Original Article

Serum levels of sclerostin in prediabetes and its correlation with bone mineral density

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Abstract

Background: Diabetes is a major burden globally, more commonly so in developing countries, as its complications are detected relatively late due to underdeveloped healthcare systems. These complications, when detected, are more or less irreversible, thereby leading to increased morbidity and mortality. Among these, complications related to bones (mainly osteoporosis) start fairly early (even in the prediabetes stage) but are less emphasized, nonetheless are major contributors to morbidity in diabetics due to increased fracture risk. One of the novel bone markers recently discovered is sclerostin, which helps in the assessment of the effect of hyperglycemia on bone homeostasis. Bone mineral density (BMD) by DXA scan is a good tool to assess the status of bone health but requires modern expensive radiological equipment. In this study, we wanted to see the correlation of serum levels of sclerostin to BMD so that by a simple serum investigation, early detection of poor bone quality in treatment-naive prediabetics can be done. **Objective:** The aim of the study was to measure serum levels of sclerostin in prediabetics, compare them with normoglycemic controls, and find the correlation of serum levels of sclerostin with BMD. **Methods:** 50 prediabetic patients and 50 age, sex, blood pressure, and BMI-matched controls were recruited in the study. In both the groups, serum levels of fasting blood glucose and postprandial glucose, glycated hemoglobin (HbA1c), Vitamin D, fasting insulin, and serum sclerostin levels were measured in both groups using ELISA. The obtained values were compared between the two groups. Bone mineral density is measured by DXA scan in cases and a correlation between BMD and serum levels of sclerostin was observed. **Results:** Serum sclerostin was significantly higher in the cases [18.22 (19.42) ng/ml] compared to the control group [11.08 (4.73) ng/ml] with a *P* value of 0.013. The mean of BMD in prediabetes is 1.06 g/cm^2, T score is − 1.02, and Z score is − 0.59. There was a significant negative correlation between serum sclerostin levels and BMD in prediabetes (r = −0.404, $P < 0.001$). **Conclusion:** Serum levels of sclerostin are increased in prediabetes and correlate well with low BMD in prediabetes, and can therefore be used for early recognition of osteoporosis and fractures in diabetes.

Keywords: Glycemic parameters, HbA1C, type 2 diabetes mellitus, Vitamin D

Introduction

Diabetes mellitus has been associated with an increased risk of fractures at any skeletal site because of the poorer quality of the bone due to decreased bone mineral density (BMD).[1] The action of glucose on bone cells has a mutual interaction between bone and glucose homeostasis.[2] Hyperglycemia itself acts like a toxin that affects the differentiation of bone marrow mesenchymal cells (MSCs).[3] Metabolic activities in bone are regulated by many pathways out of which, recently discovered Wnt signaling is one of the pathways which regulates bone homeostasis by cellular and molecular mechanisms of bone remodeling. The Wnt/β-catenin pathway increases bone formation by increasing the proliferation of osteoprogenitor cells and decreasing apoptosis of mature osteoblasts.[4] This pathway is majorly regulated by sclerostin, a product of the SOST gene, which is expressed almost exclusively

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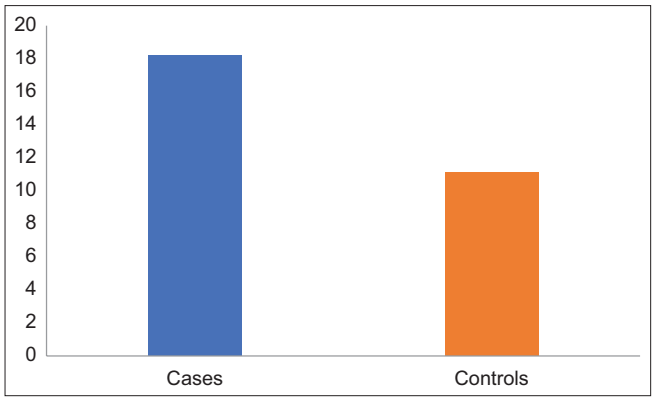

