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ORIGINAL ARTICLE

Vitamin D insufficiency in obese patients with severe mental illness taking olanzapine

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Abstract The purpose of the study was to assess the vitamin D status of obese patients with severe mental illness (SMI) treated with olanzapine. Fifteen obese SMI patients treated with olanzapine were pair-matched with healthy obese subjects. Another 52 overweight and obese SMI patients volunteered to participate in the study (total $n = 67$) and were divided into three subgroups (group A = overweight, group B = obese, group C = severely obese). Anthropometric, body composition, blood glucose, lipids, 25(OH)D, intact parathyroid hormone, and calcium measurements were performed. No differences were found between healthy and SMI subjects in any of the dependent variables ($p > 0.05$). The obese and severely obese patients demonstrated significantly lower levels of serum 25(OH)D concentration ($p < 0.01$) compared with overweight. A significant inverse correlation was found between serum 25(OH)D concentration and all anthropometric parameters ($p < 0.05$). The results indicate that obese SMI patients appear to be vitamin D deficient, similar to healthy obese subjects. The level of obesity seems to play a significant role in their vitamin D status: the greater the body fat of the patients the lower the serum 25(OH)D concentration. Thus, as in healthy individuals, an inverse association exists between the degree of adiposity and the serum 25(OH)D concentration in SMI patients

Keywords Vitamin D · Severe mental illness · Antipsychotic medications · Obesity

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Introduction

Patients with severe mental illness (SMI) represent a special at-risk population, with elevated medical co-morbidity and mortality rates [3, 14, 21, 27]. Obesity and the metabolic syndrome are among the most common medical conditions observed in these patients [3, 14, 21, 27, 30]. The high prevalence of obesity and its co-morbidities in SMI patients have been primarily attributed to the use of second-generation psychotropic drugs [2, 25]. Particularly, atypical antipsychotics such as olanzapine and clozapine are associated with significant weight gain, insulin resistance, and atherogenic lipid profile [2, 11, 25]. These conditions increase the incidence of metabolic syndrome, diabetes, and coronary heart disease, thus increasing the risk of morbidity and mortality in this population group [2, 21, 25, 27]. Apart from the side effects of psychotropic medications, the obesity epidemic observed in these patients is furthermore associated with the unhealthy lifestyle practices that this population usually engages in. These practices include poor nutrition and overeating, lack of regular physical activity, smoking, and other substance abuse [5]. The aforementioned unhealthy behaviors and the side effects of the medications further increase the risk for cardiac and metabolic diseases.

In healthy obese populations, an inverse relationship has been reported between body mass index (BMI) and serum

25-hydroxyvitamin D [25(OH)D] levels [4, 16]. More specifically, numerous studies support a direct inverse relationship between vitamin D and obesity markers. Research studies have consistently shown that serum 25(OH)D concentrations are lower in obese subjects and that both body weight and percentage of body fat increase as serum 25(OH)D concentrations fall [7, 10, 12]. Additionally, patients with vitamin D receptor gene polymorphisms, which cause reduction in vitamin D activity, tend to be associated with increased body weight [6, 15, 26]. Finally, the observation that weight increases with higher latitude, lower altitude, and during the winter, indicates that vitamin D could also be associated with weight regulation [23]. However, the mechanisms responsible for the association between body weight and vitamin D levels are not clear yet.

In SMI patients, the presence of obesity in combination with the antipsychotic medications could possibly lead to vitamin D status disorders. In studies of patients with depression, there has been an inconsistency in the findings about whether depression causes vitamin D insufficiency or whether low vitamin D levels are implicated in the pathology of the disease [8]. Moreover, no studies have been conducted on the effect of obesity and/or antipsychotic medications on the vitamin D levels and the health status of SMI patients. This is of primary importance for the treatment of these patients as low vitamin D levels have been shown to alter metabolite function and to contribute to insulin resistance and metabolic syndrome, disorders that are high in prevalence in SMI patients [24]. Hence, the purpose of the present study was first to assess the vitamin D status of obese SMI patients treated with atypical antipsychotics and to compare it to the vitamin D status of healthy obese subjects. Second, we sought to investigate whether the level of obesity could affect the vitamin D status of SMI patients. We hypothesized that the obese SMI patients will have a deficiency in serum 25(OH)D concentration, similarly to the healthy obese participants. Furthermore, we hypothesized that an inverse relationship will exist between the level of obesity and the serum 25(OH)D concentration in the SMI patients.

