Prevalence of Chronic Kidney Disease-Mineral Bone Disorder in Hemodialysis Patients in Hebei, China

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To the Editor: Chronic kidney disease-mineral bone disorder (CKD-MBD) has been found universally in hemodialysis (HD) patients. It increases the risk of cardiovascular morbidity and mortality, particularly vascular calcification.[1] Consequently, it is crucial to effectively control the biochemical indicators' abnormalities of CKD-MBD. International guidelines have provided measures for CKD-MBD, but relevant research from developing countries is limited, especially in China.[2]

The overall prevalence of chronic kidney disease in China is 10.80%, and 0.03% of the population suffers from end-stage renal disease (ESRD).[3] In order to track the development of HD and improve the quality of life of ESRD patients, the Chinese Society of Nephrology established a nationwide renal data registration system, known as the Chinese National Renal Data System (CNRDS), to record demographic, clinical, and laboratory information on dialysis patients.[4] The Hebei Quality Control Center for Dialysis Patients is one of the registered centers in the CNRDS.

Medical service levels and lifestyles differ substantially throughout China, and hospitals are organized according to a three-tiered system recognizing a hospital's ability to provide medical care and education and conduct medical research. Based on that, hospitals are designated as primary, secondary, or tertiary institutions. According to the CNRDS, HD centers in Hebei are mainly concentrated in non-tertiary institutions. This increases the difficulty of CKD-MBD management. The present study not only showed the overall CKD-MBD status based on the Hebei registered data from the CNRDS to provide evidence for better treatment in developing areas but also compared the CKD-MBD status between tertiary institutions and non-tertiary institutions in Hebei.

Data in this study covered nearly all inpatient and outpatient dialysis medical records in the Hebei province from January 1, 2016, to December 31, 2016, which were obtained from the Hebei Quality Control Center for Dialysis Patients. Inclusion criteria included: (1) ESRD patients older than 18 years, (2) receiving stable HD for at least 3 months, and (3) available serum calcium, phosphorus, and intact parathyroid hormone (iPTH) data. Exclusion criteria included: (1) patients with serious coexisting illnesses requiring intensive care or (2) acute kidney failure with temporary dialysis. This study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University, and the requirement for informed consent was waived for the retrospective design of this study.

Demographic information about the patients' age, gender, ESRD etiology, hospital type, duration of dialysis, HD frequency (times/week), urea reduction ratio, single pool-Kt/V (spKt/V), pre-dialysis systolic blood pressure (SBP), pre-dialysis diastolic blood pressure (DBP), serum hemoglobin, calcium, phosphorus, and iPTH levels were collected. The urea reduction ratio = (predialysis blood urea nitrogen [BUN] − postdialysis BUN)/predialysis BUN ×100%. The spKt/V was directly monitored automatically by a dialysis machine. All the blood samples were evaluated using commercial kits and an autoanalyzer. Serum phosphorus and serum calcium were measured using a spectrophotometry assay, and iPTH was evaluated through immunoradiometric or immunochemiluminometric assays. Based on hospital tiers, the patients were then divided into two groups: patients of tertiary or non-tertiary institutions.

According to the K/DOQI guidelines, we considered hypocalcemia as a total serum calcium level of <8.4 mg/dl, hyperphosphatemia as a serum phosphorus level of >5.5 mg/L, and high iPTH as a serum iPTH level of >300 pg/ml.[5] Associated parameters were compared between the two groups, and then overall data in Hebei province were compared to those reported in DOPPS4[6,7] and Chinese DOPPS.[8]

Statistical analyses were performed using SPSS version 19.0 software (SPSS, Inc., Chicago, IL, USA). Continuous data are expressed as mean ± standard deviation (SD) or median (P_{25}, P_{75}), and categorical variables were presented as n (%). Comparisons between groups were using Mann-Whitney U-test for continuous variables and Chi-square test for categorical variables. To observe the association between phosphate and iPTH, we compared serum phosphate levels according to different iPTH levels (<150 pg/ml, 150–300 pg/ml, 301–600 pg/ml, and >600 pg/ml) by Kruskal-Wallis

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H-test. Then, the logistic regression model was used to further analyze the risk factors for high iPTH. A value of $P < 0.05$ denoted statistically significant differences.

