Mineral and Bone Metabolism Disorders in Minority Incident ESRD Patients in an Inner-City Hemodialysis Unit

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Background: Chronic kidney disease (CKD) predisposes patients to mineral and bone metabolism disorder (CKD-MBD), which is a well-known risk factor for increased mortality. Because Medical Evidence Form 2728 from the Centers for Medicare and Medicaid Services for incident end-stage renal disease (ESRD) patients does not require documentation of CKD-MBD markers, MBD status on incident patients remains unknown.

Objective: Retrospective observational study to determine the prevalence of mineral and bone metabolism disorder in minority incident ESRD patients.

Methods: We studied all incident ESRD patients in our hemodialysis unit between January 2000 and September 2008. Patients followed for less than three months were excluded. Target values for CKD stage 5 were defined as per 2003 Kidney Disease Outcome Quality Initiative guidelines.

Results: One hundred seventy-four patients were studied, with a mean age of 53.7±16.1 years, mean body mass index of 26.67±5.98 kg/m^2, and mean estimated glomerular filtration rate of 6.7±4.03 mL/min/1.73m^2. Mean lab values with one standard deviation were as follows: corrected calcium 8.5±1.3 mg/dL, serum albumin 3.05±0.77 g/dL, phosphorus 5.5±2.2 mg/dL, calcium-phosphorus product 46.7±18.5 mg^2/dL^2, and intact parathyroid hormone (iPTH) 440.9±397.8 pg/mL. Target values for calcium, phosphorus, calcium-phosphorus product, and iPTH were met in 34%, 42%, 72%, and 31% of the patients, respectively, while only 6% of the patients met all four target values.

Conclusions: CKD-MBD is widely prevalent in minority incident dialysis patients at initiation of therapy. Its management continues to be a challenge and warrants early recognition and therapy in CKD patients.

INTRODUCTION

Chronic kidney disease (CKD) is widely prevalent in the United States, with a rate of 16.8% in adults over the age of 20 (*MMWR Weekly,* 2007). It has been associated with significantly increased all-cause and cardiovascular mortality (Tonelli et al., 2006). The disease predisposes patients to significant alteration in mineral and bone metabolism, which is now known as mineral and bone disorder (CKD-MBD). CKD-MBD starts early during the course of CKD and becomes increasingly prevalent as the disease progresses (Martin et al., 2007). CKD-MBD has been well recognized as a risk factor for increased morbidity, hospitalization, all-cause mortality, and cardiovascular mortality among CKD and end-stage renal disease (ESRD) patients (Block, Hulbert-Shearon, Levin, & Port, 1998; Ganesh, Stack, Levin, Hulbert-Shearon, & Port, 2001; Tentori et al., 2008; Wald et al., 2008). Studies conducted so far have primarily focused on prevalent ESRD patients (Table 1) regarding MBD markers and achievement of Kidney Disease Outcome Quality Initiative (K/DOQI) targets (Block et al., 1998; Young et al., 2004; Yokoyama et al., 2004; Al Aly, Gonzalez, Martin, & Gellens, 2004; Maduell, Gorriz, Pallardo, Pons, & Santiago, 2005; Mahdavi-Mazdeh, Zamyadi, Norouzi, & Heidary Rouchi, 2007). Only a few studies on CKD-MBD markers have targeted the incident ESRD population (Tangri et al., 2011; Danese, Belozeroff, Smirnakis, & Rothman, 2008; Melamed et al., 2006), but data on minority patients are lacking. Minorities receive less pre-ESRD care and are more likely to be initiated on maintenance dialysis at more-advanced stages of CKD. Because Center for Medicare and Medicaid Services (CMS) Medical Evidence Form 2728 for incident ESRD patients does not require reporting of CKD-MBD indicators, complete data on MBD status in minority incident patients remain inaccessible. We conducted a retrospective cross-sectional study to determine the MBD status of minority incident ESRD patients.

METHODS

We conducted a retrospective observational study on 174 incident ESRD patients who initiated hemodialysis at the Lincoln Medical and Mental Health Center hemodialysis unit between January 2000 and September 2008. Our hemodialysis unit, serving a predominantly minority population, is an inner-city, hospital-based unit; all patients were started on dialysis in the hospital. Patients' baseline data were collected from CMS Medical Evidence Form 2728 and electronic medical records. Laboratory data from within 15 days of the initiation of dialysis were collected. Patients followed for less than three months after dialysis initiation were excluded because of the possibility of renal recovery during that period.

