Hypophosphatemia in critically ill patients with acute kidney injury treated with hemodialysis is associated with adverse events

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Abstract

Background. Hypophosphatemia in critically ill patients may be exacerbated by renal replacement therapy (RRT). We aimed to identify risk factors and adverse outcomes associated with hypophosphatemia in intensive care patients treated with RRT for acute kidney injury (AKI).

Methods. This was a secondary analysis of data from a single-center prospective cohort study of medical and surgical intensive care patients with RRT for AKI between 18 December 2010 and 3 April 2013. Demographic, comorbidity, laboratory and RRT data were retrieved from patient case notes and electronic medical records. Outcomes assessed were hypophosphatemia (serum phosphate <0.94 mmol/L) during RRT, intensive care unit (ICU) mortality, and duration of mechanical ventilation and vasopressor support.

Results. Among 96 patients who received acute RRT, 25 (26.0%) developed hypophosphatemia. On multivariate logistic regression, serum phosphate at RRT initiation [adjusted odds ratio (OR) 0.29, 95% confidence interval (CI) (0.09, 0.91), \(P = 0.03\)] was independently associated with hypophosphatemia during acute RRT. Patients with hypophosphatemia during RRT required longer ventilatory support [median 12 (interquartile range: 8, 17) days versus 5 (3, 9) days, \(P < 0.001\)] and vasopressor support [5 (4, 15) days versus 2 (2, 6) days, \(P = 0.003\)] compared with those without hypophosphatemia but there was no significant difference in ICU mortality [5 patients (20.0%) versus 24 patients (33.8%), \(P = 0.20\)]. Hypophosphatemia during RRT was independently associated with prolonged mechanical ventilation (≥7 days) [adjusted OR 14.0, 95% CI (1.37, 143.90), \(P = 0.03\)].

Conclusion. Hypophosphatemia is common during acute RRT for critically ill patients and was associated with adverse clinical outcomes.

Key words: acute kidney injury, critical care, hemodialysis, hypophosphatemia

Introduction

Acute kidney injury (AKI) is common in critically ill patients and acute renal replacement therapy (RRT) may be required to correct severe electrolyte or acid-base abnormalities in up to 10% of patients in intensive care units (ICU) [1, 2]. However, hypophosphatemia can occur in 10–60% of patients receiving acute RRT, especially with continuous or prolonged therapy [3–7]. Moderate or severe hypophosphatemia has long been recognized as a cause of respiratory muscle weakness [8, 9].

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These effects may be attributed to the physiological role of adenosine triphosphate (ATP) as an energy source for most cellular functions. Although moderate or severe hypophosphatemia was identified as a risk factor for difficulty weaning off ventilatory support [10, 11] and increased need for vasopressors [12] among ICU patients, few studies included patients requiring RRT for AKI. This study thus aimed to identify risk factors and assess the clinical impact of mild hypophosphatemia in critically ill patients receiving acute RRT.

Materials and methods

This was a secondary analysis of prospectively collected data from a cohort study in a single-center 1782-bed tertiary-care hospital in Singapore [13]. All critically ill patients admitted to medical and surgical ICU between 18 December 2010 and 3 April 2013, who received acute RRT for AKI, were included. Patients with premorbid serum creatinine $\geq 500 \mu\text{mol/L}$, RRT prior to ICU admission, incomplete data or death within 1 day of RRT initiation were excluded.

Demographic and comorbidity data, including diabetes mellitus, hypertension, ischemic heart disease (IHD), and chronic liver disease or liver cirrhosis were collected from case notes and electronic medical records. Severity of organ dysfunction was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II score at ICU admission [14]. Premorbid serum creatinine was defined as the most recent and stable serum creatinine value within 12 months prior to hospital admission. Premorbid estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation [15]. AKI was present if serum creatinine increased $\geq 0.3 \text{mg/dL}$ (26.4 $\mu\text{mol/L}$) according to modified AKI Network criteria [16]. Oliguria was defined as urine output $<0.5 \text{mL/kg/h}$ for $\geq 6$ h. Clinical and biochemistry data including serum inorganic phosphorus were recorded at time of ICU admission and at initiation of RRT. All laboratory investigations were conducted at our center’s laboratory, which is accredited by the College of American Pathologists.

