Original Article

Relationship between subclinical hypothyroidism and distal-symmetric diabetic polyneuropathy in type 2 diabetes mellitus referred to Kosar Hospital in Semnan and related indicators in 2019–2020

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Abstract

Introduction: Diabetes is one of the most common metabolic diseases and one of its important complications is diabetic neuropathy. Due to the relationship between diabetes and thyroid disorders, the present study was performed to determine the association between subclinical hypothyroidism and end-stage diabetic polyneuropathy in patients with type 2 diabetes. **Materials and Methods:** In this descriptive, analytical study, 154 patients with type 2 diabetes referred to Kosar Hospital in Semnan were evaluated. After recording their demographic information, samples were received for biochemical testing. The patients' neuropathy was then evaluated based on the United Kingdom screening test (UKST). The results were recorded in the data collection form and then analyzed using SPSS Statistics 22 software. **Results:** In this study, 154 patients were studied, including 49 with subclinical hypothyroidism and 105 with euthyroid. The results of the present study showed that the mean age of patients in the subclinical hypothyroid group was 60.08 years and in the euthyroid group was 60.77 years. Mean ± standard deviation (SD) of the patients' age, blood pressure, duration of diabetes, body mass index, fasting blood sugar (FBS) and Glucose, and 2-hour post prandial (2HPP) were not statistically significant between the two groups. The frequency of neuropathy severity based on clinical signs during examination and symptoms mentioned by the patients in the two groups was statistically significant ($P = 0.005$ and $P = 0.001$, respectively). The severity of neuropathy was not significantly associated with thyroid-stimulating hormone (TSH) levels ($P > 0.05$). **Conclusion:** From the results of the present study, it can be concluded that the severity of neuropathy based on the clinical signs during examination and the symptoms mentioned by the patient in diabetic patients is related to subclinical hypothyroidism. Further studies are recommended.

Keywords: Diabetes, neuropathy, subclinical hypothyroidism

Introduction

Diabetes mellitus (DM) is a very common disorder that manifests itself in different degrees of insulin resistance, impaired insulin secretion, and increased glucose production. It is estimated to affect more than 285 million people worldwide.[1] The prevalence of diabetes mellitus increases with age where prevalence is approximately 0.2% in people under 20 years old, 11.3% in people over 20 years, and more than 26.9% in people over 65.[2] In addition to the high prevalence of diabetes, which imposes a heavy burden on health care systems, it also has several acute

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and chronic complications in patients, such as cardiovascular, renal, neurological, infectious and ocular complications.[1-3] Neuropathy is one of the most common, dangerous and irreversible complications of diabetes that begins with sensory disturbance and ulcers, and if left untreated, can lead to cellulite, osteomyelitis, gangrene and eventually amputation.[4]

Like the other autoimmune disorders which have many complications,[5] diabetes (type 1) is also an autoimmune disease with higher prevalence in those with thyroid disorders rather than the healthy population. Autoimmune thyroid diseases are the most common thyroid disorders in patients with type 1 diabetes. A reason for this is that patients with autoimmune diseases of a particular organ are at a higher risk of developing other autoimmune disorders, infections, and cardiovascular disorders.[6]

The clinical manifestations of diabetes are not limited to pancreatic beta cells, and affect the whole body including the retina, kidneys, nervous system and vascular system. On the other hand, thyroid hormone is the main regulator of the whole-body metabolism and energy consumption, and its dysfunction affects many organs of the whole body. Both diabetes and thyroid are very common endocrine and metabolic diseases, and some studies point out a higher prevalence of thyroid dysfunction in both type 1 and type 2 diabetes.[7-9] The clinical relationship between type 1 diabetes and thyroid disease is known in the field of autoimmunity. This combination of autoimmune diseases is known as autoimmune polyglandular syndrome type 3. However, the relationship between thyroid function and type 2 diabetes is more complex. Both hyperthyroidism and hypothyroidism carry the risk of glucose intolerance.[10]

The prevalence of hypothyroidism in patients with type 1 diabetes has been reported to be approximately 0.5%.[11] In some studies, its prevalence has been reported to be 12% in women with type 1 diabetes and 2% in men with type 1 diabetes.[12] The prevalence of hypothyroidism in patients with type 2 diabetes has been reported to be between 1% and 2%.[13]