Figure 1: Comparison of serum sclerostin between the two groups

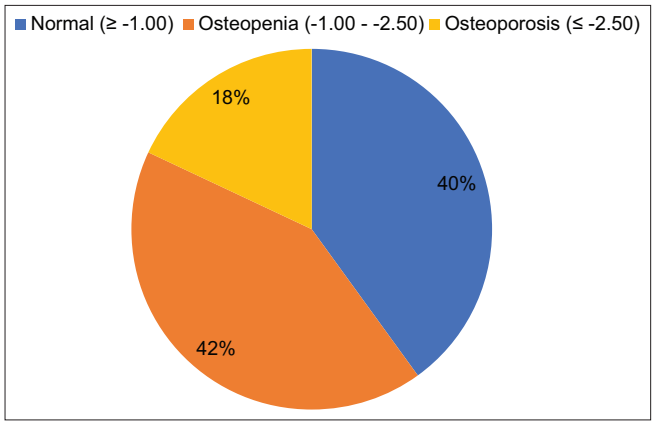

Figure 2: Distribution of cases according to subgroups of T score

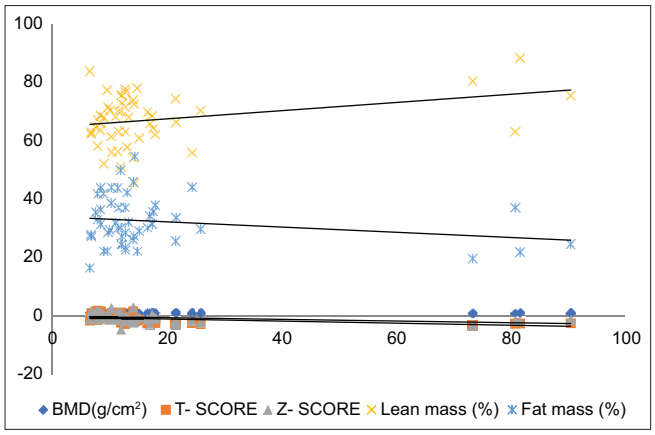

Figure 3: Scatter-plot of correlation between sclerostin and BMD, lean and fat mass

in osteocytes. It is a potent antagonist of the Wnt/β-catenin pathway, which is a major regulator of bone mass, and is an inhibitor of the Wnt/β-catenin pathway and therefore inhibitor of bone formation.[5] The Wnt/β-catenin signaling pathway also contributes to the modulation of insulin secretion, β-cell function, and insulin signaling in skeletal muscle. In previous studies, increased sclerostin levels were observed in adult patients with type 2 diabetes mellitus (DM) and atherosclerotic diseases.[6] However, the complications of diabetes start from the prediabetic state itself due to persistent hyperglycemic state, and bone markers for bony catabolism rise even in prediabetes. Skeletal complications commonly occur by a reduction in bone mineral density (BMD) and increase the risk of fractures in patients suffering from diabetes or even in a prediabetic state.

The aim of this study was to assess sclerostin level in prediabetes and healthy controls and to investigate the relationship between sclerostin levels and bone mineral density.

Material and Methods

This study was conducted in the Departments of Medicine, Biochemistry, and Radiodiagnosis at ABVIMS and RML Hospital, New Delhi.

STUDY DESIGN: cross-sectional, observational study

STUDY SIZE: The study group consisted of 50 consecutive patients with prediabetes and 50 control subjects with matching age, sex, blood pressure, and body mass index (BMI), from the Medicine department OPD, wards, and emergency.

STUDY PERIOD: January 1, 2021 to May 31, 2022

Sample size calculation

The study of Giuseppe Daniele *et al.* observed that sclerostin levels were higher in IGR compared with NGT (50.8 ± 2.4 vs. 38.7 ± 2.3 pmol/L). Sclerostin levels were positively correlated with HOMA IR with r = 0.62.[7] Taking this value as a reference, the minimum required sample size with 99% power of study and 1% level of significance is 49 patients. To reduce the margin of error, the minimum sample size to be taken is 50 per group. Taking a 1:1 ratio for cases/controls, the sample size taken is 100 (50 cases and 50 controls).

The formula used is: -

1) For comparing the mean of two groups

$N > = 2 (\text{standard deviation})^2 X (Z_\alpha + Z\beta)^2$

$(\text{mean difference})^2$

where Z_α is the value of Z at a two-sided alpha error of 1% and Zβ is the value of Z at power of 99%, and the mean difference is a difference in mean values of the two groups.

