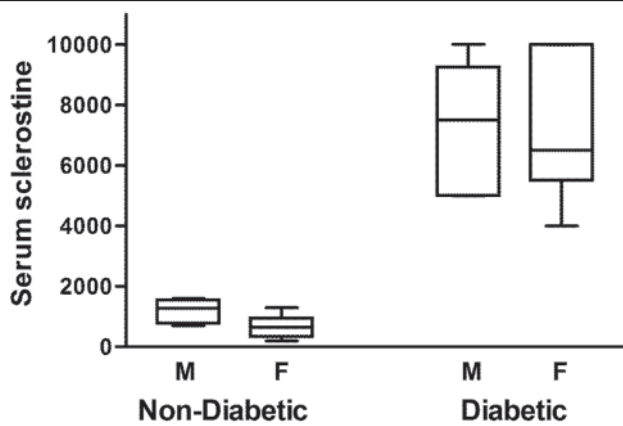
Diabetes mellitus and osteoporosis are diseases with an increasing prevalence and substantial morbidity and mortality, especially among the elderly. The relationship between both medical conditions is complex and remains controversial, although it has been investigated extensively. The role of the Wnt signaling pathway may be crucial in the pathogenesis of impaired bone quality observed in diabetes mellitus [18]. 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 LRP5 [19].

Table 1 Characteristics of diabetic patients and nondiabetic individuals

	T2DM group (mean \pm SD)	Nondiabetic group (mean \pm SD)	<i>P</i> -value	Significance
Age (years)	64.3 \pm 5.5	68.7 \pm 7.9	0.07	NS
Male/female (<i>n</i>)	6/15	6/16	0.92	NS
BMI(kg/m ²)	32.8 \pm 6.8	31.32 \pm 7.9	0.53	NS
HbA1c (%)	6.85 \pm 1.0	5.85 \pm 0.4	0.001	HS
History of falls (<i>n</i>)	10	11	0.88	NS
History of fractures (<i>n</i>)	1	2	0.58	NS
Impaired ADL (<i>n</i>)	5	4	0.65	NS
Impaired IADL (<i>n</i>)	8	7	0.66	NS
timed up test (>14) (<i>n</i>)	7	10	0.42	NS

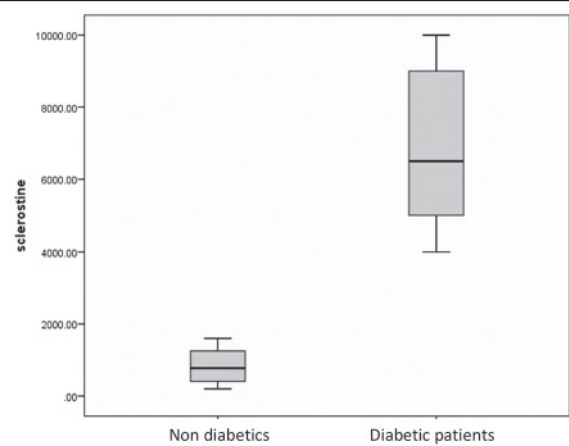
ADL, activities of daily living; HbA1c, glycated hemoglobin; HS, high significance; IADL, instrumental activities of daily living; NS, no significance; T2DM, type 2 diabetes mellitus.

Figure 1



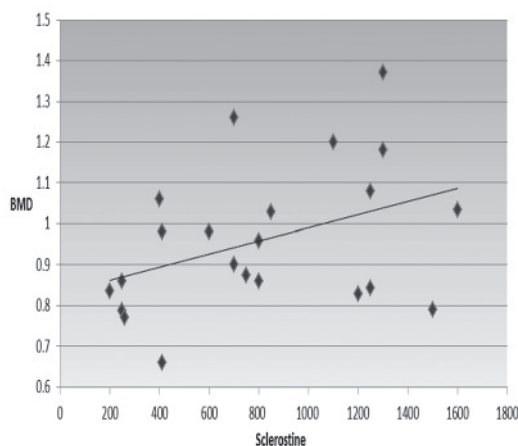
Level of serum sclerostin in men and women of both groups: nondiabetic individuals and diabetic patients.