Hypothyroidism is a common metabolic disease in which even its subclinical type has complications such as lipid disorders, hypertension and cardiovascular complications.[14] Numerous studies have shown an association between type 1 diabetes and thyroid disorders.[13] Regarding type 2 diabetes and thyroid disorders, several studies have found that the simultaneous prevalence of type 2 diabetes and thyroid disorders is 10%–50%.[15]

Subclinical hypothyroidism is an asymptomatic stage of hypothyroidism that is defined by an increase in serum thyrotropin levels and a normal serum free thyroxine level.[16-20] The diagnostic criterion for this disorder is high serum concentration (5.06 mIU/L ≥ TSH) with normal serum FT4 level (0.95 to 1.60 ng/d in men and 0.89 to 1.50 ng/d in women).[2,21-23] Subclinical hypothyroidism is associated with a vascular endothelial dysfunction, which may lead to neuropathy due to poor function of small blood vessels.

The prevalence of thyrotoxicosis in people with type 2 diabetes is higher than that in the general population. Thyroid hormone affects glucose metabolism in several ways. Elevated thyroid hormone levels cause oxyhyperglycemia (a rapid rise in blood sugar after oral glucose loading). Increased glucose uptake is affected by the thyroid hormone as a result of increased gastrointestinal motility. However, the direct effect of thyroid hormone on the gastrointestinal tract is not unimaginable. T3 treatment increases the sodium-glucose linked transporter (SGLT1) activity in Caco-2 cells. Although SGLT1 mRNA is increased by T3, the level of SGLT1 protein does not change. Since thyroid hormone increases the activity of Na^+/K^+-ATPase, it is thought that this increase in activity is the result of the flow of Na^+ due to the increase in the activity of Na^+/K^+-ATPase by thyroid hormone.[24] Thyroid hormone also increases gluconeogenesis in the liver. This is due to the direct effect of thyroid hormone or the indirect effect through glucagon or catechol amines. In the adipose tissue, thyroid hormone stimulates lipolysis and increases serum free fatty acid levels, which causes insulin resistance. GLUT4 expression and muscle glucose uptake are increased in hyperthyroidism. In beta cells, thyroid hormone stimulates insulin secretion, though thyroid hormone also destroys insulin. In pancreatic alpha cells, thyroid hormone increases glucagon secretion. The sum of these effects is that thyroid hormone impairs glucose metabolism and causes glucose intolerance or diabetes mellitus. In addition, since thyroid hormone increases lipolysis, hyperthyroidism carries a risk of ketosis if it is associated with insulin deficiency. Even in the normal range of thyroid hormone, it is positively associated with insulin resistance in the early stages of type 2 diabetes.[25]

Given that various studies have been conducted on the effect of subclinical hypothyroidism on nephropathy and retinopathy in patients with type 2 diabetes but no studies have been conducted on its effect on neuropathy in people with diabetes, it seems that more and more extensive studies should be carried out to clarify the relationship between subclinical hypothyroidism and the incidence of neuropathy in people with type 2 diabetes. Given that the results of a small number of similar studies have not indicated a fully confirmed association between subclinical hypothyroidism and the incidence of neuropathy in people with type 2 diabetics, and considering the lack of complete knowledge about the pathogenesis of this common and very high-risk and costly disease, by finding a link between subclinical hypothyroidism and type 2 diabetes, we may be able to prevent complications by better controlling them. Hence, the present study was designed and conducted to determine the relationship between subclinical hypothyroidism and distal symmetric polyneuropathy (DSP) in patients with type 2 diabetes mellitus admitted to the internal clinics of Kosar Hospital in Semnan in 2019–2020.

Patients and Methods

In a descriptive, analytical study, all diabetic patients admitted to the diabetes clinic of Semnan University of Medical

Sciences were included in the study by the convenience method. Inclusion criterion was a history of diabetes or having diagnostic criteria for diabetes. Patients with signs and symptoms of thyroid disease including fatigue, weakness, dry skin, feeling cold and puffy on the face, hands and feet, or laboratory signs of clinical thyroid disease including high TSH levels with decreased free T4 level who had a history of thyroid medications, or were being treated with levothyroxine or Methimazole, or were using medications affecting thyroid such as glucocorticoids, oral contraceptives, and nonsteroidal anti-inflammatory medications, and also patients with certain diseases such as cancer, liver and kidney disorders, and chronic infection or with neuropathy for reasons other than diabetes were excluded from the study.