Pooled standard deviation = $\sqrt{(S1^2 + S2^2) / 2}$

where S_1 is the standard deviation of 1group and S_2 is standard deviation of the other group.

2) Correlation

$$N = \left(\frac{Z_\alpha + Z_\beta}{C(r)}\right)^2 + 3$$

$$C(r) = \frac{1}{2}\text{Log}\frac{1+r}{1-r}$$

where Z_α is the value of Z at two-sided alpha error of 1% and Zβ is the value of Z at a power of 99%.

Calculations

1) For comparing the mean of two groups

Pooled standard deviation $= \sqrt{(2.4^2 + 2.3^2)/2}$

$=2.35$

$N> = \frac{2\,(2.35)^2 \times (2.58 + 2.33)^2}{(12.1)^2}$

$> = 1.82 = 2$ (approx.)

Correlation of sclerostin levels with HOMA IR

C (r) =0.5*(ln((1+ (.62))/(1-(.62)))) =0.725

N = ((2.58 + 2.33)/(.725))^2 + 3 = 48.8 = 49(approx.)

Inclusion criteria

1. Fifty cases of prediabetes of age 30–65 years as defined by fasting plasma glucose between 100 and 125 mg/dL OR 2 hours postprandial glucose/2 hours OGTT (after 75 gm of glucose solution ingestion) between 140 and 199 mg/dL OR HbA1c = 5.7–6.4% (ADA 2019).
2. Fifty control subjects, matched for age, sex, ethnicity, and body mass index and with fasting blood glucose of less than 100mg/dl AND 2 hours postprandial glucose/2 hours OGTT of less than 140mg/dl AND HbA1c less than 5.7 with no known comorbidities as per exclusion criteria.

Exclusion criteria

1. Known hypertensives
2. Diabetics
3. Serum creatinine > 1.6 mg/dL
4. Hematocrit < 35%
5. Evidence of any known case of chronic kidney disease (CKD), chronic liver disease (CLD), or any malignancy.
6. Use of any oral hypoglycemic agent (OHA).
7. All study subjects had a stable body weight for at least 3 months and had not participated in strenuous exercise before enrolment.

Methods

All the cases and controls underwent the following tests and examinations:

1. CLINICAL EXAMINATION

The study participants were called to the Department of Medicine, Dr. RML hospital, and asked to fill a predetermined questionnaire which included baseline data about age, sex, and family history of diabetes or hypertension. They then underwent a detailed clinical examination including measurement of height (using a stadiometer), weight (using a digital weight measurement scale), and waist circumference at the upper borders of both hip bones (using a standard measuring tape). BMI was calculated as weight (kg) divided by the square of height (meters). Resting systolic and diastolic blood pressures were recorded twice using an automated sphygmomanometer after a 5-min rest and a mean of two values of systolic BP taken as systolic BP, and a mean of two values of diastolic BP taken as diastolic BP.

2. LABORATORY INVESTIGATIONS

Investigations done in cases and controls were:

- Fasting plasma glucose
- 2-hour postprandial plasma glucose
- HbA1c (measured by immunoturbidimetry method on Vitros dry chemistry analyzer by NSGP guidelines).
- Serum lipid profiles including triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, and VLDL-cholesterol were estimated on a fully automated clinical chemistry analyzer.
- Fasting plasma insulin levels (measured by chemiluminescence immuno assay (CLIA) on Vitros ECiQ by orthoclinical diagnostics).
- Serum uric acid levels (by uricase reaction estimated on a fully automated clinical chemistry analyzer).
- Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as: HOMA-IR = (FPI × FPG)/22.5, where FPI is fasting plasma insulin (mIU/L) and FPG is fasting plasma glucose (mmol/L)
- Samples for **serum sclerostin levels** were centrifuged at 3000 rpm for 10 minutes. Serum was separated and then stored in aliquots at − 20°C in the Department of Biochemistry until the batch was analyzed by ELISA.