Figure 2



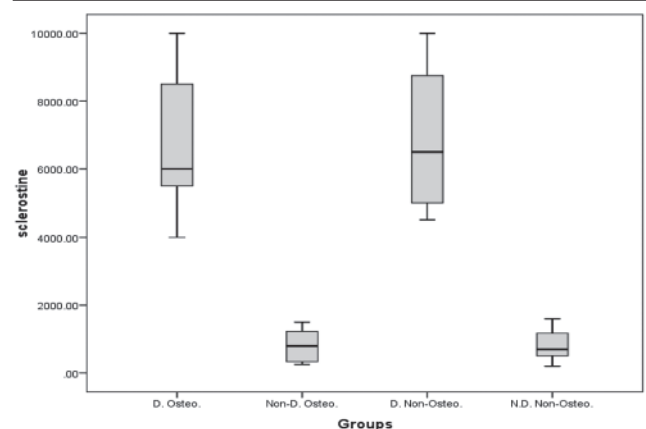
Serum sclerostin level in T2DM patients and in nondiabetic individuals. T2DM, type 2 diabetes mellitus.

Figure 3



Correlation between serum sclerostin level and BMD in nondiabetic individuals. BMD, bone mass density.

Figure 4



Serum sclerostin levels in different subgroups.

Table 2 Comparison between the mean BMD and *t*-values of T2DM patients and nondiabetic individuals

	T2DM (mean ± SD)	Nondiabetic group (mean ± SD)	<i>t</i> -value	<i>P</i> -value	Significance
Lumbar BMD (g/cm ²)	0.96 ± 0.20	0.96 ± 0.18	-0.067	>0.05	NS
Lumbar <i>T</i> value	-2.10 ± 1.60	-2.00 ± 1.43	-0.123	>0.05	NS
Femoral BMD (g/cm ²)	0.83 ± 0.14	0.78 ± 0.15	1.03	>0.05	NS
Femoral <i>t</i> -value	-1.10 ± 1.50	-1.65 ± 1.21	1.384	>0.05	NS

BMD, bone mass density; T2DM, type 2 diabetes mellitus.

The role of sclerostin in bone physiological and pathological processes opens a new area for the development of therapeutic strategies for metabolic bone diseases, as monoclonal antibodies that inhibit the biological activity of sclerostin have already been shown to increase BMD in animal studies [4,20]. Consistent with these observations, neutralizing monoclonal antibodies against sclerostin have been developed and are under investigation as potential novel anabolic therapy for osteoporosis [21]. The possibility that these new bone-forming agents could be useful in

the future to T2DM patients with osteoporosis needs to be further investigated [22].

The aim of this study was to investigate the relationship between serum sclerostin level and BMD in T2DM patients in comparison with nondiabetic individuals.

In this study, serum sclerostin levels did not correlate significantly with age in both diabetic and nondiabetic groups. This finding disagrees with that of Gennari

et al. [22], who stated that serum sclerostin levels significantly increased with age in their overall cohort of T2DM and T1DM patients. In addition, Martin *et al.* [18] reported that sclerostin levels were positively correlated with age in male patients with T2DM and controls. Our results can be attributed to studying serum sclerostin levels in a narrower age group, which includes the elderly, as they are the most liable age group to have several coexisting morbidities. BMI, functional impairment, and risk of falls did not show statistical difference among both groups and thus could be eliminated as influencing factors in this study.

Our results showed significantly higher serum sclerostin levels in men compared with women in the nondiabetic group. Similar findings were reported by another group [23] that explained the difference by the presence of a larger skeleton in men, which results in the increased production and release of sclerostin from osteocytes. Moreover, sclerostin concentrations were proven to be downregulated by estrogen [23,24]. The latter group noticed that circulating sclerostin levels were inversely associated with estrogen levels in postmenopausal women. However, in our study this relationship was disturbed in diabetic patients. This partially disagrees with the findings of Martin *et al.* [18], who stated that serum sclerostin levels were significantly higher in men than in women both in their T2DM group and in their control group, as well as with those of Gennari *et al.* [22], who noticed that in their overall cohort sclerostin levels were higher among men than among women.

T2DM patients had significantly higher serum sclerostin levels than nondiabetic individuals, independent of sex and age. These results are consistent with those of Van Lierop *et al.* [18] and Martin *et al.* [25]. The latter group even added that sclerostin concentrations were positively associated with glycosylated hemoglobin levels in T2DM patients independent of age, as PTH levels were lower in T2DM patients, as proven by researchers [24], and sclerostin levels were negatively associated with PTH, which has an inhibitory role in sclerostin production in humans, as described by several authors [25,26]. This reduced effect of PTH on bone could explain in part the increase in sclerostin that we observed in T2DM patients. Another explanation is the reported impairment of the Wnt signaling pathway in T2DM patients, which affects sclerostin, it being a regulator of the Wnt pathway [18]. Further, if sclerostin expression is decreased by mechanical loading of the skeleton, an association which has been noted before in immobilized patients by Gaudio *et al.* [27], thus, low levels of physical activity, which are often found in patients with T2DM, might contribute to the elevation in serum sclerostin levels in diabetic patients. Finally, sclerostin

glycosylation or glycation could explain the increase in sclerostin levels in T2DM, and this hypothesis requires additional investigations [18].