Finally, 154 patients entered the study after obtaining informed consent. A description of the procedure and purpose of the present study, and their demographic information such as age, gender, body mass index (BMI), systolic and diastolic blood pressure, duration of having diabetes and type of diabetes treatment were recorded. The weight of the subjects was measured by a digital scale with an accuracy of 100 grams and the heights of the subjects was measured by a tape measure with an accuracy of 0.1 cm by an experienced expert. Blood pressure was measured using a sphygmomanometer with a cuff model 710 made in Taiwan from the left arm. To measure hormonal and biochemical levels, blood samples were taken after 12 hours of fasting. Fasting plasma glucose was measured by enzymatic colorimetric method using glucose oxidase kit. Serum TSH and FT4 levels were measured by immunoenzymometric method using ELISA test. Glucose tolerance test was performed after consuming 75 grams of oral glucose for 5 minutes. Fasting blood sugar of 126 mg/dl or more was considered hyperglycemia.[26]

Diabetic neuropathy was also examined based on the UKST.[27,28]

In this study, neuropathy referred to distal symmetric polyneuropathy, which is the most common diabetic neuropathy and usually does not need to rule out other causes of neuropathy.

The examination is scored according to the British Screening Table including two parts: scoring based on the symptoms mentioned by the patient and clinical symptoms during examination.

128 Hz tuning fork, monofilament, hot and cold water, and reflex elastic were used to examine the sensations of vibration, heat, pain and reflex.[29]

Using a monofilament test, a 10-gram monofilament was used. First, it was touched on the sternum or forehead to examine the patient's sensation. Then, while the patient's eyes were closed, the monofilament hit on the dorsal aspect of the great toe near the nail bed to the extent that the monofilament bent to ninety degrees. The test was performed for each foot at each point. In case of lack of sensation of zero, the sensation score of less than the sternum was considered to be half a point, and the normal sensation was considered to be one point.

A score of 3 out of 8 means that the presence of neuropathy is likely. A score of 3.5 to 5 means that the risk of new-onset neuropathy in the next 4 years is high, and a score of 5.5 or greater indicates that there is a low risk of neuropathy onset in the next 4 years.[30] After completing the list of demographic, clinical and laboratory information, the subjects were divided into two groups based on their TSH and FT4 levels. Group A consisted of a person with diabetes with subclinical hypothyroidism and Group B consisted of a person with diabetes and euthyroid. The diagnostic criterion for subclinical hypothyroidism was based on a study by Amouzegar *et al*.,[22] including serum TSH concentration (≥5.06 mIU/L) with normal serum FT4 level (0.95 to 1.60 ng/dl in men and 0.98 to 1.50 ng/dl in women). Then, the indicators of neurological disorders in the two groups were studied and compared.

Data was analyzed using statistical *t* tests or its non-parametric equivalent (Mann-Whitney) for quantitative variables and chi square test or Fisher's exact test for qualitative variables in SPSS Statistics Version 16. In all tests, the level of confidence was 95% and the level of significance was less than 5%. Demographic characteristics of the samples were shown using mean ± SD and median (quartile of 25–75). The normality of the quantitative data distribution was evaluated using the Kolmogorov-Smirnov test. The difference between the means was analyzed by one-way analysis of variance (ANOVA) and post hoc test for multiple comparisons (after evaluating the assumption of equality of variances using Levine's test).

Given the concurrence of this study with the COVID-19 pandemic and the fact that patients with diabetes are among the high-risk groups in terms of the COVID-19 disease, the presence of patients in the hospital for examination was severely limited due to the risks of this disease.

This research was conducted in accordance with the principles set out in the Declaration of Helsinki. Informed consent was obtained from all patients. The study was carried out after the approval of the ethics committee of Semnan University of Medical Sciences (code: IR.SEMUMS.REC.1394.131). This article is taken from the Ph.D. dissertation of Dr Sara Reshadat, Semnan University of Medical Sciences (Plan No. 1743).