Methods

Subjects

Fifteen obese SMI patients (14 women, 1 man) were pair-matched with 15 obese healthy subjects (14 women, 1 man) according to BMI and age. All SMI patients were recruited for the study from March 2010 to May 2010. Inclusion criteria for the SMI patients were BMI >30 kg/m^2 and stable use of the antipsychotic medication olanzapine for a minimum of 1 year. Patients were diagnosed with mood or psychotic disorder according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) by a certified psychiatrist. They were recommended to participate in the study from the clinical psychologists of Iaso Hospital in Athens, Greece, and from private psychiatry offices located in Athens.

Healthy participants were recruited among the clients of the Dietetic Department of Iaso Hospital. Inclusion criteria for the healthy subjects were BMI >30 kg/m^2, the absence of any severe mental illness and abstinence from antipsychotic medications for the past 3 years. Prior to participation in the study, all healthy participants underwent an interview with a certified clinical psychologist to certify that they had not experienced any mental health problems during the past 3 years.

In order to investigate the effect of the level of obesity in the vitamin D status of our SMI subjects, we additionally recruited another 52 overweight and obese SMI patients taking olanzapine (42 women, 10 men) to participate in the study. Inclusion criteria were the aforementioned. The total group of SMI patients ($n = 67$) was divided into three groups (group A = overweight, BMI = 25–29.9 kg/m^2, group B = obese, BMI = 30–34.9 kg/m^2, group C = severely obese, BMI $\geq$35 kg/m^2). Institutional Review Board approval for the study was obtained by the Ethical Committee of the Iaso Hospital and all subjects signed an informed consent form prior to participation in the study.

Assessment

Anthropometric measurements were performed for all participants in the beginning of the study. Body height was measured without shoes on a wall-mounted stadiometer (SEGA, Germany). Waist circumference was measured at the narrowest part of the subjects' waist using a non-stretch tape. In addition, measurement of body weight and body composition (body fat and fat free mass) was performed using the BodPod (Life Measurement Inc, CA, USA) following the manufacturers' instructions. This is a whole-body air-displacement plethysmography method of body composition assessment [13].

All subjects had venous blood drawn (5 ml) between 7:00 a.m. and 8:00 a.m. after overnight fasting. All blood samples were collected in the Spring of 2010 (from March to May) to have control over the effect of season on serum 25(OH)D concentration. The samples were analyzed on the day of collection using chemiluminescence methods for glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides (COBAS 800, Roche Diagnostics Corporation, Indianapolis, IN, USA), intact parathyroid hormone (PTH), and calcium (ELECSYS, Roche Diagnostics Corporation, Indianapolis, IN, USA) in the central laboratory of the

hospital using clinical routine methods. Analysis of Serum 25(OH) D was analyzed using the 25(OH) D I-radioimmunoassay kit with an assay sensitivity of 1.5 ng/ml (DiaSorin Inc, Stillwater, MN, USA). The definition of vitamin D levels was vitamin D sufficiency (≥75 nmol/l), vitamin D insufficiency (50–74.9 nmol/l), and vitamin D deficiency (<50 nmol/l) [9].

Statistical analysis

Continuous variables are expressed as mean ± standard error and categorical variables are expressed as frequencies (%). A paired *t* test was used to assess differences between the two matched subject groups (patients and healthy individuals). A one-way analysis of variance (ANOVA) was used to assess differences among the three groups of SMI patients based on obesity level, followed by post hoc tests. Correlations were evaluated by calculating the Pearson coefficient (*r*). Multiple regression was performed, using serum 25(OH)D concentration as the dependent variable. Age, body weight, BMI, waist circumference, and percent body fat were accounted for independent variables. The threshold for significance in all tests was set at $p = 0.05$. Statistical analysis was performed using SPSS for Windows, version 17 (SPSS Inc, IL, USA).

