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Abdel Rahman G. Sloma
Department of Internal Medicine, Faculty of Medicine, Al-Azhar University, Assuit, Egypt,
abdogamalsloma@gmail.com

Mohamed Ismail Mohamed Abdelkareem
Rheumatology , Physical Medicine and Rehabilitation, Faculty of Medicine , Al-Azhar University, Assuit, Egypt

Alaa Mohamed Hashim
Clinical Pathology, Faculty of Medicine, Al-Azhar University, Assuit, Egypt

Haitham A. Azeem
Internal Medicine, Faculty of Medicine, Al-Azhar University, Assuit, Egypt

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ORIGINAL ARTICLE

Effect of Vitamin D Supplementation on Disease Activity and Fatigue In Systemic Lupus Erythematosis Patients with Hypovitaminosis D: A Randomized Controlled Trial

Abdel Rahman G. Sloma [a,*], Mohamed I. M. Abdelkareem [b], Alaa M. Hashim [c], Haitham A. Azeem [a]

[a] Department of Internal Medicine, Faculty of Medicine, Al-Azhar University, Assuit, Egypt
[b] Department of Rheumatology, Faculty of Medicine, Al-Azhar University, Assuit, Egypt
[c] Department of Clinical Pathology, Faculty of Medicine, Al-Azhar University, Assuit, Egypt

Abstract

Background: ***Systemic Lupus Erythematosus (SLE) is an autoimmune disease that affects many systems, characterized by an inflammatory process induced by an immune- complex formed by autoantibodies and autoantigens.***

Aim: ***To detect the effect of Supplementation with vitamin D on fatigue degree & activity in SLE disease patients with vitamin D deficiency.***

Patients and methods: ***This randomized controlled research was carried out on 100 female cases of SLE & vitamin D deficiency in Al-Azhar University Hospital (Assuit) from January 2019 to November 2021. Patients were randomized into two groups.***

Results: ***The SELDAI and FSS scores after 3 months of follow-up presented a statistically significant variance among both groups (P-value<0.05). After following up, an inverse non-statistically significant correlation between vitamin D level & disease activity (SLEDAI) in both groups (P-value= 0.117, r= -0.204 in the intervention group), (P-value=0.223, r= -0.197 in the control group) was detected.***

Conclusion: ***The overall FSS value was enhanced in the current study with vitamin D supplementation. Therefore, correction of vitamin D insufficiency may be critical for reducing fatigue symptoms and improving overall health in SLE patients.***

Keywords: SLE; Vitamin D; FSS; SELDAI

1. Introduction

SLE is an autoimmune disease that affects many systems, characterized by an inflammatory process induced by an immune-complex formed by autoantibodies and autoantigens.[1] It can affect any system, such as skin, CNS, lungs, serous membranes, joints, kidneys, or any system. SLE mainly affects middle-aged females between 20 and 30 years, especially non-caucasians, but can affect children, males, and neonates.[2]

The etiology of SLE remains uncertain; many risk factors have been involved in its pathogenicity, such as genetic factors, epigenetic factors, and environmental factors. The gene's inheritance alone is not sufficient for SLE development, as environmental triggers can affect these gene expressions.[3]

The phenotypic expression and SLE progression are related to a mix of genetic, environmental, & hormonal factors. One ecological factor is vitamin D, a vital hormone that has many actions on minerals' metabolism, musculoskeletal system health, and cardiovascular system health.[4]

Vitamin D is a steroid-based vitamin that mainly controls calcium absorption from the intestine, regulates calcium reabsorption in the kidney, & activates osteoclasts that mobilize phosphate and calcium from bones.[5]

Two well-known sources of vitamin D for humans, a small quantity, come from nourishment, although the majority is produced in the epidermal layer of the skin.[6] Apart from the maintenance of homeostasis of calcium & phosphate, vitamin D has proven to have different effects on numerous physiological aspects, as shown by the fact that its lack might result in general health problems.[7]

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* Corresponding author at: Internal Medicine, Faculty of Medicine, Al-Azhar University, Assuit, Egypt.
E-mail address: abdogamalsloma@gmail.com (A. G. Sloma).