Results

Out of the 154 patients with diabetes, 49 had subclinical hypothyroidism and 105 had euthyroid. In subclinical hypothyroid group, 13 were male (26.5%) and 36 were female (73.5%). In the euthyroid group, 28 were male (26.7%) and 77 were female (73.3%). The two groups were significantly different in terms of gender distribution of patients ($P < 0.001$) and the frequency of women in both groups was higher than men.

In terms of the type of diabetes treatment in the subclinical hypothyroid group, 36 patients (73.5%) were being treated with oral medications for diabetes and 13 patients (26.5%) were being treated with oral medications along with insulin. In the euthyroid group, 71 patients (67.6%) were being treated with oral medications, 25 patients (23.8%) were being treated with oral medications along with insulin, and 9 patients (8.6%) were receiving no treatment. The frequency of treatment was not significantly different between the two groups ($P = 0.107$) [Table 1].

Table 2 shows mean ± SD of the patients' age, systolic and diastolic blood pressure, duration of diabetes, weight, height and BMI as well as values of fasting and 2HPP blood sugar parameters and thyroid stimulating hormone and free thyroxine in two groups with subclinical hypothyroidism and euthyroid. Patients in the two groups had a significant difference only in terms of mean level of TSH ($P < 0.001$) and other parameters were not significantly different between the two groups [Table 2].

There was a significant difference between the two groups in terms of the frequency of neuropathy severity based on clinical symptoms during examination ($P = 0.005$) and also based on the symptoms mentioned by the patient ($P = 0.005$). The severity of neuropathy based on clinical symptoms during examination was higher in the group of subclinical hypothyroid patients. In the hypothyroid group, 2 patients (4.1%) had severe neuropathy and 6 patients (12.2%) had moderate neuropathy, while in the euthyroid group, 2 patients (1.9%) had moderate neuropathy and 10 patients (9.5%) had mild neuropathy, and no severe neuropathy was observed.

The severity of neuropathy was higher in patients with subclinical hypothyroidism based on the symptoms mentioned by the patient. 17 patients (34.6%) had severe neuropathy, 8 patients (16.3%) had

Table 1: Frequency distribution of gender and type of treatment in two groups of subclinical hypothyroidism and no subclinical hypothyroidism

Variable	Group				*P*
	Euthyroid		Subclinical hypothyroidism		
	Frequency	Percentage (%)	Frequency	Percentage (%)	
Gender					
Female	36	73.5	77	73.3	<0.001
Male	13	26.5	28	26.5	
Type of treatment					
Oral	36	73.5	71	67.6	0.107
Oral and insulin	13	26.5	25	23.8	
None	0	0	9	8.6	

*Chi square test

Table 2: Evaluation of mean and standard deviation of demographic variables and laboratory values in two groups of subclinical hypothyroidism and euthyroid

Variable	Subclinical hypothyroidism	Mean	Std. deviation	Min	Max	*P*
Age	Yes	60.08	12.49	30	85	0.604
	No	60.77	10.09	32	86	
Systolic blood pressure (mmHg)	Yes	127.50	13.36	90	150	0.482
	No	126.53	13.52	90	160	
Diastolic blood pressure (mmHg)	Yes	78.43	7.51	60	95	0.578
	No	78.81	7.91	60	100	
Duration of diabetes (years)	Yes	9.10	6.75	1	22	0.252
	No	10.61	7.59	1	33	
Weight (kg)	Yes	78.56	14.62	40	123	0.439
	No	75.33	10.78	41	103	
Height (cm)	Yes	162.1	9.3	148	188	0.713
	No	161.7	9.6	145	187	
Body mass index (m^2/kg)	Yes	29.86	4.7	16.23	41.41	0.165
	No	28.85	3.9	17.07	37.17	
Fasting blood sugar (FBS)	Yes	144.86	41.6	75	259	0.977
	No	145.93	45.9	70	513	
2-hour postprandial blood sugar (2HPP)	Yes	208.89	54.83	75	329	0.888
	No	216.87	82.03	91	480	
Thyroid stimulating hormone (TSH)	Yes	7.43	4.59	5	28	< 0.001
	No	2.23	1.12	0	5	
Free thyroxine (FT4)	Yes	7.03	1.92	4	12	0.056
	No	7.40	1.72	1	10	

*Mann-Whitney *U*-test

moderate neuropathy and 18 patients (36.7%) had mild neuropathy. On the other hand, 17 patients (16.2%) in the euthyroid group had severe neuropathy and 22 patients (21%) had moderate neuropathy and 29 patients (27.6%) had mild neuropathy [Table 3].