In total, 2577 patients (43.7% from tertiary institutions and 56.3% from non-tertiary institutions) who matched the inclusion criteria were analyzed. The characteristics of the patients are shown in Table 1. The median age was 53 years old, 58.9% were male, and their median duration of dialysis was 32 months. Glomerulonephritis was the primary etiology of ESRD, and diabetic nephropathy was the second cause. In comparison, among the patients at the tertiary institutions, the rates of glomerulonephritis and diabetic nephropathy were both lower. The ages and dialysis duration of the patients at the tertiary institutions were significantly older and longer than those at the non-tertiary institutions.

The proportion of patients with hypocalcemia was 35.9%. The percentage of hyperphosphatemia was 58.6% and high iPTH was 45.4%. When serum phosphorus levels were compared according to different iPTH levels, the elevated iPTH levels had a significant association with increased hyperphosphatemia ($\chi^2 = 214.00$, $P < 0.001$). Furthermore, a logistic regression analysis showed that after adjusting for age, sex, etiology, hospital, time on dialysis, HD frequency, urea reduction ratio, spKt/V, SBP, DBP, and hemoglobin, every 1 mg/dl increase in phosphorus was associated with a 2.1-fold increase in high iPTH risk (95% confidence interval [CI]: 1.825 to 2.475, $P < 0.001$).

Table 1 shows a comparison between the patients at the tertiary and non-tertiary institutions. The condition of the CKD-MBD markers in the patients at the tertiary hospitals was better than that in the patients at the non-tertiary institutions. However, after adjusted for age, sex, time on dialysis, urea reduction ratio, spKt/V, SBP, DBP, and hemoglobin, different hospital tiers were not associated with hyperphosphatemia and high iPTH ($P = 0.312$ and $P = 0.157$, respectively). The all-cause mortality rate was 3.7% in whole patients, 3.6% in the patients of tertiary institutions, and 3.7% in the patients of non-tertiary institutions.

This study presented systematic comparisons in practice patterns between tertiary or non-tertiary institutions and provided a unique dataset to explore effective variables for the prevention and treatment of CKD-MBD. In this study, we observed that the status of MBD in Hebei province was sub-optimal compared to that in DOPPS4. The serum calcium level was 8.72 mg/dl, lower than that in DOPPS4[6] and in the Chinese DOPPS.[8] Moreover, the overall incidence of hypocalcemia in Hebei Province was 35.9%, higher than that in DOPPS4 (12.4%).[7] The mean serum phosphorus level in Hebei was 6.06 mg/dl, and the hyperphosphatemia rate was 58.6%. Compared to DOPPS4, the phosphorus levels and hyperphosphatemia rates in Hebei were higher. However, the status of phosphorus in Hebei was similar to other Asian countries,[9] other Chinese provinces,[1,10] and the Chinese DOPPS report.[8] In short, the hypocalcemia and hyperphosphatemia rates in Hebei HD patients were both higher than those reported in DOPPS4. We speculate that one of the reasons of this might be related to inexperienced nephrology teams in CKD-MBD management in most areas of Hebei. The usage of phosphate-binding agents, particularly non-calcium-based phosphate binders, is very important for preventing hyperphosphatemia and associated with a lower risk of mortality.[11] Another possible reason may be the lower educational levels and compliance in the patients. It is paramount to know phosphate bioavailability when considering sources of phosphates,[12] and dietitians may provide additional benefit for controlling hyperphosphatemia in HD patients,[13] but these aspects are barely satisfactory in Hebei.

According to the K/DOQI guidelines, optimal PTH levels of 150–300 pg/ml are recommended for dialysis patients. However, analysis from the DOPPS found an increased risk for all-cause mortality only when PTH >600 pg/ml.[14] Therefore, it is presently suggested that iPTH levels should be in the range of two to nine times the upper normal limit. In our study, the percentage of iPTH over 600 pg/ml was 19.1% and the rate of iPTH over 300 pg/ml was higher than that in DOPPS4 but similar to other Chinese provinces.[1] This is consistent with higher rates of hyperphosphatemia and

Table 1: Characteristics and comparison between patients at tertiary and non-tertiary institutions