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Vitamin D insufficiency has been proposed to play a role in hypertension pathogenesis, cardiovascular disorders, and periodontal disease. Respiratory infections, some malignancies such as prostate, colon, and breast cancers[8], and autoimmune disorders such as DM type I, SLE, multiple sclerosis, & rheumatoid arthritis.[9]

The present investigation aimed to assess the impact of vitamin D supplementation on fatigue and disease activity in individuals with SLE who have a shortage of vitamin D.

2. Patients and methods

This randomized controlled research was carried out on 100 female cases with SLE & vitamin D deficiency in Al-Azhar University Hospital (Assuit) throughout the time span of January 2019 to November 2021.

Randomization of patients

G*Power 3.1.9.2 for widows computed the sample size based on an Independent T-test to detect the difference between both groups regarding the level of SLEDAI scores. FSS scores at the power of a study were 95%, and the accepted error was 0.05, with an effect size of 0.75 and an allocation ratio of 1.5. The sample size was 100 SLE patients. Patients were randomized by a research randomizer.[10] into 2 different groups as follows: Group I (Treatment group): Sixty SLE cases with vitamin D deficiency were supplemented with vitamin D3; cholecalciferol of vitamin D3 2000 IU/day for 3 months. Group II (Control group): Forty SLE patients get standard SLE treatment without vitamin D supplementation for 3 months.

Inclusion criteria: All SLE Women from 18 to 43 years old, disease duration ≤ one year, hypovitaminosis D, SLEDAI scores ≥5, and not taking any medication containing vitamin D (Any diet that includes vitamin D was not considered a form of vitamin D supplementation) were eligible to participate in the current research.

Exclusion criteria: All SLE women with sepsis (evidence of severe infection), liver disease with AST & ALT exceeded 2.5, trauma, renal disorders with GFR less than or equal to sixty (cockrofgault), oliguria below 400 CC/day, pregnancy, & breastfeeding were excluded from the research.

Methods

After obtaining informed consent from the studied cases, they were subjected to a complete physical examination and calculation of SLEDAI and FSS scores. Then, the Supplementation of vitamin D3 was 2000 IU/day, while the control group did not administer anything. To check the adverse events of vitamin D supplements for the next month, patients were frequently followed up during the study. Patients and their family members supervised drug use by measuring the number of the remaining medications to measure the quantity of taken medicine. The surveillance took place for three months. At the end of the trial, each element of the study had to repeat monitoring of the Vitamin D levels, SLEDAI, and FSS scores.

Fatigue Severity Scale

The Fatigue Severity Scale (FSS) is one of the most frequently used inventories for measuring fatigue in people with chronic illnesses. The original FSS is a nine-item questionnaire that measures fatigue severity as a unidimensional concept.

Some measures are multidimensional and assess several dimensions of fatigue, such as mental and physical fatigue, but the FSS is designed to measure fatigue in a single dimension using the nine items, which represent a single scale. Each FSS item consists of statements that are scored on a seven-point ranging from 1 ("strongly disagree") to 7 ("strongly agree"). The mean of the nine-item scores is used as the FSS score, which ranges from 1 to 7. However, some studies have calculated an FSS score as the sum of all nine items, ranging from 9 to 63.[11]

Outcomes of the study

Before and after Supplementation, scores for SLEDAI and FSS were determined. SLEDAI: SLE Disease Activity Index is a proven worldwide evaluation of lupus disease activities.[11] FSS Score (Fatigue Severity Scale): a nine-item scale that deals with symptoms of fatigue; every item is scored from 1 to 7. A greater score signifies an elevated degree of weariness.[12]

Statistical analysis

Data were collected & entered into SPSS version 25 for Windows. Scale variables were presented in the form of numbers and percentages. A comparison among both groups was conducted using an independent T-test, and a follow-up on the change of scale variables was done using a paired T-test. Pearson correlation was done to assess the association among scale variables.