Mean ± SD levels of thyroid stimulating hormone had no significant difference in patients with different neuropathic severity based on symptoms mentioned by the patient ($P = 0.133$) and clinical symptoms during examination ($P = 0.256$) in patients with subclinical hypothyroidism. In euthyroid patients, mean ± SD level of thyroid stimulating hormone had no significant difference in patients with different neuropathic severity based on the symptoms mentioned by the patient ($P = 0.585$) and clinical symptoms during examination ($P = 0.434$) [Table 4].

Discussion

Diabetic neuropathy is one of the long-term complications of diabetes that affects about 50% of patients with diabetes.[31] Studies have shown that between 4% and 17% of patients with diabetes are at risk for subclinical hypothyroidism.[32] Among type 2 DM patients, the rate of albuminuria in subclinical hypothyroidism group was significantly higher than that of euthyroid patients and with increasing initial and recurrent TSH levels, urine albumin-creatinine ratio (uACR) values and consequently albuminuria increased.[33]

A meta-analysis by Han *et al*.[34] indicates that patients with type 2 diabetes who also have subclinical hypothyroidism are more susceptible to diabetic neuropathy. The relationship between diabetic neuropathy in patients with diabetes and subclinical hypothyroidism has been less studied, and in this study, the results indicate a higher frequency of neuropathy based on clinical symptoms during examinations and symptoms mentioned by the patient in the two groups. However, there was no significant difference in the mean TSH with severity of neuropathy based on the patient's symptoms and clinical symptoms during examination in the two groups.

Table 3: Frequency distribution of neuropathy based on severity in two groups of subclinical hypothyroidism and euthyroid

Severity	Group				*P*
	Euthyroid		Subclinical hypothyroidism		
	Frequency	Percentage	Frequency	Percentage	
Severity of neuropathy based on clinical symptoms during examination					
Medium	6	12.2	2	1.9	0.005
Mild	10	20.4	10	9.5	
Sever	2	4.1	0	0	
Normal	16	32.7	20	19.0	
No information listed	15	30.6	73	69.5	
Severity of neuropathy based on the symptoms mentioned by the patient					
Medium	8	16.3	22	21.0	0.001
Mild	18	36.7	29	27.6	
Sever	17	34.7	17	16.2	
Normal	6	12.2	37	35.2	
No information listed					

Table 4: Comparison of mean TSH in patients with subclinical hypothyroidism and euthyroid based on the severity of neuropathy mentioned by the patient and clinical symptoms during examination

Subclinical hypothyroidism	Variables	Severity of symptoms	Mean	Std. deviation	Min	Max	*P*
Yes	Symptoms mentioned by the patient	Medium	7.0	1.8	5	11	0.133
		Mild	9.4	6.8	5	28	
		Sever	6.0	1.7	5	12	
	Clinical symptoms during examinations	Medium	7.0	2.6	5	12	0.256
		Mild	7.8	7.1	5	28	
		Sever	6.0	-	6	6	
		Normal	8.6	5.1	5	24	
No	Symptoms mentioned by the patient	Medium	2.5	1.2	0	5	0.585
		Mild	2.1	1.0	0	4	
		Sever	2.3	1.2	1	5	
	Clinical symptoms during examinations	Medium	1.5	0.7	1	2	0.434
		Mild	2.3	1.0	1	4	
		Sever	--	-	-	-	
		Normal	2.5	1.2	-	5	

*One-way ANOVA

In the present study, the age of patients was not significantly different between the two groups. In this regard, the studies of Yang *et al*.[35] and Chen *et al*.[36] also state that the patients with diabetes in the subclinical hypothyroidism group and euthyroid group are not different in terms of age. The results of a study by Yasuda *et al*.,[37] in contrast to our results, indicate that age of patients with diabetes with subclinical hypothyroidism was significantly higher than that of euthyroid patients. The reason for the difference in the results of these two studies may be the difference in sample size. Epidemiological studies on the prevalence of subclinical hypothyroidism in patients with type 2 diabetes have reported that the age of patients with diabetes is not relevant in the development of subclinical hypothyroidism.[32] It seems that according to the results of the present study and previous studies, there is no relationship between age of patients with diabetes and development of subclinical hypothyroidism.