Acute RRT was performed using one of the following modalities: continuous renal replacement therapy (CRRT) or intermittent RRT. CRRT was delivered using Frisma or Prismaflex platform with AN69 hollow fibre filter (Gambro, Lund, Sweden). Intermittent RRT was executed as sustained low-efficiency dialysis with filtration (SLED-f) with a Fresenius 4008S machine (ArTeP) using Ultraflux AV600 filter (Fresenius Medical Care, Bad Homburg, Germany), or SLED with Fresenius 4008S or Gambro AK96 machine using Polysulfone 14L filter (Gambro). Each SLED session lasted 3–4 h with blood flow rates ranging between 150 and 200 mL/min and dialysate flow rates ranging between 300 and 400 mL/min. RRT-related parameters such as modality of acute RRT at initiation, flow rates of blood, dialysate, replacement fluid and effluent, and duration of RRT were recorded. Delivered RRT dose (reported as effluent volume, mL/kg/h) was calculated from cumulative effluent volume averaged per kilogram body weight per hour of dialysis. For CRRT, we had a standardized protocol for potassium and phosphate supplementation. In patients with serum phosphate $>1.5 \text{mmol/L}$ and serum potassium $<5.5 \text{mmol/L}$, each 0.5 mmol/L decrement in serum potassium below 5.5 mmol/L was corrected by addition of 5 mL of potassium chloride solution (KCl) with K$^+$ at 1 mmol/mL to each 5 L bag of replacement and dialysate solution. In patients with serum phosphate $<1.5 \text{mmol/L}$ and serum potassium $<5.5 \text{mmol/L}$, 5 mL of the total calculated KCl supplementation dose, was substituted with 5 mL potassium dihydrogen phosphate 13.6% solution (KH2PO4 with K$^+$ at 1 mmol/L and PO4 at 1 mmol/L). The aforementioned substitution by KH2PO4 permitted a phosphate concentration of 1 mmol/L in the dialysate and replacement fluid. In contrast, for intermittent RRT, commercially available bicarbonate-buffered dialysate concentrate with no phosphate was used for online preparation of dialysate and replacement fluid (HD-1B liquid concentrate bicarbonate and HD-7A liquid concentrate acid from B Braun Medical Industries, Penang, Malaysia).

Serum phosphate was measured daily for patients who were receiving CRRT, and at least twice a week, pre-dialysis, for patients receiving intermittent RRT. Inorganic phosphorus was measured using colorimetric, spectrophotometric assay (Beckman Coulter Unicel DxC 800, Brea, CA, USA) with normal serum phosphate levels between 0.94 and 1.50 mmol/L. Thus, hypophosphatemia was defined by serum phosphate concentrations $<0.94 \text{mmol/L}$.

Patient outcomes recorded were ICU and hospital mortality; as well as duration of mechanical ventilation and vasopressor support. Prolonged mechanical ventilation was defined as need for ventilator support for $\geq 7$ days. Prolonged vasopressor support was defined as need for vasopressors for more than 3 days.

This study abided by the Declaration of Helsinki and was approved by the local institutional review board (2011/379/E).

Statistical analysis was performed using IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as proportions and continuous variables summarized as medians with interquartile ranges [IQRs (25th percentile, 75th percentile)]. Pearson chi-square test or Fisher’s exact test was used to compare categorical variables and Mann–Whitney U-test for continuous variables. Binary logistic regression analysis (enter method) was used to calculate odds ratio (OR) and 95% confidence interval (CI) for factors associated with outcomes. Covariates were chosen if P-value was $<0.05$ on univariate analysis. All analyses were two-tailed. P-values $<0.05$ were considered statistically significant.

Results

Ninety-six critically ill patients with AKI requiring acute RRT were included in this analysis. Demographic, clinical and RRT data are presented in Table 1. Median premorbid MDRD eGFR was 62.8 (IQR: 37.0, 82.5) mL/min/1.73 m$^2$. Forty-four patients (45.8%) received only CRRT, 28 patients (29.2%) received only intermittent RRT and 24 patients (25.0%) received both CRRT and intermittent RRT. Median serum phosphate at ICU admission was 1.67 (1.19, 2.32) mmol/L and at RRT initiation was 1.63 (1.23, 2.43) mmol/L. Nine patients (9.4%) had hypophosphatemia prior to RRT initiation. Twenty-five patients (26.0%) developed hypophosphatemia during RRT. Among patients who received only a single RRT modality, hypophosphatemia was more common in patients who received only CRRT compared with patients who received only intermittent RRT, but this was not statistically significant [13 patients (29.5%) versus 4 patients (14.3%), $P = 0.14$].