The percentage of osteoporosis in the T2DM group (43%) and the nondiabetic group (50%) did not show significant statistical difference. This observation is in accordance with the findings of Romana and Li-Yu [28], who concluded that diabetes was indeed a protective factor for osteoporosis. In addition, the mean BMD and *t*-values of T2DM patients at the LS and femoral neck were within normal ranges and did not show a significant difference when compared with those of nondiabetic individuals. These findings are in agreement with those of Kumeda [29], who stated that bone fragility in diabetic patients is unrelated to BMD, which is a pathological condition peculiar to diabetes. This study suggests that osteoblastic cell function deteriorates in diabetic patients because of both absolute and relative insulin deficiency. Other researchers have also found that in T2DM fracture risk is increased despite increased BMD [30]. The presence of diabetic vascular complications, advanced glycation of bone collagen, and deranged bone turnover, and possibly administration of certain types of antidiabetic medications were related to the increased risk for fracture in such patients. Blakytyn *et al.* [31] reported that T2DM patients had normal bone mineral density, yet they had poorer quality of the bone. They explained this by the detrimental effects of impaired glucose metabolism on bone health and stated that hyperglycemia had both direct effects on bone cells and indirect effects through the formation of advanced glycation end products that have been shown to reduce bone strength. Later on, a cross-sectional study including a diabetic group and a control group found nonsignificant differences between both groups as regards osteoporosis percentage, BMD at both LS and femoral neck, as well as *t*-scores at both LS and femoral neck [18]. They suggested that impairment of the Wnt signaling pathway in T2DM patients promoted the deterioration of osteoblastogenesis and increased bone fragility regardless of the normal BMD. Unexpectedly, other groups documented that BMD in T2DM patients was even increased [32,33].

According to our results in the nondiabetic group, a significant positive correlation was found between serum sclerostin level and lumbar spine BMD ($r = 0.4$, $P < 0.05$). Other groups also found that serum sclerostin levels were lower in women with postmenopausal osteoporosis and were positively correlated with LS BMD [34,35]. Other groups went as far as stating that serum sclerostin level was an independent predictor and even the most significant determinant of both whole-body and lumbar spine

BMD [36]. Cejka *et al.* [37] also stated that serum sclerostin levels were positively correlated with BMD and some microarchitecture parameters of bone. However, it is worth mentioning that the latest study was conducted on hemodialysis patients. Our results disagree with those of Ardawi *et al.* [38, who observed significant negative correlations between serum sclerostin level and BMD for both LS and femoral neck in premenopausal and postmenopausal women; however, these correlations disappeared after adjustment for age and BMI. Some differences in the study population and the sclerostin kit used may explain this discrepancy. As sclerostin inhibits bone formation, a negative correlation was expected between sclerostin level and BMD. However, there have been some clinical findings that support the theory that serum sclerostin levels might be positively correlated with BMD. First, as sclerostin is produced exclusively by osteocytes, lower bone mass may possibly lead to release of lower levels of sclerostin [34]. Second, in postmenopausal women with osteoporosis, treatment with risedronate led to an increase in both serum sclerostin level and BMD [35]. Similar findings were reported in patients with rheumatoid arthritis, in whom the administration of tocilizumab (an anti-IL6 agent) resulted in increased serum sclerostin levels irrespective of disease response to therapy [39].

In our study, a correlation between sclerostin level and BMD was absent in T2DM patients, suggesting that the increase in sclerostin levels associated with T2DM masks and disrupts the relation between sclerostin level and BMD. In contrast to our findings, Martin *et al.* [18] reported that sclerostin levels were positively related to LS, femoral neck, and total hip BMD in their T2DM group. In addition, serum sclerostin levels did not show a significant difference between diabetic osteoporotic patients and diabetic nonosteoporotic patients. This finding is also in disagreement with that of Martin and colleagues, who observed that sclerostin levels were significantly lower in osteoporotic compared with nonosteoporotic patients with T2DM. In contrast, the significant difference between nondiabetic osteoporotic patients and diabetic osteoporotic patients in our study as regards serum sclerostin levels indicates that in diabetic patients T2DM is an independent predictor and a more significant determinant of serum sclerostin levels than is osteoporosis.

Conclusion

Patients with T2DM have raised sclerostin levels, which, unlike that in nondiabetic individuals, are not correlated with BMD. This pathological condition peculiar to

diabetes necessitates further study, careful assessment of the role of antisclerostin therapy, and probable dose adjustment for osteoporosis in patients with T2DM.

Acknowledgements

Conflicts of interest

None declared.

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