Table 1 Baseline characteristics of SMI patients ($n = 15$) and healthy subjects ($n = 15$)

	SMI patients	Healthy subjects	*p* value
Age (years)	38.54 ± 2.70	37.18 ± 3.39	0.802
Height (m)	1.67 ± 0.02	1.62 ± 0.02	0.142
Weight (kg)	89.80 ± 5.10	85.97 ± 5.50	0.259
BMI (kg/m^2)	31.97 ± 1.29	32.08 ± 1.24	0.212
Waist circumference (cm)	100.63 ± 3.52	105.90 ± 6.81	0.375
Fat mass (kg)	39.57 ± 2.97	38.96 ± 2.94	0.668
Body fat (%)	45.10 ± 1.56	44.89 ± 1.99	0.923
Glucose (mg/dl)	88.40 ± 1.79	87.77 ± 2.32	0.834
Total cholesterol (mg/dl)	197.45 ± 14.96	211.63 ± 17.08	0.553
LDL cholesterol (mg/dl)	123.20 ± 13.93	136.72 ± 15.35	0.539
HDL cholesterol (mg/dl)	49.95 ± 2.88	51.36 ± 2.96	0.758
Triglycerides (mg/dl)	119.07 ± 23.35	115.09 ± 17.41	0.905
Calcium (mg/dl)	9.15 ± 0.10	9.39 ± 0.09	0.106
25(OH)D (nmol/l)	49.06 ± 4.72	48.64 ± 3.40	0.933
Parathyroid hormone (pg/ml)	41.99 ± 6.64	27.50 ± 4.09	0.097

Results

No significant differences were found in all anthropometric and body composition parameters between the healthy and SMI subject groups as expected, as subjects were pair-matched for BMI (Table 1). All subjects were obese with an average BMI of 31.97 ± 1.29 kg/m^2 in the SMI patients and 32.08 ± 1.24 kg/m^2 in the healthy obese. Furthermore, there were no significant differences between the two paired groups in serum 25(OH)D concentration, PTH, calcium, glucose, and lipid levels ($p > 0.05$). The vitamin D status of both SMI patients and healthy controls was characterized as vitamin D deficiency with an average serum 25(OH)D concentration at 49.06 ± 4.72 nmol/l in the SMI patients and 48.64 ± 3.40 nmol/l in the healthy subjects.

In the larger sample of SMI patients ($n = 67$), 22 subjects were overweight (BMI = 26.84 ± 0.47 kg/m^2), 23 subjects were obese (BMI = 32.56 ± 0.26 kg/m^2), and 22 subjects were obese grade II and III (BMI = 41.85 ± 1.28 kg/m^2) (Table 2). As expected, there were significant differences in all anthropometric and body composition markers among the three groups ($p < 0.05$).

Significant differences were found in serum 25(OH)D concentration among the three obesity groups in the SMI patients. More specifically, the obese and those characterized as grade II and III obese patients demonstrated significantly lower serum 25(OH)D concentration ($p < 0.01$) compared with the overweight patients (overweight 79.79 ± 3.68 nmol/l vs. obese 58.29 ± 5.24 nmol/l vs. grade II and III obese 56.48 ± 4.82 nmol/l). Moreover, the vitamin D status of the overweight patients was characterized as within the normal range, while the vitamin D level of the obese and grade II and III obese was characterized as vitamin D insufficiency. No significant differences were found among all three groups in PTH and calcium levels ($p > 0.05$). Furthermore, no significant differences were found in glucose and lipid levels in all the three groups ($p > 0.05$).

A significant inverse correlation was found between serum 25(OH)D concentration and all anthropometric parameters. Specifically, serum 25(OH)D concentration was significantly inversely correlated with body weight ($r = -0.273$, $p = 0.03$), fat mass ($r = -0.282$, $p = 0.02$), % body fat ($r = -0.303$, $p = 0.01$), BMI ($r = -0.287$, $p = 0.01$), and waist circumference ($r = -0.308$, $p = 0.01$) (Fig. 1).