Table 1 compares patients with and without hypophosphatemia during RRT. Patients who had hypophosphatemia during RRT tended to be younger and female; more required vasopressors at ICU admission, had lower serum creatinine and serum phosphate at time of RRT initiation and longer total dialysis duration. However, only serum phosphate at RRT initiation was independently associated with hypophosphatemia during RRT [adjusted OR 0.29, 95% CI (0.09, 0.91), $P = 0.03$]. A subgroup analysis of patients who received only CRRT ($n = 44$) further
confirmed this finding. Patients who developed hypophosphatemia during CRRT were younger (52.0 (42.3, 58.1) years versus 67.9 (53.4, 75.9) years, \( P = 0.004 \)), less likely to have hypertension (15.1% versus 58.1%, \( P = 0.009 \)) or IHD (0% versus 35.5%, \( P = 0.02 \)), had a longer interval between hospital admission and ICU admission (5 (1, 16) days versus 1 (0, 3) days, \( P = 0.007 \)) and lower serum phosphate at time of RRT initiation (0.90 (0.71, 1.65) mmol/L versus 1.99 (1.38, 2.69) mmol/L, \( P = 0.003 \)). In multivariate analysis, only serum phosphate at time of CRRT initiation was independently associated with hypophosphatemia during CRRT [adjusted OR 1.81, 95% CI (1.07, 2.98), \( P = 0.04 \)].

ICU mortality occurred in 29 patients (30.1%) and hospital mortality in 46 patients (47.9%). There were no significant differences in ICU mortality [5 patients (20.0%) versus 24 patients (33.8%), \( P = 0.20 \)] or hospital mortality [12 patients (48.0%) versus 34 patients (47.9%), \( P = 0.99 \)] in those with hypophosphatemia during RRT compared with those without. Complete data for duration of mechanical ventilation and vasopressor use were available in 51 and 47 ICU survivors, respectively. Median duration of ventilatory support was 8 (4, 12) days and duration of inotropic or vasopressor requirement was 4 (2, 8) days. ICU survivors with hypophosphatemia during RRT received longer duration of ventilatory support [12 (8, 17) days versus 5 (3, 9) days, \( P < 0.001 \)] and vasopressor support [5 (4, 15) days versus 2 (2, 6) days, \( P = 0.003 \)] than patients who did not have hypophosphatemia. Univariate analysis of factors associated with prolonged mechanical ventilation >7 days and vasopressor requirement >3 days are presented in Tables 2 and 3, respectively. In multivariate analyses, hypophosphatemia during RRT was independently associated with prolonged mechanical ventilation [adjusted OR 14.04, 95% CI (1.37, 143.90), \( P = 0.02 \]) but not with prolonged vasopressor support [adjusted OR 3.06, 95% CI (0.36, 25.94), \( P = 0.30 \)]. Unadjusted and adjusted OR of factors associated with prolonged ventilatory and vasopressor support are shown in Table 4.

### Discussion

#### Adverse effects of hypophosphatemia during acute dialysis

Critically ill patients receiving care in the ICU may experience hypophosphatemia due to malnutrition, re-feeding syndrome, severe sepsis, or use of insulin and parenteral nutrition [17]. In addition, RRT removes phosphate from plasma [18]. Earlier studies evaluated only moderate to severe hypophosphatemia in ICU patients who may not be receiving RRT [6, 18]. An Australian study found that hypophosphatemia <0.6 mmol/L was associated with increased need and longer duration of mechanical ventilation [19], while Demirjian et al. established that serum phosphate <2 mg/dL (0.67 mmol/L) during CRRT was associated with an increased need for tracheostomy [11]. However, in clinical practice,
Table 2. Comparison of ICU survivors with and without prolonged mechanical ventilation for 7 days or longer