It was our standard practice to check for MBD markers at or prior to initiation of hemodialysis. Calcium level was corrected for serum albumin using the formula of observed

Table 1 | National and International Experiences in Prevalent ESRD Patients Regarding CKD-MBD Markers

CKD Stage 5 Target Values	DOPPS I (1998)	DOPPS II (2004)	Yokoyama et al. (2004)	Al Aly et al. (2004)	Maduell et al. (2005)	Mahdavi-Mazdeh et al. (2007)
Calcium (8.4–9.5 mg/dL)	40.5%	42.5%	49%	49%	45%	53.2%
Phosphorus (3.5–5.5 mg/dL)	40.8%	44.4%	50%	36%	55%	52.2%
Calcium x Phosphorus (<55 mg^2/dL^2)	56.5%	61.4%	—	57%	73%	75.1%
iPTH (150–300 pg/mL)	21.4%	26.2%	27%	20%	26%	27.7%
All Four Target Values Met	4.6%	5.5%	9%	7%	7.3%	1.8%

Table 2 | Patients' Baseline Characteristics

	Our Study Population	USRDS (2000–2006)	p-value
Total Patients	**n=174**	**n=709,212**	**—**
Female	89 (51.1%)	45.4%	0.14
Hispanic	116 (66.7%)	13.2%	<0.0001
African American	49 (28.1%)	28%	0.96
Asian	9 (5.2%)	2.6%	0.05
Mean Age (years)	53.7±16.1	62.8	0.001
Mean eGFR ($mL/min/1.73m^2$)	6.7±4.03	9.9	0.001
Mean BMI (kg/m^2)	26.67±5.98	27.7	0.02
ESRD Etiology			
Diabetes Mellitus	39.1%	44.8%	0.14
Hypertension	20.1%	27.4%	0.03
Chronic Glomerulonephritis	19.5%	9.9%	<0.0001
HIV Nephropathy	3.4%	0.8%	0.0005
Polycystic Kidney Disease	2.3%	2.2%	0.9
Obstructive Uropathy	2.3%	—	—
Other	13.3%	14.9%	0.6

calcium + 0.8 x (4.0 - serum albumin [g/dL]). Corrected calcium was used to calculate calcium-phosphorus product. Glomerular filtration rate (GFR) was estimated with the modification of diet in renal disease formula (Levey et al., 1999). Target values of MBD markers for CKD stage 5 were established per K/DOQI guidelines (calcium 8.4–9.5 mg/dL, phosphorus 3.5–5.5 mg/dL, calcium-phosphorus product less than 55 mg^2/dL^2, and intact parathyroid hormone [iPTH] 150–300 pg/mL) (*K/DOQI Clinical Practice Guidelines,* 2003).

Statistical Analysis

Data were analyzed using a two-tailed Student's t-test, chi square test, logistic regression analysis, and analysis of variance (ANOVA). A p-value of less than 0.05 was considered statistically significant. We also analyzed the trend of achievement of target CKD-MBD marker values between the years 2000 and 2008 by dividing the time period into two-year intervals. We attempted to assess the impact of the K/DOQI guidelines publication in our study population. All analyses were performed with Stata Version 11.2 (Stata Corp., Odessa, TX). The study protocol was reviewed and approved by our Institutional Review Board.

RESULTS

One hundred seventy-four patients were included in the study, with a mean age of 53.7±16.1 years, mean body mass index (BMI) of 26.67±5.98 kg/m^2, and mean estimated

Table 3 | Mean Values of CKD-MBD Markers in Pre- and Post-K/DOQI Guidelines

MBD Markers	Pre-K/DOQI	Post-K/DOQI	p-value
Calcium (mg/dL)	8.6±1.2	8.4±1.3	0.2
Phosphorus (mg/dL)	5.4±2.2	5.7±2.1	0.28
iPTH (pg/mL)	377±307	523±480	0.01
Calcium x Phosphorus (mg^2/dL^2)	45.7±19	47.4±17.8	0.55

GFR (eGFR) of 6.7±4.03 mL/min/1.73m^2. Hispanic, African American, and Asian ethnicity made up 66.7%, 28.1%, and 5.2% of the studied patients respectively. Table 2 summarizes patients' baseline characteristics compared with United States Renal Data System (USRDS) incident ESRD patients from 2000 to 2006 (U.S. Renal Data System, 2008). Health coverage was as follows: Medicaid, 36%; Medicare, 13%; both Medicaid and Medicare, 16%; other, 3%. Thirty-two percent of patients were without any coverage. Most patients were unemployed (82%) or retired (11% due to age and 1% due to disability).

Mean lab values with one standard deviation in incident ESRD patients were as follows: albumin 3.05±0.77 g/dL, calcium 8.5±1.3 mg/dL, phosphorus 5.5±2.2 mg/dL, iPTH 440.9±397.8 pg/mL, and calcium-phosphorus product 46.7±18.5 mg^2/dL^2. The impact of the K/DOQI guidelines was assessed as shown in Table 3. We compared mean values of CKD-MBD markers before December 31, 2003, and after January 1, 2004 (three months after the guidelines were published in October 2003), and found no difference, aside from higher iPTH levels in the post-K/DOQI era.