Variables	All patients (N = 2577)	Patients of tertiary institutions (n = 1125)	Patients of non-tertiary institutions (n = 1452)	χ^2/Z	P
Age (years)	53 (43, 63)	54 (44, 65)	52 (62, 41)	−4.86*	<0.001
Male	1520 (58.9)	700 (62.2)	820 (56.5)	8.66[†]	0.003
Duration of dialysis (months)	32 (14, 57)	33 (15, 60)	30 (13, 55)	−2.72[†]	0.007
Etiology of ESRD					
Primary glomerulonephritis	1288 (50.0)	532 (47.3)	756 (52.1)	5.79[†]	0.016
Diabetic nephropathy	575 (22.3)	230 (20.4)	345 (23.7)	4.02[†]	0.045
Hypertensive renal damage	206 (8.0)	97 (8.6)	109 (7.5)	1.07[†]	0.300
Polycystic kidney disease	101 (3.9)	45 (4.0)	56 (3.9)	0.04[†]	0.853
Others	407 (15.8)	221 (19.6)	186 (12.8)		
HD frequency (times/week)	3.0 (2.4, 3.0)	3.0 (2.5, 3.0)	3.0 (2.3, 3.0)	−7.01*	<0.001
Urea reduction ratio	65.7 (59.6, 69.7)	66.2 (59.8, 70.0)	65.3 (59.2, 69.4)	−2.56*	0.010
spKt/V	1.25 (1.08, 1.39)	1.27 (1.09, 1.40)	1.24 (1.07, 1.38)	−2.67*	0.008
Predialysis SBP (mmHg)	150 (140, 163)	150 (136, 160)	150 (140, 166)	−5.01*	<0.001
Predialysis DBP (mmHg)	87 (79, 95)	85 (78, 93)	89 (80, 98)	−5.51*	<0.001
Hemoglobin (g/L)	105 (93, 116)	106 (93, 118)	105 (92, 115)	−3.65*	<0.001
Calcium (mg/dl)	8.72 ± 1.36	8.84 (8.28, 9.48)	8.48 (8.00, 9.24)	−7.67*	<0.001
Phosphorus (mg/dl)	6.06 ± 1.89	5.84 (4.70, 6.92)	5.87 (4.85, 7.20)	−2.20*	0.028
iPTH (pg/ml)	269 (151, 499)	263 (137, 467)	273 (158, 516)	−2.35*	0.019

Data are expressed by median (P_{25}, P_{75}), n (%), or mean ± SD. *χ^2 value; [†]Z value. ESRD: End-stage renal disease; HD: Hemodialysis; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; iPTH: Intact parathyroid hormone; SD: Standard deviation; spKt/V: Single pool-Kt/V.

hypocalcemia in HebeiHD patients. Hence, comprehensive MBD therapy programs must be enforced in Hebei.

In the present study, the patients at the tertiary institutions were older and had longer time on dialysis. For dialysis-related indicators, such as the urea reduction ratio, spKt/V, predialysis blood pressure, and hemoglobin, the patients at the tertiary institutions were superior to the patients at the non-tertiary institutions. In addition to different medical levels, this may be related to the fact that most of the patients at the non-tertiary institutions lived in rural areas and most of the patients at the tertiary institutions lived in urban areas where economic status and medical insurance were better. Moreover, the urea reduction ratio and spKt/V showed that the dialysis prescription was reasonable, but there were significant differences in the CKD-MBD markers in the two groups. However, after adjusting for possible confounding factors, the difference in hyperphosphatemia and high iPTH no longer existed. This result reveals that standardized management according to the guidance for diagnosis and treatment should be improved in all medical institutions in Hebei.[15]

There were several limitations to this study. First, some information on factors related to the MBD was not available, such as serum albumin, dietary phosphorus intake, and detailed doses of phosphate binders, and Vitamin D. Second, laboratory tests were not performed in one central laboratory; therefore, variations between laboratories may exist. Third, the nature of this cross-sectional cohort study limited our ability to make causal inferences. Finally, the laboratory data we collected were only from the last quarter of 2016, so we could not perform mean and time-dependent data analyses. More effective medical care for dialysis patients in Hebei can be achieved based on our results.

In summary, serum calcium levels in Hebei HD patients were lower than those reported in DOPPS4 and the Chinese DOPPS. This study demonstrated higher serum P and iPTH levels in Hebei HD patients than those reported in DOPPS4, but similar to Chinese DOPPS. High hypocalcemia, hyperphosphatemia, and high iPTH rates may suggest that HD services in Hebei are insufficient. Comprehensive therapy programs should be enforced to improve conditions for CKD-MBD patients in Hebei, especially at non-tertiary institutions.

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Conflicts of interest

There are no conflicts of interest.

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