3. Results

There was no significant variance among the studied participants as regards baseline demographic & clinical characteristics p above 0.05. (Table 1)

Table 1. Baseline demographic & clinical characteristics of the studied participants; (N= 100):

	INTERVENTION GROUP N= 60	CONTROL GROUP N= 40	P-VALUE
AGE; (YEARS)	26.80 ±4.57	28.15 ±5.99	0.205
DISEASE DURATION; (MONTHS)	3.86 ±1.78	4.25 ±1.93	0.312
ESR; (MM/HR)	47.81 ±26.16	42.32 ±22.02	0.227
C3;	69.61 ±23.47	69.75 ±18.68	0.976

(MG/DL)		
C4; (MG/DL)	12.61 ±8.89	12.57 ±13.73	0.985
ANTI-DNA	70.60 ±33.54	67.37 ±36.58	0.651
EGFR	96.80 ±1.88	96.87 ±1.45	0.832
WBCS /µL	3494.17 ±1092.97	3557.50 ±1126.09	0.780
PLATELETS /µL	169.90 ±42.71	175.75 ±41.66	0.500
VITAMIN D; (NMOL/L)	45.36 ±11.50	47.72 ±13.04	0.344
ACR	18.38 ±7.08	18.80 ±9.76	0.817
FSS	4.90 ±1.09	4.73 ±1.19	0.470
SLEDAI	15.13 ±4.93	13.97 ±4.54	0.239

*p-value ≤0.05 is considered statistically significant (ESR): Erythrocyte sedimentation rate; (C3): Complement component 3; (C4): Complement component 4, (anti-DNA): Anti-double stranded antibodies, (eGFR): Estimated Glomerular Filtration Rate; (WBCs): White Blood Cells; (ACR): Albumin creatinine ratio, (FSS): Fatigue Severity Scale; (SLEDAI): Systemic Lupus Erythematosus Disease Activity Index. Vitamin D unit: nmol/L

The intervention group saw a substantial rise in blood vitamin D levels after receiving vitamin D supplementation. The mean rise in vitamin D levels was 24.63 ±15.2 nmol/L (p below 0.001) in the intervention group & 2.93 ±4.5 nmol/L (p=412) in control group. Following a three-month period of medication, the vitamin D group had a notable reduction in ESR levels, but the control group did not show any statistically significant improvements. The levels of Ant-DNA exhibited a significant drop in both the vitamin D group & control group. Nevertheless, the levels of C3, C4, eGFR, WBCs, and platelets exhibited a substantial rise in the vitamin D group as contrasted to control group. (Table 2)

Table 2. Mean levels of serum vitamin D & other SLE disease activity markers of the research cases at baseline & after 3 months; (N=100)

		INTERVENTION GROUP N= 60	CONTROL GROUP N= 40	P-VALUE (BETWEEN GROUPS)
VITAMIN D	Baseline	45.36 ±11.50	47.72 ±13.04	
	3 months	70.00 ±11.34	50.65 ±12.72	0.001*
	p-value (between before and after)	0.001*	0.412	
ESR	Baseline	47.81 ±26.16	42.32 ±22.02	
	3 months	36.71 ±23.29	40.52 ±25.22	0.440
	p-value (between before and after)	0.001	0.735	
C3	Baseline	69.61 ±23.47	69.75 ±18.68	
	3 months	85.53 ±19.24	77.87 ±18.86	0.052
	p-value (between before and after)	0.001	0.057	
C4	Baseline	12.61 ±8.89	12.57 ±13.73	
	3 months	18.56 ±7.20	14.32 ±7.74	0.218
	p-value (between before and after)	0.001	0.485	
ANT-DNA	Baseline	70.60 ±33.55	67.37 ±36.58	
	3 months	50.25 ±31.25	58.92 ±38.36	0.218
	p-value (between before and after)	0.001*	0.011*	
EGFR	Baseline	96.80 ±1.88	96.87 ±1.45	
	3 months	97.20 ±1.218	97.00 ±1.33	0.442
	p-value (between before and after)	0.049*	0.690	
WBCS	Baseline	3494.17 ±1092.97	3557.50 ±1126.09	
	3 months	4171.66 ±948.52	3603.75 ±991.78	0.005*
	p-value (between before and after)	0.001*	0.846	
PLT	Baseline	169.90 ±42.71	175.75 ±41.66	
	3 months	187.20 ±53.47	160.05 ±48.34	0.011*
	p-value (between before and after)	0.002*	0.124	
SLEDAI	Baseline	15.13 ±4.93	13.97 ±4.54	
	3 months	9.90 ±3.78	12.22 ±4.35	0.001*
	p-value (between before and after)	0.001*	0.001*	
FFS	Baseline	4.90 ±1.09	4.73 ±1.19	
	3 months	3.98 ±0.89	4.63 ±1.10	0.002*
	p-value (between before and after)	0.001*	0.041*	