In an effort to establish if anthropometric variables such as BMI, body weight, percent body fat, and waist circumference are significant predictors of the variance observed in serum 25(OH)D concentration, multiple regression analysis was run. Multiple regression showed that percent body fat and waist circumference were

Table 2 Differences in dependent variables among three levels of obesity (overweight, obese, severely obese) in SMI patients ($n = 67$)

	Overweight ($n = 22$)	Obese ($n = 23$)	Severely obese ($n = 22$)
Age (years)	38.72 ± 2.75	39.78 ± 2.68	41.68 ± 2.35
Height (m)	1.66 ± 0.02	1.63 ± 0.001	1.66 ± 0.002
Weight (kg)	75.02 ± 2.89	87.69 ± 2.02	117.29 ± 5.97**,†
BMI (kg/m^2)	26.84 ± 0.47	32.56 ± 0.26*	41.85 ± 1.28**,†
Waist circumference (cm)	91.31 ± 2.38	104.08 ± 1.21*	123.14 ± 3.41**,†
Fat mass (kg)	28.33 ± 1.37	39.53 ± 0.82*	61.54 ± 3.45**,†
Body fat (%)	37.43 ± 1.40	46.09 ± 0.86*	51.73 ± 1.15**,†
Glucose (mg/dl)	92.03 ± 2.53	99.40 ± 4.05	109.96 ± 7.04**
Total cholesterol (mg/dl)	215.45 ± 11.10	210.60 ± 9.47	206.32 ± 9.41
LDL cholesterol (mg/dl)	135.96 ± 9.13	131.22 ± 7.64	125.14 ± 7.90
HDL cholesterol (mg/dl)	53.41 ± 2.72	53.36 ± 3.58	51.43 ± 3.08
Triglycerides (mg/dl)	134.71 ± 21.24	154.43 ± 27.99	140.18 ± 17.07
Calcium (mg/dl)	9.37 ± 0.11	9.27 ± 0.006	9.31 ± 0.10
25(OH)D (nmol/l)	79.79 ± 3.68	58.29 ± 5.24*	56.48 ± 4.82**
Parathyroid hormone (pg/ml)	35.40 ± 3.16	43.87 ± 4.81	49.20 ± 6.83

* $p < 0.05$ between overweight and obese

** $p < 0.05$ between overweight and severely obese

† $p < 0.05$ between obese and severely obese

significant predictors of serum 25(OH)D concentration as opposed to BMI and body weight. More specifically, percent body fat was a significant predictor of the variance in serum 25(OH)D concentration, explaining 29.7 % of the variation ($p = 0.015$). Furthermore, waist circumference was also a significant predictor of the variance in serum 25(OH)D concentration, explaining 30.6 % of the variation ($p = 0.013$).

Discussion

A high prevalence of obesity and its related co-morbidities have been demonstrated in patients with severe mental illness. In healthy obese populations, an inverse association exists between obesity markers and vitamin D status, as increased fat mass has been shown to decrease the bioavailability of vitamin D. To our knowledge, no studies have been reported investigating the levels of vitamin D in obese SMI patients and its association with obesity markers. Our study demonstrates for the first time that obese SMI patients exhibit a similar level of vitamin D deficiency with healthy obese populations. Furthermore, we found an inverse relationship between serum 25(OH)D concentration and obesity markers. More specifically, as the obesity level of the SMI patients increases, serum 25(OH)D concentration significantly decreases, a fact that is also true for healthy obese populations.

To our knowledge, this is the first study that has demonstrated a deficiency in vitamin D status for obese SMI patients, similar to that observed in obese healthy subjects. In healthy obese subjects, whole-body obesity, as defined by BMI, has been related to or contributes to low vitamin D status [4, 7, 10, 12, 16]. Wortsman et al. [31] have found lower vitamin D3 levels in healthy obese subjects after experimental UV irradiation, deducing that "obesity-associated vitamin D insufficiency is likely due to the decreased bioavailability of vitamin D3 from cutaneous and dietary sources because of its deposition in body fat compartments". Moreover, it has been established that insufficient serum 25(OH)D alters metabolite function and is related to insulin resistance and metabolic syndrome, causing perturbation of many cellular functions [24]. The mechanism by which vitamin D deficiency affects the metabolic and overall health of SMI patients is not clear, as no other studies have been conducted on this population. More research is required to establish the role of vitamin D deficiency in the health of SMI patients and whether vitamin D supplementation could possibly contribute to the treatment of these high-risk patients.

