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Prediction of Nonadherence and Renal Prognosis by Pre-Transplantation Serum Phosphate Levels

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Background:

Identifying characteristics of patients at high risk of poor adherence before transplantation would be advantageous. However, the optimal approach for characterizing such patients remains unknown. We aimed to evaluate the association between factors for hemodialysis nonadherence and post-transplant renal prognosis. We hypothesized that these factors would influence post-transplantation adherence and worsen renal prognosis.

Material/Methods:

We reviewed patients on hemodialysis who underwent kidney transplantation at our hospital between 2000 and 2017 to identify risk factors associated with poor prognosis. The patients' background and pre-transplantation data, known hemodialysis nonadherence factors, serum phosphate and potassium levels, and interdialytic weight gains were evaluated. The primary endpoint was renal death. We also evaluated the fluctuation of calcineurin inhibitor concentration and weight gain after transplantation.

Results:

Seventy-seven patients were eligible, and the mean observational period was 83.2 months (standard deviation, 50.5). Thirteen patients reached the endpoint. Cox proportional hazards regression analysis showed that pre-transplantation serum phosphate level was a risk factor for renal death ($p < 0.05$), while serum potassium levels and weight gain were not. In addition, fluctuation of calcineurin inhibitor concentration was observed in patients with higher phosphate levels before transplantation ($p = 0.03$). Weight gain after transplantation was not associated with the hemodialysis nonadherence factors.

Conclusions:

High pre-transplantation serum phosphate levels are considered to represent poor drug adherence and/or an unhealthy lifestyle. Patient education that conveys the importance of adhering to medications and provides nutritional guidance is crucial for improving post-transplantation renal prognosis.

MeSH Keywords:

Dialysis • Kidney Transplantation • Medication Adherence • Patient Compliance

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Background

While the development of novel immunosuppressive agents has improved long-term renal outcomes after transplantation, several other factors can also be modified to improve renal prognosis [1]. Nephroprotective strategies, including blood pressure control, proteinuria reduction, and administering statins for hyperlipidemia, are important for kidney transplant recipients. Furthermore, patient education is also critical and has favorable effects on renal prognosis [1,2]. Education of patients with kidney disease involves providing nutritional guidance, offering advice about lifestyle modifications, and promoting adherence to medical regimens [3]. Some patients may have little knowledge or motivation to learn about their own health, and may also be reluctant to change their lifestyle or habits [4]. Intensive education is crucial for patients who have low levels of adherence to medical regimens or who have lifestyle factors that worsen renal prognosis. However, it is difficult to predict the characteristics of patients at high risk of poor adherence to medical regimens after kidney transplantation before the procedure.

The factors associated with poor adherence of patients on hemodialysis to medical regimens, which reportedly lead to poor prognosis, include blood urea levels, serum potassium concentration, interdialytic weight gain (IDWG)/dry weight (DW) [5–7], skipping dialysis sessions, and shortened dialysis sessions [5,7]. Although questionnaires and food records are commonly used to investigate dietary adherence [8], indirect approaches, including the measurement of serum albumin, potassium, and phosphate levels, and the IDWG/DW [9], have also been employed.

Adherence after transplantation can be evaluated by monitoring fluctuations of calcineurin inhibitor (CNI) trough level [10] and weight gain [11]. Nevertheless, it would be better to predict the patients' characteristics before transplantation in order to improve graft outcomes.

This study aimed to evaluate the relationship between factors associated with hemodialysis nonadherence and post-transplant renal prognosis. We hypothesized that factors related to poor adherence to treatment and dietary regimens in hemodialysis patients may also be involved in poor adherence after transplantation, leading to poor outcomes.

Material and Methods

Patients on maintenance hemodialysis who underwent kidney transplantations at Nagasaki University Hospital between 2000 and 2017 were enrolled in this study. Patients with preemptive

kidney transplantation, those who did not receive dialysis, and those on maintenance peritoneal dialysis were excluded.