|                                | N = 28 | N = 23 | P-value |
|--------------------------------|--------|--------|---------|
| Age, years                     | 56.9 (50.2, 67.8) | 59.4 (54.3, 75.0) | 0.18    |
| Male gender, n (%)             | 18 (64.3%) | 15 (65.2%) | 0.94    |
| MICU, n (%)                    | 18 (64.3%) | 15 (65.2%) | 0.94    |
| Diabetes mellitus, n (%)       | 8 (28.6%) | 11 (47.8%) | 0.16    |
| Hypertension, n (%)            | 12 (42.9%) | 19 (82.6%) | 2.004   |
| IHD, n (%)                     | 3 (10.7%) | 10 (43.5%) | 0.008   |
| Chronic liver disease or liver cirrhosis, n (%) | 1 (3.6%) | 2 (8.7%) | 0.58    |
| APACHE II score                | 23 (20, 28) | 23 (18, 25) | 0.82    |
| Time from hospital admission to ICU admission, days | 1 (0, 3) | 1 (0, 10) | 0.80    |
| Premorbid serum creatinine, μmol/L | 87 (65, 97) | 108 (70, 154) | 0.12    |
| AKI cause: sepsis, n (%)       | 21 (87.5%) | 17 (89.5%) | 1.00    |
| Oliguria, n (%)                | 21 (75.0%) | 14 (77.8%) | 1.00    |
| Mechanical ventilation at ICU admission, n (%) | 27 (96.4%) | 18 (94.7%) | 1.00    |
| Vasopressor at ICU admission, n (%) | 23 (82.1%) | 12 (63.2%) | 0.18    |
| Serum creatinine at RRT initiation, μmol/L | 256 (164, 354) | 311 (184, 539) | 0.28    |
| Serum calcium at RRT initiation, mmol/L | 1.76 (1.62, 1.89) | 1.85 (1.9, 1.98) | 0.29    |
| Serum phosphate at RRT initiation, mmol/L | 1.30 (0.96, 2.09) | 1.76 (1.63, 2.74) | 0.03    |
| Serum albumin at RRT initiation, g/L | 23 (16, 24) | 23 (17, 28) | 0.14    |
| Initial modality: CRRT, n (%)  | 22 (78.6%) | 16 (69.6%) | 0.46    |
| Effluent flow rate in CRRT, mL/kg/h | 34.4 (28.1, 40.0) | 33.0 (26.8, 37.3) | 0.51    |
| CRRT duration, days            | 7 (4, 11) | 5 (4, 8) | 0.13    |
| Hypophosphatemia during dialysis, n (%) | 14 (50.0%) | 2 (8.7%) | 0.002   |

Categorical variables are expressed as number (percentage) and compared using chi-square or Fisher’s exact test as appropriate. Continuous variables are expressed as median (IQR) and compared using Mann–Whitney U-test. MICU, medical intensive care unit.

Table 3. Comparison of ICU survivors with and without prolonged inotropic or vasopressor support for more than 3 days