Both groups' SLEDAI scores showed a substantial change before and after supplementation. p<0.001 for the experimental group. After a three-month study, the SLEDAI scores in both groups significantly reduced (p below 0.001). (Figure 1)

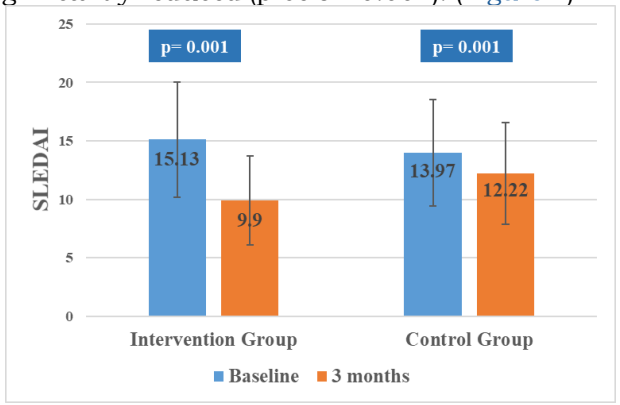

Figure 1. Comparison of the reduction in SLEDAI scores in SLE patients among the intervention & control groups after & before supplementing.

In intervention & control groups, there was a statistically significant variance in FSS score

before and after supplementation. A significant decrease in the average FSS score was noted in the group that received vitamin D supplementation, with a mean decrease of 0.95 ± 0.12. It indicates that fatigue alleviated considerably following oral vitamin D supplementation. The reduction in the control group was considerably less than that of the intervention group (p=0.002), averaging 0.1 ± 0.31; the variance was statistically significant (p equals 0.041). (Figure 2)

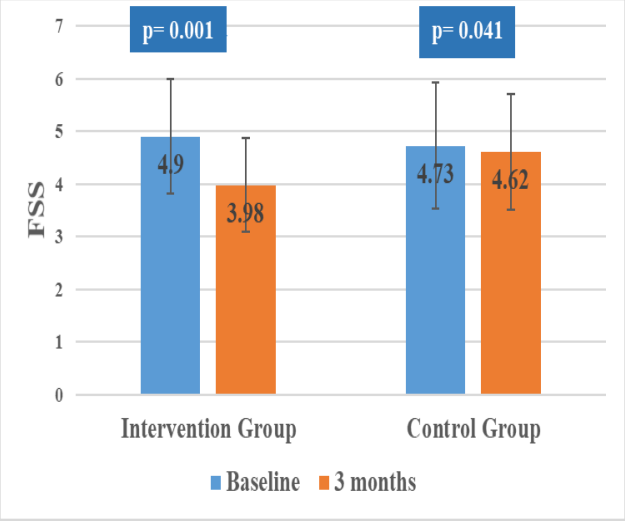

Figure 2. A comparison of the reduction in FSS score among individuals suffering from SLE before and after supplementation in the intervention & control groups.

There was an inverse significant linear association among vitamin D level & disease activity (SLEDAI) prior supplementation in all studied population (p=0.007; r= -0.268), and in each group separately (p=0.029, r=-0.283 in intervention group) and (p=0.153, r=-0.230 in control group). (Figure 3)

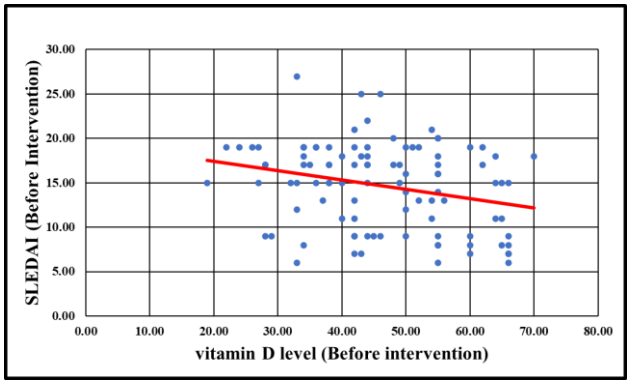

Figure 3. The relationship among Vitamin D level and SLDAI before intervention

Prior to supplementation, FSS and vitamin D levels exhibited an inverse correlation in all studied population (p=0.037; r= -0.209). However, when studying each group separately we lost this statistical significance, (p=0.100, r=-0.215, in intervention group) and (p=0.190, r=--0.240, in control group). (Figure 4)