The pre-transplantation data, including the hemodialysis status, the laboratory data from within 1 month before transplantation, and the medications prescribed, were collected from the patients' medical referral letters. The hemodialysis data were collected from the dialysis charts of the 3 dialysis sessions immediately preceding the patients' kidney transplantation. The IDWGs were calculated using the average weekly body weight gains (defined as pre-dialysis weight minus post-dialysis weight) over the previous 3 dialysis sessions. The corrected calcium levels were obtained using the Payne equation, as follows: $corrected\ calcium = calcium - serum\ albumin + 4$ [12]. Due to the extremely low rates of skipped and shortened dialysis sessions in Japan [7], these factors were not measured. Instead, the serum potassium and phosphate levels and the IDWG/DW were adopted as the hemodialysis nonadherence parameters [7,9]. Since the Japanese Society for Dialysis Therapy (JSDT) clinical practice guidelines [13] clearly state the target serum phosphate level, we divided the patients into 2 groups based on their levels: >6 mg/dL and ≤ 6 mg/dL. The study's primary endpoint was renal death; graft loss, and death with a functioning graft (DWFG). As indices of adherence, we investigated the fluctuation of the CNI trough level and weight gain for 1 year after transplantation. CNI trough level changes were evaluated based on methods in a previous report [10]. In brief, the variability in CNI trough levels was estimated by the coefficient of variation (CV), which was calculated by dividing the standard deviation by the average value. A ratio of 1: 200 was applied to convert the darbepoetin-alfa and epoetin-beta pegol doses to their equivalent epoetin doses [14].

Statistical analyses

The data were analyzed using the Wilcoxon rank sum test, Fisher's exact tests, linear regression models, and univariate and multivariate Cox proportional hazards regression analyses. Since the number of patients who reached the primary endpoint was not expected to be large, multivariate Cox proportional hazards regression analysis was only performed by adjusting the dialysis vintage because it reflects arteriosclerosis [13] and donor type (living or deceased) [15] in Japan. All analyses were performed using JMP® software, version 13 (SAS Institute Inc., Cary, NC, USA). A value of $p < 0.05$ was considered statistically significant.

Ethical considerations

All procedures involving human participants were performed in accordance with the ethical standards of the institutional review board (IRB) of Nagasaki University Hospital (18041606) and with the 1964 Helsinki Declaration and its later amendments.

Table 1. Patients' baseline characteristics.

Basic transplantation data		Hemodialysis conditions	
Age at transplantation (years)	46.1±12.6	Dialysis time (hour)	4.06±0.57
Sex, men: women	51:26	DW (kg)	57.9±11.0
Body mass index (kg/m ²)	21.4±3.2	Mean IDWG/DW (%)	4.30±1.58
Dialysis vintage (months)	103±93	Mean systolic BP (mmHg)	148±21
Donor, living: deceased	52: 25	Mean diastolic BP (mmHg)	85±13
ABO incompatible transplant	19 (25%)	Blood examinations	
HLA mismatch AB	2.06±1.09	Hemoglobin (g/dL)	10.8±1.1
HLA mismatch DR	0.91±0.67	Corrected Ca (mg/dL)	9.31±0.75
Donor age (years)	53.3±11.6	Phosphate (mg/dL)	6.19±1.43
Total ischemic time (minutes)	327±371	iPTH (pg/mL)	172±177
Complications		K (mEq/L)	4.80±0.62
Hypertension	56 (73%)	Alb (g/dL)	3.87±0.37
Diabetes mellitus	10 (13%)	Drugs	
Ischemic heart disease	8 (10%)	Vitamin D use	53 (69%)
Past history of stroke	3 (4%)	Phosphate binder use	71 (92%)
Causes of renal failure		Cinacalcet use	11 (14%)
Chronic glomerulonephritis	48 (63%)	Erythropoietin use	67 (87%)
Diabetic nephropathy	8 (10%)	Erythropoietin dose (U)	4737±3623
Others	18 (20%)	Intravenous Fe use	17 (22%)
Unknown	3 (4%)	Immunosuppressants	
		MMF + Tac + mPSL	53 (69%)
		MMF + CyA + mPSL	8 (10%)
		MMF + Tac + Eve + mPSL	15 (19%)
		Other	1 (1%)

The data presented are the means (standard deviations) and the number of patients [frequencies (%)] for the nominal variables. HLA – human leukocyte antigen; DW – dry weight; IDWG – interdialytic weight gain; BP – blood pressure; Ca – calcium; iPTH – intact parathyroid hormone; K – potassium; Alb – albumin; Fe – iron; MMF – mycophenolate mofetil; Tac – tacrolimus; CyA – cyclosporine; Eve – everolimus; mPSL – methylprednisolone. A ratio of 1: 200 was applied to convert the darbepoetin-alfa and epoetin-beta pegol doses to the equivalent epoetin doses. The bold font indicates the factors associated with hemodialysis nonadherence.