Human Sclerostin ELISA Test

- Kits of human sclerostin were imported from BT Lab, Batch No. E3068H
- Human sclerostin kit is an enzyme-linked immunosorbent assay (ELISA) for the measurement of human sclerostin levels in serum, plasma, cell culture supernates, ascites, and tissue homogenates. The plate was precoated with human sclerostin (SOST) antibody.

Test procedure

1. All reagents and serum samples were brought to room temperature; the assay is performed at room temperature.
2. Standard was diluted with standard diluent using the method of multiple proportion dilution. Fifty µl of standard was added to the standard well.
3. Forty µl sample was added to sample wells and then add 10 µl anti-SOST antibody to sample wells, then add 50 µl streptavidin HRP to sample wells and standard wells, and was mixed well. The plate was covered with a sealer and incubated for 60 minutes at 37°C.
4. The sealer was removed and washed the plate five times with wash buffer by soaking wells with 300 µl wash buffer for 30 seconds to 1 minute for each wash by automated ELISA washing machine.
5. Fifty µl of substrate solution A was added to each well, and then, 50 µl of substrate solution B was added to each well. Then, the plates were covered with new sealer and incubated for 10 minutes at 37°C in the dark.
6. Fifty µl stop solution was added to each well to stop the reaction (the blue color will change into yellow immediately).

7. Final measurement: ELISA microplate reader (at Biochemistry Lab RML Hospital) was used to measure optical density (OD) at 450 nm wavelength within 10 minutes after adding the stop solution.
8. According to standards concentration and the corresponding OD values, the standard curve linear regression equation was calculated. Then OD values of the sample were applied to the regression equation to calculate the corresponding sample's concentration.

3. Dual-Energy X-ray Absorptiometry (DXA) Scan:
A whole-body DXA scan was done, and then, the whole-body minus head bone mineral density was calculated. Lean body mass and fat mass percentage were also calculated with the help of a DXA scan. All BMD measurements were done by the same experienced operator. We used the World Health Organization criteria for osteoporosis. T scores were calculated as (BMD respondent—mean BMD reference group)/S. D. reference group. Osteopenia was defined as a T score between − 1.0 and − 2.5, while osteoporosis was defined as a T score <−2.5, as recommended by the World Health Organization.[8] The Z score is the number of standard deviations away from the average value of the reference group. This reference group usually consists of people of the same age and sex Z score calculated, Z score = (Patient's BMD – Expected BMD)/SD.

Statistical analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. The normality of data was tested by the Kolmogorov–Smirnov test. If the normality was rejected, then nonparametric tests were used.

Statistical tests were applied as follows:
1. Quantitative variables were compared using an unpaired t test/Mann–Whitney test (when the data sets are not normally distributed) between the two groups.
2. Qualitative variables were compared using Chi-square test/Fischer's exact test.
3. Pearson correlation coefficient/Spearman rank correlation coefficient was used to correlate quantitative parameters with each other.

A *P* value of < 0.05 was considered statistically significant.

The data were entered in MS Excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. 38

Results

The aim of this study was to assess the serum levels of sclerostin in prediabetics and compare them with the normoglycemic control group. It was a cross-sectional study, with 50 prediabetic cases and 50 controls (matching in age, gender, BMI, and blood pressure). The following observations were made [Tables 1 and 2].

Table 1: Demographic and anthropometric characteristics among cases and controls

Parameters	Cases (*n*=50)	Controls (*n*=50)	*P*
Age in years (Mean SD)	45.74 (7.59)	44.86 (7.26)	0.555
Gender (%) Males	31 (62%)	26 (52%)	0.313
Females	19 (38%)	24 (48%)	
BMI (Kg/m^2) (Mean SD)	23.64 (3.68)	24.15 (2.49)	0.427
Waist circumference (cm) (Mean SD)	87.54 (6)	87.1 (5.59)	0.705
Systolic BP (mm Hg) (Mean SD)	119.36 (6.09)	120.84 (6.94)	0.260
Diastolic BP (mm Hg) (Mean SD)	77.04 (4.76)	75.92 (4.88)	0.249