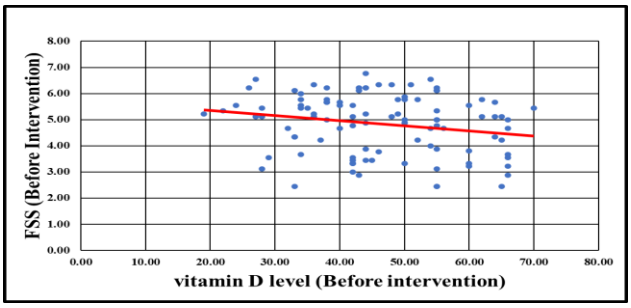

Figure 4. Correlation between vitamin D level and FSS before intervention

Relationship analysis revealed strong positive correlation among disease activity (SLEDAI) & fatigue condition as assessed by (FSS) score before getting supplementation (p=0.001, r=0.792 in intervention group) and (p=0.001, r=0.976, in control group). (Figure 5)

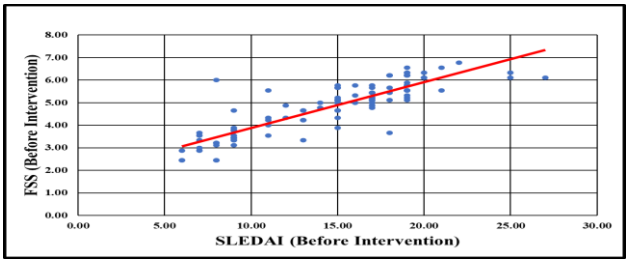

Figure 5. Correlation between SLEDAI and FSS before intervention

Relationship analysis revealed strong positive correlation among disease activity (SLEDAD & fatigue condition as assessed by (FSS) score after getting supplementation P-0022.4-0295 in intervention group) and (P=0.0011-0.914 in control group). (Figure 6)

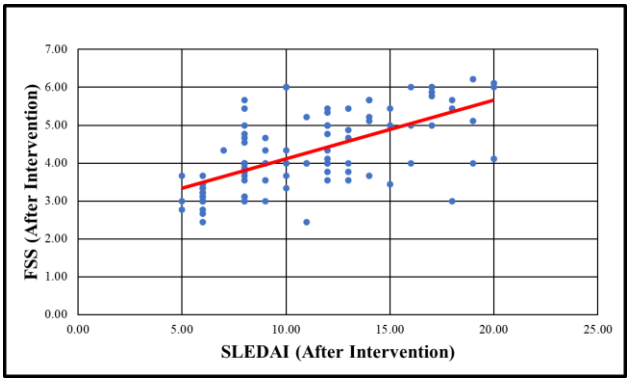

Figure 6. Correlation between SLEDAI and FSS after intervention

4. Discussion

There is widespread evidence that the pathophysiology and progression of autoimmune illnesses such as SLE are influenced by vitamin D.[7] At the At the start of the trial, all the individuals with SLE included had a deficit of vitamin D. no significant variance was noted

among the intervention & control groups in terms of their levels of vitamin D in the blood & indicators of disease activity.

Supplementation of vitamin D3 2000 IU/day for three months had a favorable impact on rising 25(OH) D serum levels. This was shown by a significant rise in levels of vitamin D in the intervention group, with an average rise of 24.63 ±15.2 (P-value <0.001) nmol/ L from the baseline. The rise in serum levels of vitamin D is higher than in a previous analysis, which reported an increase in vitamin D level of approximately 6.55 ±1.27 nmol/L from the initial baseline[13] and higher than another study reported an average rise in the level of vitamin D by 10 nmol/L after Supplementation with cholecalciferol 1000 IU daily for three to four months.[12] Furthermore, according to another report, there has been a rise in serum vitamin-D level to 40 nmol/Lafter 3000 IU supplementation of cholecalciferol for three months.[12] But changes in the level of Vitamin D are not necessarily related to the supplementing by vitamin D, which means that the same dose of vitamin D supplements does not always raise serum vitamin D; it relies on the individual features of each person. [13]