Although all patients in this study were informed of the investigations being performed, the study was a medical record-based retrospective analysis and the included patients were anonymized. Therefore, the IRB approved the exemption from obtaining written informed consent.

Results

Patients' demographic data

During the study period, 110 patients received kidney transplants at our hospital, of which 77 met the inclusion criteria and were enrolled in this study. We excluded patients with preemptive kidney transplants (n=20), patients on maintenance peritoneal dialysis (n=10), and patients whose data described factors associated with hemodialysis nonadherence that were unavailable (n=3). The patients' mean (standard deviation [SD]) age at transplantation was 46.1 years (12.6 years).

Table 2. Univariate Cox proportional hazards regression analysis for primary endpoint (renal death).

	HR	95% CI	P value
Age at transplantation, per year	1.00	0.95–1.04	0.9
Sex: men vs. women	0.59	0.20–1.85	0.4
Dialysis vintage, per month	1.00	1.00–1.01	0.2
Donor: living vs. deceased	0.64	0.21–2.00	0.4
ABO incompatible transplantation	0.66	0.17–3.15	0.6
HLA mismatch AB	1.15	0.71–1.91	0.6
HLA mismatch DR	1.89	0.85–4.35	0.1
Donor age, per year	1.02	0.97–1.09	0.4
Total ischemic time (min.)	1.00	1.00–1.00	0.9
Hypertension	0.98	0.32–3.62	0.9
Diabetes mellitus	5.54	1.40–19.6	0.02
Ischemic heart disease	2.21	0.34–8.28	0.4
Dialysis time (hours)	0.90	0.32–2.48	0.8
Dry weight (DW) (kg)	1.04	0.99–1.09	0.1
Mean IDWG/DW	1.13	0.80–1.59	0.5
Mean sBP, per mmHg	1.00	0.97–1.02	0.9
Hb, per g/dL	1.02	0.61–1.70	0.9
Corrected Ca, per mg/dL	3.05	1.35–7.30	0.007
Phosphate, per mg/dL	1.63	1.08–2.47	0.02
iPTH, per pg/mL	1.00	0.99–1.00	0.7
K, per mEq/L	0.62	0.23–1.64	0.3
Alb, per g/dL	0.67	0.10–4.88	0.7
Vitamin D use	5.11	1.30–34.1	0.04
Phosphate binder use	1.05	0.20–19.1	0.9
Cinacalcet use	2.51	0.37–10.3	0.3

HLA – human leukocyte antigen; DW – dry weight; IDWG – interdialytic weight gain; sBP – systolic blood pressure; Hb – hemoglobin; Ca – calcium; K – potassium; iPTH – intact parathyroid hormone; HR – hazard ratio; CI – confidence interval; Alb – albumin. The bold font indicates the factors associated with hemodialysis nonadherence.

The study population comprised 51 men and 26 women, and the kidneys were transplanted from both living (n=52) and deceased donors (n=25). Table 1 presents the patients' baseline characteristics and kidney transplantation details. The mean (SD) IDWG/DW was 4.30% (1.58%), serum phosphate level was 6.19 mg/dL (1.43 mg/dL), and serum potassium level was 4.80 mEq/L (0.62 mEq/L). Although phosphate binders were prescribed to 92% of the patients, the serum phosphate levels of 36 patients (47%) exceeded 6.0 mg/dL.

The mean (SD) post-transplant observational period was 83.2 months (50.5 months). Thirteen patients (17%) reached the study's endpoint. Ten patients (13%) experienced graft losses

and 3 (4%) were categorized as DWFG. The etiology of graft loss was not always determined because not all patients underwent renal biopsies or were checked for donor-specific antibodies; however, based on the clinical course, most seemed to be due to chronic rejection. The etiology of the 3 cases of DWFG was infectious diseases, such as pneumonia.