A significant reduction in serum 25(OH)D concentration was found as the level of obesity rose for the SMI patients. More specifically, we found that serum 25(OH)D concentration significantly decreases from vitamin D insufficiency to vitamin D deficiency as the SMI patients change from overweight to obese and grade II and III obese. Furthermore, we have found a significant inverse relationship between serum 25(OH)D concentration and markers of obesity such as body weight, percent body fat, and waist circumference in the SMI patients. Finally, multiple regression revealed that only percent body fat and waist circumference, and not the crude measurements of body weight and BMI, are independent predictors of the variance in serum 25(OH)D concentration, both explaining

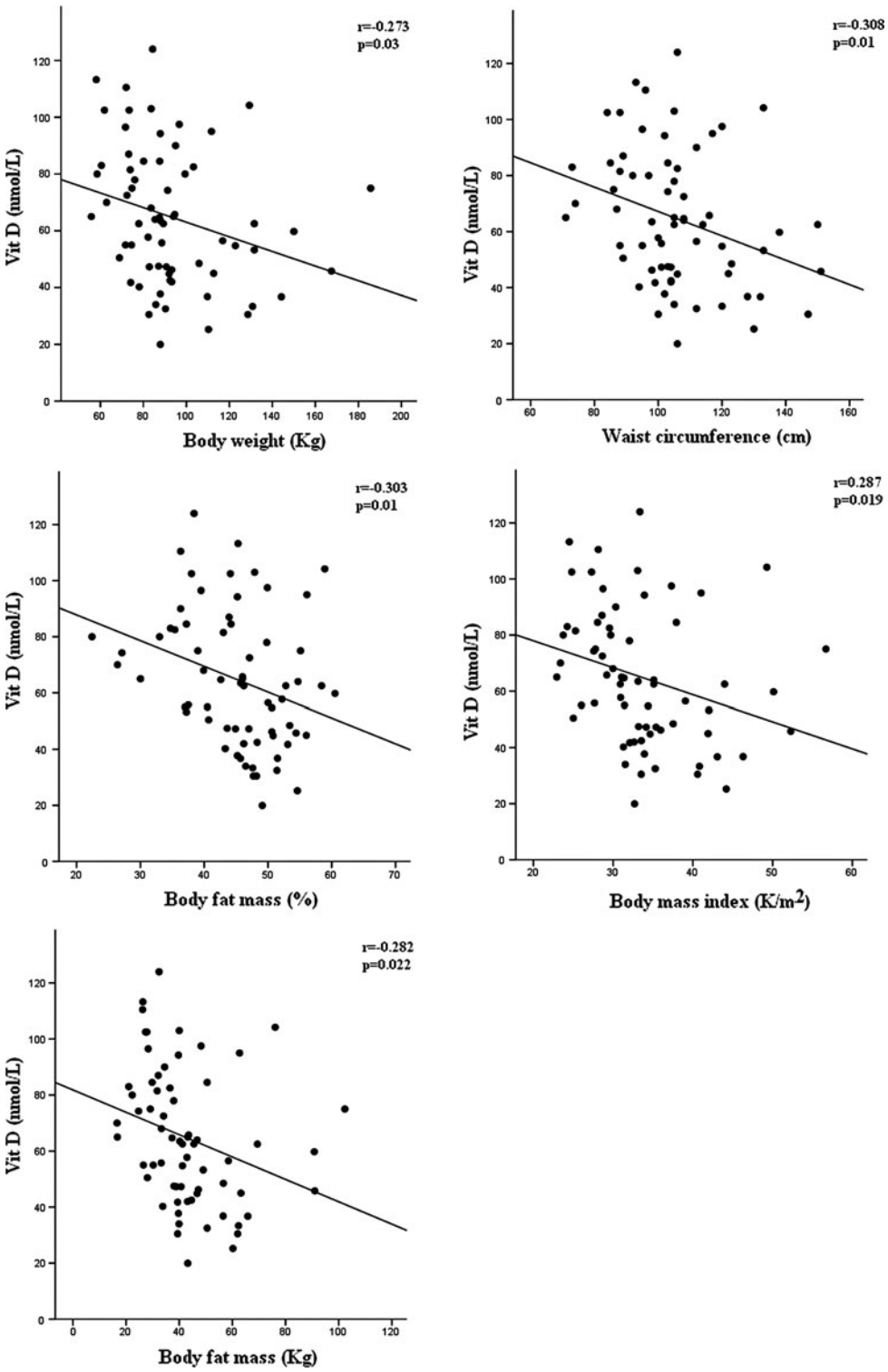

Fig. 1 Relationship between serum 25(OH)D concentration and anthropometric markers in 67 overweight and obese severe mental illness patients

approximately 30 % of the concentration of serum 25(OH)D in this population. Our findings are in agreement with studies on healthy obese individuals where levels of vitamin D are inversely related to BMI, body fat, waist circumference, and markers of the metabolic syndrome [18]. To the authors' knowledge, no studies have been reported on the relationship between serum 25(OH)D concentration and markers of obesity in SMI patients. This

is of special interest as this group of patients is highly susceptible to obesity and metabolic disorders, primarily due to the effect of second-generation antipsychotic medication.

In the present study, the level of obesity in SMI patients appeared to clinically affect the PTH levels of our patients, although not in a statistically significant manner. More specifically, we found a ~20 % increase in PTH concentration in obese patients and a ~30 % increase in grade II and III obese patients, compared with overweight patients. Secondary hyperparathyroidism is a common finding in cases with chronic vitamin insufficiency and it can have major consequences in bone metabolism [17]. In SMI patients, an increased fractured risk has been identified but its possible association with low vitamin D concentrations has not been studied [1, 22, 28]. However, as the levels of PTH in our study did not exceed normal ranges, we cannot draw a conclusion and more research is needed to identify a possible association between vitamin D deficiency and bone metabolism.