|                                | N = 24 | N = 23 | P-value |
|--------------------------------|--------|--------|---------|
| Age, years                     | 58.7 (52.1, 69.2) | 58.9 (53.4, 75.9) | 0.29    |
| Male gender, n (%)             | 16 (66.7%) | 13 (56.5%) | 0.47    |
| MICU, n (%)                    | 13 (54.2%) | 20 (87.0%) | 0.01    |
| Diabetes mellitus, n (%)       | 10 (41.7%) | 10 (43.5%) | 0.90    |
| Hypertension, n (%)            | 10 (41.7%) | 16 (69.6%) | 0.05    |
| IHD, n (%)                     | 2 (8.3%) | 12 (52.2%) | 0.001   |
| Chronic liver disease or liver cirrhosis, n (%) | 2 (8.3%) | 2 (8.7%) | 1.00    |
| APACHE II score                | 22 (19, 27) | 24 (22, 29) | 0.38    |
| Time from hospital admission to ICU admission, days | 2 (0, 7) | 1 (0, 2) | 0.20    |
| Premorbid serum creatinine, μmol/L | 91 (68, 176) | 134 (90, 241) | 0.09    |
| AKI cause: sepsis, n (%)       | 18 (85.7%) | 16 (84.2%) | 1.00    |
| Oliguria, n (%)                | 17 (73.9%) | 13 (68.4%) | 0.74    |
| Mechanical ventilation at ICU admission, n (%) | 20 (95.2%) | 15 (75.0%) | 0.09    |
| Vasopressor at ICU admission, n (%) | 20 (95.2%) | 16 (80.9%) | 0.18    |
| Serum creatinine at RRT initiation, μmol/L | 255 (164, 330) | 305 (173, 605) | 0.17    |
| Serum calcium at RRT initiation, mmol/L | 1.78 (1.62, 1.89) | 1.89 (1.64, 1.77) | 0.37    |
| Serum phosphate at RRT initiation, mmol/L | 1.40 (0.93, 2.17) | 1.63 (1.31, 1.77) | 0.15    |
| Serum albumin at RRT initiation, g/L | 23 (15, 24) | 21 (17, 26) | 0.84    |
| Initial modality: CRRT, n (%)  | 22 (91.7%) | 16 (69.6%) | 0.07    |
| Effluent flow rate in CRRT, mL/kg/h | 31.1 (27.1, 36.7) | 36.4 (29.1, 41.0) | 0.28    |
| CRRT duration, days            | 2 (0, 4) | 1 (0, 5) | 0.75    |
| Intermittent dialysis sessions, n (%) | 1 (0, 6) | 1 (0, 4) | 0.92    |
| Total dialysis duration, days  | 7 (4, 11) | 4 (3, 9) | 0.11    |
| Hypophosphatemia during dialysis, n (%) | 14 (58.3%) | 4 (17.4%) | 0.004   |

Categorical variables are expressed as number (percentage) and compared using chi-square or Fisher’s exact test as appropriate. Continuous variables are expressed as median (IQR) and compared using Mann–Whitney U-test. MICU, medical intensive care unit.
patients requiring acute RRT may receive either continuous, intermittent or both modalities [22]. Our study showed that even mild hypophosphatemia (serum phosphate cut-off of 0.94 mmol/L) during acute RRT, regardless of dialysis modality, was associated with prolonged mechanical ventilation. The clinical impact of hypophosphatemia on mortality and hemodynamics is less clear [5, 21, 23]. Our study found no significant association between hypophosphatemia during RRT and mortality or need for prolonged vasopressor support, confirming the association between hypophosphatemia during RRT and mortality or need for prolonged vasopressor support, confirming the results of other multivariate analyses [5, 11, 19]. This observation suggests that hypophosphatemia may be a marker of illness severity rather than a predictor of mortality.

Factors associated with hypophosphatemia during acute dialysis

Serum phosphate level at RRT initiation was associated with hypophosphatemia during RRT in our study, although this was not consistently found in earlier studies [4, 11]. Other authors have previously identified RRT intensity and duration, as risk factors for hypophosphatemia during CRRT [4, 11]. In a secondary analysis by Bellomo et al., higher intensity CRRT (effluent flow rates of 40 mL/kg/h versus 25 mL/kg/h) was independently associated with hypophosphatemia [4]. Among our patients who received only CRRT, patients with hypophosphatemia did tend to have higher average effluent flow rate [36.1 (31.3, 44.8) mL/kg/h versus 29.9 (26.0, 36.9) mL/kg/h, \(P = 0.08\)], but this was not statistically significant. Hypophosphatemia was associated with longer duration of CRRT [11], but not with longer sessions (10 h versus 6 h) of intermittent RRT [3]. Although Ratanarat et al. found that total phosphate removal was greater in CRRT than intermittent RRT (66.7 ± 18.9 mmol compared with 29.9 ± 7.7 mmol, \(P = 0.001\)) [6], clinical hypophosphatemia was not significantly different between continuous and intermittent modalities [7].