Univariate Cox proportional hazards regression analysis

To elucidate the relationships between the pre-transplantation factors and the transplanted kidney's prognosis, we performed univariate Cox proportional regression analyses of the primary endpoint (Table 2). Diabetes mellitus ($p=0.02$), corrected

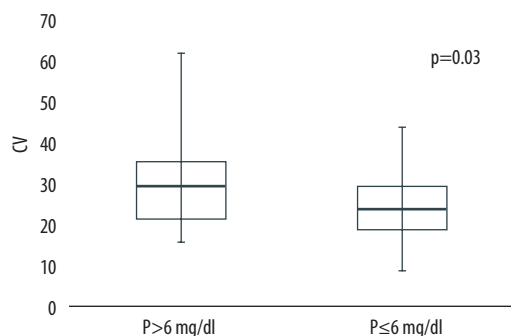


Figure 1. Box plots of the fluctuation in calcineurin inhibitor concentration in the first year after transplantation. CV – coefficient of variation. P>6 mg/dL – the patients whose serum phosphate level were >6 mg/dL; P≤6 mg/dL – the patients whose serum phosphate level were ≤6 mg/dL.

calcium level ($p=0.007$), serum phosphate level ($p=0.02$), and the administration of vitamin D ($p=0.04$) were significantly correlated with the primary endpoint. Among the predetermined factors associated with hemodialysis nonadherence, only serum phosphate level was significantly associated with the renal prognosis.

Dialysis vintage-adjusted Cox proportional hazards regression analysis of serum phosphate levels

Next, we performed dialysis vintage-adjusted Cox proportional hazard regression analysis of serum phosphate levels. The dialysis vintage clearly differed between living (60 months, SD: 64 months) and deceased donor kidney transplantations (194 months, SD: 80 months; $p<0.001$) and may have reflected preexisting arterial calcification. Even after adjusting for the dialysis vintage, the serum phosphate level remained a good predictor of renal outcomes (hazard ratio [HR]: 1.93; 95% confidence interval (CI): 1.24-3.03; $p=0.006$).

The association between serum phosphate level and nonadherence parameters

When dividing patients based on their pre-transplantation serum phosphate concentrations, those whose serum phosphate was >6 mg/dL ($n=36$) exhibited more fluctuation in their CNI trough levels than those whose serum phosphate was ≤6 mg/dL ($n=41$) ($p=0.03$) (Figure 1). On the other hand, there was no significant difference in weight gain 1 year after transplantation between the patients in the higher and lower serum phosphate groups ($p=0.4$) (Figure 2).

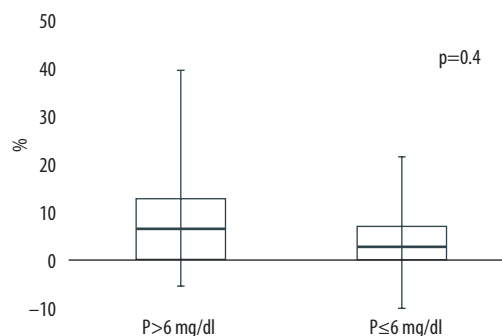


Figure 2. Box plots of the weight gain at 1 year after transplantation. P>6 mg/dL – The patients whose serum phosphate levels were >6 mg/dL; P≤6 mg/dL – the patients whose serum phosphate levels were ≤6 mg/dL.

Correlations among the factors associated with hemodialysis nonadherence

The correlations between the predetermined factors associated with hemodialysis nonadherence were evaluated by linear regression models. The linear regression models' correlation coefficients (r^2) were as follows: serum phosphate and serum potassium, $r^2=0.07$; serum phosphate and IDWG/DW, $r^2=0.11$; and serum potassium and IDWG/DW, $r^2=0.05$. Although there was a weak correlation between the serum phosphate level and IDWG/DW, no significant linear relationships existed among the other parameters.

The pretransplant serum phosphate and potassium levels may be affected by body mass; therefore, we evaluated the association among these factors. There were no significant correlations between body mass index and serum phosphate ($r^2=0.003$) or serum potassium levels ($r^2=0.03$). In addition, there was no significant correlation between IDWG/DW and post-transplant weight gain ($r^2<0.01$).