Table 2: Biochemical parameters among cases and controls

Parameters	Cases (*n*=50)	Controls (*n*=50)	*P*
Fasting blood sugar (mg/dL)	111.84 (7.49)	83.84 (7.7)	0.0001
Postprandial blood sugar (mg/dL)	173.34 (13.76)	124.52 (9.09)	0.0001
HbA1c (%)	5.97 (0.22)	4.99 (0.76)	0.0001
S. Fasting insulin	15.09 (2.11)	5.77 (1.56)	0.0001
HOMA-IR	4.16 (0.55)	1.21 (0.36)	0.001
Sclerostin (ng/ml)	18.22 (19.42)	11.08 (4.73)	0.013

Table 3: Comparison of serum sclerostin between the two groups. (*N*=100)

	Mean (SD)		*P*
	Cases (*N*=50)	Controls (*N*=50)	
Sclerostin (ng/ml)	18.22 (19.42)	11.08 (4.73)	0.013

Table 4: Mean bone mineral density and lean/fat mass among the cases. (*N*=50)

Parameter	Mean	Range
BMD (g/cm^2)	1.06 (0.14)	0.85 to 1.38
T score	−1.02	−3.30 to 1.80
Z score	−0.59 (1.55)	−4.70 to 2.90
Lean mass	67.20 (8.63)	45.50 to 88.30
Fat mass	32.29 (8.39)	16.30 to 54.50

Table 5: Distribution of cases according to subgroups of T score. (*N*=50)

T score subgroups	Number of cases (%)
Normal (≥ −1.00)	20
Osteopenia (−1.00 to−2.50)	21
Osteoporosis (≤ −2.50)	9

Serum sclerostin was significantly higher in the cases [18.22 (19.42) ng/ml] compared to the control group [11.08 (4.73) ng/ml] with a *P* value of 0.013 [Figure 1 and Table 3]. In prediabetics, the mean of BMD was 1.06 g/cm^2, T score was − 1.02, Z score was − 0.59, lean mass% was 67.20, and fat mass % was 32.29 [Table 4]. According to T score, 42% of the cases had osteopenia (T score between − 1 and − 2.5) [Figure 2 and Table 5]. Nine cases had osteoporosis, while 20 cases

had normal T score. There was a significant correlation observed between serum sclerostin and BMD, T score, Z score, and lean mass [Figure 3]. The correlation between serum sclerostin and BMD, T score, and Z score was fair and negative, while with lean mass, the correlation was fair and positive [Table 6].

Discussion

Sclerostin is emerging as a new bone marker in the endocrine regulation of bone, and higher serum levels of sclerostin were seen in people with prediabetes, type 1, and type 2 diabetes. In our study, mean serum levels of sclerostin were significantly higher in prediabetes compared to controls (18.22 ng/mL vs 11.08 ng/mL, $P = 0.013$), and the mean BMD in prediabetics was 1.06 g/cm^2 (0.85–1.38) which is lower compared to normal Indian reference range (whole-body BMD = 1.095 ± 0.083.73). There was a significant negative correlation between serum sclerostin levels and BMD in prediabetics ($r = -0.404$, $P < 0.001$).

Giuseppe Daniele e*t al.* showed elevated levels of sclerostin in the IGR group in comparison with the NGT group (50.8 ± 2.4 vs. 38.7 ± 2.3 pmol/L; $P = 0.01$).[7] Sclerostin levels were also assessed in diabetes patients too, Gennari *et al.*[9] in 2012, mean serum levels of sclerostin were found to be two times higher in T2DM patients as compared to the nondiabetes control group. In this study, levels of sclerostin correlated positively with duration of disease, higher age, HbA1c, fasting glucose levels, and males. In our study, although no significant correlation was seen with higher age, HbA1c, or fasting glucose levels, higher levels of sclerostin, although nonsignificant, were seen in males compared to females in both case and control group [(19.22 vs 16.60 $P = 0.648$ and 11.22 vs 10.95 $P = 0.841$)], respectively. A significant difference was also observed by García-Martín *et al.*, which noted that serum sclerostin levels were significantly higher in males compared to females in cases and controls (*P*-0.001 and *P*-0.048), respectively). In males, a positive correlation of serum sclerostin with age was also observed in both the diabetes group and controls ($P = 0.031$ and $P = <0.001$), but no such correlation was seen with age in female patients in both the groups.[10] Sclerostin levels also correlated with the age of diabetic patient and duration of illness, Agostino Gaudio *et al.* conducted a cross-sectional study and observed similar results that, serum sclerostin levels in T2DM patients were higher compared with nondiabetes were 53.18 ± 10.94 pmol/liter vs 47.50 ± 12.62 pmol/liter, respectively, with significant difference of $P < 0.05$. Serum levels of sclerostin positively correlated in both the groups with the age in diabetic group patients ($P < 0.0001$) and controls ($P < 0.001$) and also positively correlated with years since diagnosis in diabetes ($P < 0.001$).[6]