The etiology of obesity in the specific population of SMI patients has primarily been attributed to different physiological mechanisms compared with healthy obese populations. While healthy obese people gain weight primarily due to unhealthy lifestyle practices such as lack of exercise and poor eating habits, the obesity development of SMI patients has primarily been attributed to the effects of antipsychotic medications. Second-generation antipsychotics are associated with significant weight gain through a direct cellular effect on adipocytes by increasing lipogenesis and reducing lipolysis [20, 29, 32]. The relative obesity risk of these medications varies, with the highest weight gain reported with clozapine and olanzapine, followed by risperidone and quetiapine, and finally by ziprasidone and aripiprazole [19]. Despite the different physiological mechanisms implicated in the development of obesity in obese healthy and obese SMI patients, it is possible that the same physiological mechanism applies for both populations in terms of vitamin D. The existence of an inverse association between obesity markers and serum 25(OH)D concentration in obese SMI patients as in healthy obese individuals, suggests that vitamin D deficiency is a common feature of obesity between these two different populations, despite the different reasons for the development of obesity. This vitamin D deficiency is likely to be attributed to the decreased bioavailability of vitamin D3 because of its deposition in the increased body fat stores [31]. Hence, it is important that SMI patients are advised to try and increase their vitamin D intake either through vitamin D supplementation or through more light exposure to achieve an optimal vitamin D status.

In conclusion, the present study demonstrates for the first time low levels of serum 25(OH)D concentration in obese SMI patients taking olanzapine. Furthermore, an inverse relationship exists between serum 25(OH)D concentration and obesity levels, as also seen in healthy obese individuals. More research is required to establish such a phenomenon and investigate whether vitamin D supplementation or greater light exposure could benefit the vitamin D status of SMI patients.

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Conflict of interest None.

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