Chronic kidney disease and mineral bone disorder associated factors

Since the univariate Cox proportional hazards regression analysis showed that chronic kidney disease (CKD) and mineral bone disorder (MBD)-related factors (corrected calcium level, serum phosphate level, and vitamin D use) were significantly associated with the renal prognosis, and that these factors could interact with one other, we analyzed the relationships among them.

Table 3. Vitamin D administration, and the corrected serum calcium, serum phosphate, and intact parathyroid hormone levels.

	Vitamin D (+) (n=53)	Vitamin D (-) (n=24)	P value
Corrected Ca (mg/dL)	9.41±0.73	9.06±0.71	0.06
Phosphate (mg/dL)	6.08±1.61	6.53±0.98	0.2
iPTH (pg/mL)	172±188	171±157	0.5
Cinacalcet use	11 (20.8%)	0 (0%)	0.01

The data presented are the means (standard deviations) and the number of patients (frequencies (%)) for the cinacalcet use. Vitamin D (+): The patients who were administered vitamin D. Vitamin D (-): The patients who were not administered vitamin D. Ca – calcium; iPTH – intact parathyroid hormone.

Vitamin D was administered to 53 patients (68.5%) (Table 1). The vitamin D analogues administered were intravenous maxacalcitol (n = 23), oral alfacalcidol (n=21), and intravenous or oral calcitriol (n=15), which included duplicate-use cases. All of the patients who were administered cinacalcet also received vitamin D. Since vitamin D increases the serum calcium and phosphate levels, the differences in the MBD parameters (mean corrected calcium, mean serum phosphate, and mean intact parathyroid hormone [iPTH] levels) between the individuals who were or were not administered vitamin D were assessed (Table 3). The corrected serum calcium level was higher in the patients who were administered vitamin D compared with that in those who were not, but the difference was not significant ($p=0.06$). Notably, the serum phosphate level tended to be lower in patients who received vitamin D in comparison to those who did not ($p=0.2$). The iPTH level was similar in both patient groups ($p=0.5$). The linear regression model showed that there was no correlation between the serum calcium and phosphate levels ($r^2<0.001$).

Discussion

In this study, we hypothesized that the factors associated with hemodialysis nonadherence may also be valid for predicting post-kidney transplantation nonadherence. Among these factors, only serum phosphate levels were associated with poor postoperative outcomes. Moreover, we found that the CNI concentration after transplantation may fluctuate more in patients with higher phosphate levels before transplantation.

The important adherence factors in transplantation are drug adherence and dietary modifications; however, these are difficult to evaluate quantitatively, even though we used the fluctuation of CNI concentration and weight gain as indices of non-adherence after transplantation in this study.

Although the data from the Dialysis Outcomes and Practice Patterns Study indicated that overall compliance with medication was extremely high in Japan, about 35% of the patients in

that study did not take the prescribed phosphate binders [7]. Unfortunately, patients who are prescribed more phosphate binders tend to be less compliant with their medication [16]. In the present study, almost all patients were prescribed phosphate binders, and there was no significant correlation between the administration of vitamin D and the serum phosphate level. Therefore, the higher serum phosphate levels may have been caused by poor adherence to the drugs or due to lifestyle modifications [3,16]. Higher serum phosphate levels may themselves affect renal prognosis, but may also be a marker of patient characteristics that could lead to poorer outcomes after transplantation.

Drug adherence and food counseling are important components of patient education at our institution. Accordingly, the pharmacists and dietitians schedule multiple appointments with the patients before and after transplantation. However, given the time constraints on patient education at busy and understaffed facilities, it may be difficult to adequately educate all post-transplantation patients at all facilities.

Among the factors associated with hemodialysis nonadherence analyzed in this study, only the serum phosphate level predicted the renal outcomes; the serum potassium level and the IDWG/DW were not significant predictors. Since the serum potassium level is affected by a range of other factors, it is considered to have a low level of specificity as a predictor of nonadherence [5]. The IDWG/DW is higher in Japan compared with that in other countries [7], and this is thought to be reflective of sodium intake [17]. Although the patients' post-renal transplantation sodium intake can cause severe metabolic syndrome and weight gain, which affects renal prognosis [18,19], there was no significant association between the IDWG/DW and renal prognosis in this study.