In the present research, the intervention & control groups showed that the average SLEDAI score was reduced after three months of Supplementation. The patients in the Lima et al. study were given vitamin D supplementation at a dosage of 50,000 IU weekly for six months, while the control group was given a placebo. After 6 months of Supplementation, SLEDAI changes in the two groups were significantly different, with P-value= 0.011.[14] In the research by Rifaâ et al., the SLEDAI score showed a substantial differential in both oral vitamin D and oral placebo groups before and after supplementing. [15]

In contrast to Al-Saleem et al.study that showed Following a 3-month therapy period, there was a reduction in SLEDAI scores from (6 ±5.6 to 5.1 ±6.3). However, this drop was not statistically significant.[16]

Correlation tests -before Supplementation- between baseline vitamin D levels and SLEDAI revealed an inverse significant linear association in all the studied population and in each group separately in the present investigation; after providing vitamin D, a negative correlation was seen between vitamin D levels & the activity of SLE illness. However, the statistical analysis did not show a significant outcome, with P-values of 0.117 & 0.223 in the intervention and control groups, respectively. Low levels of vitamin D are related to higher SLE activity.

Amital et al.performed a multicenter study in four European countries that included both children and adults and found a robust negative relationship between levels of low vitamin D & disease activity (P-value = 0.018; r = -0.125).[17]

According to Thudi et al., 20% of SLE patients with clinical and immunological manifestations had a lower level of vitamin D (47.7 nmol/L) in their study of 37 female SLE cases. Patients with low vitamin D levels have substantially greater disease activity than those with average vitamin D levels (p 0.003).[18]

Similar outcomes were also reported in Petri and his colleagues' study, where there was a reduction in disease activity among 21% of the studied patients when the serum vitamin D level increased by 20 nmol/ml.[19] In a substantial adult population of systemic lupus erythematosus in Australia, vitamin D deficiency has been associated with heightened disease activity. A prolonged association has been observed between elevated levels of vitamin D in the bloodstream and a decline in disease activity.[20] Abou-Raya et al. conducted research in Egypt to investigate the impact of taking 2000 IU/day of oral cholecalciferol for 12 months on disease activity among individuals with SLE who had serum Vitamin D levels of 30 nmol/L. They showed a substantial reduction in disease activity in the population studied.[19]

There are still uncertain signs of vitamin D insufficiency. Vitamin D insufficiency can, however, lead to fatigue, musculature illnesses (such as muscular pain throughout the body, muscular stiffness), elevated blood pressure, weight gain, joint pain, sleep disorders, headache, worsening concentration, diarrhea, and constipation.[21] In the current study, and before getting any medications, our studied patients experienced severe fatigue conditions with an average FSS score of greater than four. After the trial, the FSS scores in the supplements group (compared to the controls) reduced significantly, suggesting an improvement in the patient's fatigue symptoms.

Vitamin D insufficiency was initially found to contribute to fatigue in patients with SLE in a cross-sectional research that measured fatigue with a visual analog scale (VAS). SLE cases with vitamin D <10 nmol/L showed more fatigue than those with vitamin D >10 nmol/L.[22]

A previous review article involving twenty-two researchers with a total of 3,670 musculoskeletal pains and fatigue patients shows that 48 percent of these patients had significant vitamin D deficiencies and that the pain, muscle weakness, and physical function of subjects improved after the vitamin D concentration was improved.[23]

The shortage of vitamin D was long related to weakness in muscles. This is because skeletal

muscle has a vitamin D receptor. Proximal weakening of the muscles, lower stability of the body, and greater risk of falling were linked with hypovitaminosis D.[24]

Limitations: The relatively small sample size is considered to be of the current study's limitations. Still fatigue is a subjective parameter which may affect accuracy of scoring in Egyptian patients.

4. Conclusion

The overall FSS value was enhanced in the current study with vitamin D supplementation. Therefore, correction of vitamin D insufficiency may be critical for reducing fatigue symptoms and improving overall health in SLE patients.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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There are no conflicts of interest.

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