Table 6: Correlation of serum sclerostin with BMD. (*N*=50)

BMD w/Serum sclerostin	Correlation coefficient	*P*
BMD (g/cm^2)	−0.404	0.001
T score	−0.475	0.001
Z score	−0.361	0.001
Lean mass	0.315	0.026
Fat mass	−0.206	0.151

It is evident from past studies that patients with diabetes are predisposed to osteoporotic fractures due the low BMD. In consistence with previous studies, in our study, sclerostin levels were higher in prediabetes and BMD was low, with a negative correlation between serum sclerostin and BMD. Sclerostin is the risk factor for bone loss in diabetes. In 2021, Ulaş Serkan Topaloğlu *et al.* conducted a cross-sectional study on BMD and fracture risk in prediabetes, and found results similar to our study that bone mineral density and T scores at the lumbar spine and femoral neck region were lower in the prediabetes group compared to the control group ($P = 0.042$, $P = 0.039$, $P = 0.039$, and $P = 0.042$, respectively), and osteoporosis was also significantly higher in prediabetes group compared to the control group (23.3% vs 6.7%, $P = 0.045$).[11] In our study, mean T score was − 1.02(−3.30 to 1.80) which was lower compared to the normal WHO reference range. We also found that 42% of patients have osteopenia and 18% of patients have osteoporosis in the prediabetes group.

Few studies have also been conducted in the Asian region and also observed that low BMD is found in the diabetes population along with higher levels of sclerostin. In 2017, Wang *et al.*[12] conducted a study on diabetes patients in China to find the role of sclerostin in bone remodeling and observed that serum levels of sclerostin were higher in T2DM as compared to nondiabetes, and a significant inverse correlation was found between BMD and sclerostin in T2DM.

However, few studies did not corroborate with our study in terms of BMD loss and no correlation was seen between BMD and prediabetes. Lee *et al.*,[13] conducted a study on prediabetes and observed that there was no significant difference in the BMD and T scores between prediabetic subjects and the control group, but an inverse association was seen between both BMD and T score with higher age. Gennari *et al.* also did not find a significant correlation between serum sclerostin and BMD in T2DM with higher serum levels of sclerostin.[9]

There is a lot of research being done globally which uniformly indicates that serum levels of sclerostin are higher in prediabetes and diabetes as compared to the normal population. Studies to see the correlation between sclerostin levels and BMD in diabetes showed a bidirectional correlation (with most showing a negative and a few showing a positive correlation) with BMD. However, insofar as prediabetes is concerned minimal research is done in this group regarding skeletal complications and the effects of sclerostin on BMD. The spectrum of diabetes mellitus and its complications pose a vast and rapidly expanding health challenge in the current scenario in India as we are progressing toward becoming the diabetes capital of the world. As one of the few markers which increase in serum even before the development of overt diabetes, sclerostin is the one that is related to bone

homeostasis. As the number of diabetes patients increases in our country, it is of vital importance for secondary prevention to have some easily available biomarkers to detect the risk of osteoporosis and fractures early on in these patients.

Conclusion

The rapidly burgeoning number of diabetics in our country mandates early detection of complications and timely intervention. Easily available serum biomarker sclerostin is one such tool that can help us detect the risk of osteoporosis and fractures early on in these patients for timely intervention. Trials are even ongoing on antibodies against sclerostin (romosozumab) for the treatment of osteoporosis and prevention of it in diabetes.[14] It is important to note the relative deficiency of Vit D in patients with prediabetes. This fact is especially important in a primary healthcare setting, where a simple intervention of supplementing Vit D in patients of prediabetes may go a long way in preventing bony complications besides slowing the progression of prediabetes itself.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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