As serum calcium and phosphate levels and vitamin D use are very important factors associated with CKD and MBD, we investigated the relationship among these factors. Several factors are known to influence serum phosphate level, including hyperparathyroidism, diet, administration of phosphate binders and

vitamin D, and compliance with medications [16,20]. Although the mean serum phosphate level slightly exceeded the normal range (3.5–6.0 mg/dL) stated in the JSDT clinical practice guidelines, the treatments were based on these guidelines [13], despite slight variations among the different facilities.

A previous study showed worse renal prognosis in patients whose pre-transplantation serum phosphate levels were more than 7.5 mg/dL or less than 3.5 mg/dL [21]. However, our study indicated that the serum phosphate level was linearly correlated with renal prognosis. Our study cohort seemed to have no patients with poor nutritional status, which may reflect the reduced access to kidney transplantation in Japan because of donor shortages [15], and living donor organs being available only to healthier and younger patients.

Preexisting arterial calcification should also be considered, and our study's findings indicate that MBD-related factors can predict renal prognosis. Notably, patients who were administered vitamin D exhibited a poor renal prognosis. Although there was no significant relationship between the administration of cinacalcet and renal prognosis, the HR for the administration of cinacalcet was 2.51, which suggests that continuous hyperparathyroidism affected renal prognosis. A previous report showed that cinacalcet cessation at the time of kidney transplantation resulted in continuous hyperparathyroidism and hypercalcemia [22]. Other studies have demonstrated that persistent hyperparathyroidism affects renal prognosis; patients with iPTH levels of >65 pg/mL at 5 years post-transplantation had poor transplanted kidney outcomes [23], and 5% of patients required parathyroidectomies after transplantation as a consequence of hypercalcemia [24]. Our results show that the pre-transplantation iPTH levels did not differ between patients that did or did not receive vitamin D. Nevertheless, vitamin D treatment might be a predictive factor for continuous hyperparathyroidism after kidney transplantation, especially in long dialysis vintage cases.

The fluctuation of CNI trough levels is thought to be associated with patients' adherence to prescribed drugs. Previous studies have shown that patients with high variability had a greater risk of poor graft outcomes [25,26]. Weight gain after transplantation should be avoided because of its association with poor renal outcomes [19,27]. In this study, only the fluctuation in CNI trough level was associated with the serum phosphate level before transplantation. Weight gain may be associated not only with nonadherence, but also the patients' characteristics. Further studies are needed to elucidate these associations.

The results from this study should be interpreted in the context of its limitations. First, this study's results may not be applicable to other patient populations. In Japan, the waiting time for deceased donor kidneys is significantly longer than

in other countries because of the shortage of organs, and the mean dialysis vintage before transplantation is approximately 15 years [15]. Therefore, the proportion of patients who receive kidneys from living donors is comparatively higher in Japan [15]. Nevertheless, the proportion of living kidney donors is relatively low in the Nagasaki prefecture, where our hospital is located; therefore, this study included several patients who had received deceased donor kidneys and had more prolonged dialysis vintages compared with those in other areas of Japan. Second, since this study's sample size was small, we were unable to adjust for several of the confounding factors, and this study was likely underpowered for identifying other associations that may be present (type 2 error). Third, the pre-transplantation parameters were measured at different facilities; therefore, the assays may have been executed slightly differently and the results from the blood tests may be subject to interlaboratory discrepancies. Fourth, we used a simple model; therefore, other factors that may affect renal prognosis, such as post-transplant blood pressure and new-onset diabetes mellitus after transplantation, were not considered. As factors associated with nonadherence after transplantation, we evaluated the fluctuation of CNI concentration and weight gain; however, other factors could have affected these parameters. Patient education has been recently improved at our facility, but the quality and quantity of patient education has not been assessed and thus may not be reflected in our results.

Conclusions

We have described the prognosis of transplanted kidneys with a focus on nonadherence to hemodialysis. The serum phosphate level was a robust predictor of the transplanted kidney prognosis. Although several factors influence the serum phosphate level, dietary habits and adherence to use of phosphate binders seem to be associated with the serum phosphate level. Hence, the serum phosphate level is a crucially important marker and should be given the appropriate level of attention. Furthermore, kidney transplant patients whose serum phosphate levels are outside the acceptable range should receive intensive education about nutrition and the importance of adherence to medical regimens.

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Conflict of interests

None.

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