Prevention and treatment of hypophosphatemia during acute dialysis

Despite our existing phosphate repletion protocol in CRRT, a large proportion still developed hypophosphatemia. Troyanov et al. advocated addition of phosphate to conventional phosphate-free dialysate and replacement fluid when serum phosphate was <1.50 mmol/L to prevent hypophosphatemia in patients receiving CRRT for more than 24 h [24]. Alternatively, commercially prepared phosphate-containing solutions such as Phoxilium (Gambro Lundia AB, Lund, Sweden) may effectively prevent hypophosphatemia in patients receiving CRRT [25–28]. Currently, there is no randomized controlled evidence or consensus as to the optimal serum phosphate target in critically ill patients [29]. Hypophosphatemia was generally corrected if it was symptomatic or severe [17, 30], with phosphate repletion to achieve physiological levels [31]. However, some authors contest that phosphate repletion based on serum levels may not correlate with intracellular concentrations and ATP synthesis [32]. Others were concerned about the risks of adverse effects of phosphate replacement, such as hypocalemia, arrhythmia and renal injury, especially with aggressive replacement [33]. Although intravenous phosphate replacement was shown by recent studies to be safe in critically ill patients, these studies generally excluded patients with severe renal impairment [31, 34, 35]. Given our findings that even mild hypophosphatemia was associated with prolonged need for mechanical ventilation among patients with AKI receiving acute RRT, further studies are required to establish optimal serum phosphate levels and evaluate safe and effective phosphate repletion regimens during acute RRT to prevent and treat RRT-induced hypophosphatemia.

Strengths and limitations

The strengths of this study are, firstly, inclusion of patients from both medical and surgical ICUs and, secondly, use of continuous and intermittent acute RRT therapies. This makes it relevant to the clinical practice of most intensivists and critical care nephrologists [22, 36]. Thirdly, a standardized phosphate repletion protocol was instituted for patients receiving CRRT and regular serum phosphate measurements were done in all patients receiving RRT. Although this was a single-center study, the patient demographics and critical illness severity were comparable to studies reported by other ICUs internationally [5, 11, 23]. However, hypophosphatemia was identified based on a single-time point measurement during acute RRT therapy, hence this study was unable to assess the effects of phosphate repletion therapy or prolonged hypophosphatemia over time [5, 23]. Information on nutritional supplementation was not available, although most patients in MICU received enteral nutrition within 48 h per institutional protocol. The small sample size of this study also limits its power to detect significant differences. Despite finding a strong association after accounting for possible confounders, these results from an observational study cannot conclusively prove a causal relationship between hypophosphatemia and need for prolonged ventilation.

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**Table 4. Unadjusted and adjusted OR and 95% CI for factors associated with adverse outcomes**

|                          | Prolonged mechanical ventilation | Prolonged vasopressor support |
|--------------------------|---------------------------------|------------------------------|
|                          | Unadjusted OR (95% CI)          | Adjusted OR (95% CI)         | P-value | Unadjusted OR (95% CI) | Adjusted OR (95% CI) | P-value |
| MICU                     |                                 |                              |         |                      |                          |         |
| Hypertension             | 0.16 (0.04, 0.59)               | 0.19 (0.03, 1.02)            | 0.05    | 0.18 (0.04, 0.76)    | 0.24 (0.05, 1.28)     | 0.09    |
| IHD                      | 0.16 (0.03, 0.67)               | 0.56 (0.09, 3.31)            | 0.53    | 0.31 (0.09, 1.04)    | 0.69 (0.14, 3.26)     | 0.64    |
| Serum phosphate at RRT initiation | 1.02 (0.81, 1.27)       | 1.04 (0.77, 1.41)            | 0.78    | 0.08 (0.02, 0.44)    | 0.26 (0.03, 1.98)     | 0.19    |
| Hyponatremia during RRT  | 10.50 (2.06, 53.51)            | 14.04 (1.37, 143.90)         | 0.03    | 6.65 (1.72, 25.64)   | 3.34 (0.68, 16.37)    | 0.14    |

Binary logistic regression analysis (enter method) was used to calculate OR and 95% CI. Covariates were chosen if \(P < 0.05\) on univariate analysis. MICU, medical intensive care unit.
Conclusion

Hypophosphatemia was common among critically ill patients receiving RRT for AKI despite normal to high levels of serum phosphate before RRT initiation. Even mild hypophosphatemia during RRT was associated with need for prolonged mechanical ventilation and thus there should be greater emphasis on its prevention and treatment in the ICU.

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Conflict of interest statement

None declared.

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