The results of the present study showed that BMI and duration of diabetes were not different in the two groups. The results of the study by Yang *et al*.[35] and Chen *et al*.[36] are similar to the present study and no studies were found that contradict the results of the present study. Subclinical hypothyroidism in patients with diabetes does not appear to be related to BMI and duration of diabetes.

The results of our study showed that systolic and diastolic blood pressure was not significantly different in the two groups of patients. The study results of Yasuda *et al*.[37] were similar to the results of the present study and indicates that there is no significant difference in blood pressure levels between the two groups. The results of Yang *et al*.[35] showed that diastolic blood pressure was significantly different between the two groups but systolic blood pressure was not different between the two groups. The results of Chubb *et al*.[32] showed a weak relationship between subclinical hypothyroidism and systolic blood pressure, but no relationship with diastolic blood pressure. The results of these two studies are not consistent with the results of the present study, which may require further studies in this regard.

The results of the present study showed that there is no significant difference between the types of diabetes medications used in patients with diabetes in the two groups. The results of the study of Chubb *et al*.[32] showed that there was no difference between the use of insulin or metformin in the two groups. No studies have been found to show there is a relationship between medications used in patients with diabetes with subclinical hypothyroidism. The use of diabetes medications in patients with diabetes does not appear to be related with subclinical hypothyroidism.

The results of the present study showed that the levels of FBS and 2HPP were not significantly different in the two groups of patients. In other words, controlling blood sugar in patients with diabetes is not related to subclinical hypothyroidism. Yasuda *et al*.[37] and Yang *et al*.[35] in their study showed that the level of HbA1c in the two groups of patients did not differ, which is consistent with the results of the present study. Blood sugar control in patients with diabetes does not appear to be related to subclinical hypothyroidism.

In the study on the relationship between diabetic neuropathy and subclinical hypothyroidism, the results of the present study showed that the frequency of neuropathy severity based on clinical signs during examination and symptoms mentioned by the patients in the two groups was statistically significant. Han *et al*.[34] in a meta-analysis study showed that there is an association between subclinical hypothyroidism and diabetic neuropathy. Numerous studies have confirmed the association between chronic complications of diabetes and subclinical hypothyroidism, most of which are related to nephropathy, retinopathy and cardiac complications.[38,39] On the other hand, studies on the relationship between diabetic neuropathy and subclinical hypothyroidism are few.[34] Shirabe *et al*.[40] stated that neuropathic changes in patients with hypothyroidism may be associated with cross-sectional demyelination due to basal metabolic disorders in Schwann cells. On the other hand, distal motor delays increase in subclinical hypothyroidism, Therefore, it can be stated that there is an axonal change in subclinical hypothyroidism.[41] Also, like other type of disorders such as cancers and infections,[42,43] the role of genetics should be considered in this disease.

One of the features of this study that distinguishes it from other studies is the simultaneous study of the relationship between subclinical hypothyroidism and diabetic neuropathy based on clinical signs during examination and symptoms mentioned by the patient. One of the limitations of this study is that it is a cross-sectional study in which dependence on time and place is an inevitable component. Furthermore, it is not possible to determine the causal relationship in these studies, so data analysis should be carried out with more caution. Undoubtedly, other confounding factors such as tobacco use, genetics, and lifestyle can affect the results of this study. It is not possible to study all of these cases in one study and it requires prospective studies with a larger sample size.

Conclusion

BMI, 2HPP, FBS, blood pressure, type of treatment and duration of diabetes in patients with diabetes were not associated with subclinical hypothyroidism. However, the severity of neuropathy in patients with diabetes was associated with hypothyroidism based on clinical symptoms and symptoms mentioned by the patient, which requires attention in this group of patients.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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