Figure 1 shows trends of proportions of patients achieving target CKD-MBD markers over eight years. Target value for the calcium-phosphorus product was achieved in 65% to 77% of the patients, whereas the other CKD-MBD marker targets were met in only 28% to 45% of the patients. Logistic regression analysis showed trends to be nonsignificant for all values. Similarly, trends of CKD-MBD marker mean values over the years were nonsignificant as analyzed by ANOVA (Figures 2A–C).

The target calcium value was met in 34% of the patients, while 45% of the patients had calcium less than 8.4 mg/dL and 21% of the patients had calcium greater than 9.5 mg/dL. The target value of phosphorus was met in 42% of the patients, while 16% of the patients had phosphorus less than 3.5 mg/dL and 42% of the patients had phosphorus greater than 5.5 mg/dL. Seventy-two percent of the patients had calcium-phosphorus product in the target range, while 28% of the patients had an elevated calcium-phosphorus product of greater than 55 mg^2/dL^2. The target iPTH level was met in 31% of the patients, while an iPTH level of <150 pg/mL was seen in 17% of the patients. An elevated iPTH level of greater than 300 pg/mL was seen in 52% of the patients.

Only 6% of the patients met all four target values. Age, gender, ethnicity, and BMI did not have a statistically significant impact on the achievement of target CKD-MBD marker values, except that patients with calcium within the target range were significantly older than patients with calcium less than 8.4 mg/dL (57.5±17.9 years vs. 51.3±14.9 years, p-value = 0.03).

DISCUSSION

Results of our study showed that there were no significant changes in the trends of CKD-MBD markers and the proportion of patients achieving target values in minority incident ESRD patients over the years of our study. The introduction of the K/DQOI guidelines also did not result in significant improvement in mean values of CKD-MBD markers; we found significantly higher iPTH values after the publication of the guidelines.

Our patients were significantly younger compared with the national average and had lower eGFR at initiation of dialysis and lower BMI, but they also had a significantly higher proportion of HIV nephropathy and chronic glomerulonephritis as the etiology of ESRD. Lower eGFR at dialysis initiation likely reflects late presentation for medical care in our population. The remaining comorbidities were comparable.

Our study population consists predominantly of minorities and is considerably different from the USRDS population, with a significantly higher proportion of Hispanics. Minorities constitute about one third of the U.S. population, with Hispanics being the largest minority group. Minority populations tend to be poorer and have less education, and

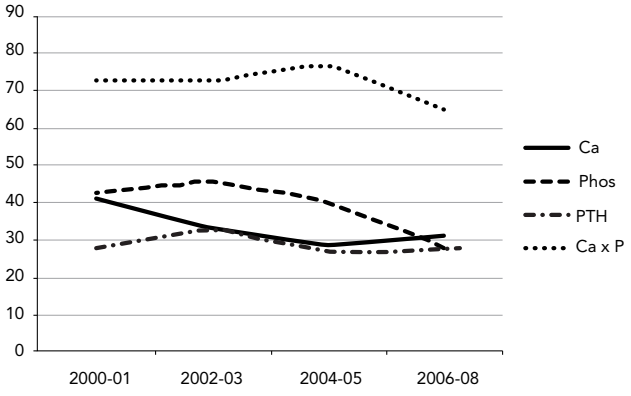

Figure 1 | Percentage of patients achieving CKD-MBD targets. p > 0.05 (nonsignificant) for all trends

they are more likely to lack health insurance coverage and to suffer from a severe disease burden. These factors could be significant barriers to obtaining appropriate healthcare in our patient population. According to 2011 U.S. Census Bureau data, 30.1% of Hispanics and 19.5% of blacks were without health insurance (U.S. Census Bureau, 2011). Eighty-two percent of our patients were unemployed, and 32% of our patients were without any medical coverage. According to the USRDS, in 2005–2007, 20.2% of incident ESRD patients were unemployed and 7.6% were without health insurance (U.S. Renal Data System, 2012). MBD is widely prevalent in minority incident ESRD patients, which could be due to lack of pre-ESRD care and lack of health insurance, and may be related to unemployment, poor socioeconomic status, or poverty.

Nephrologists have to complete CMS Medical Evidence Form 2728 upon initiation of maintenance dialysis. The requested information includes all demographic data, comorbid conditions, and laboratory values except CKD-MBD markers. Thus, the nationwide prevalence of CKD-MBD abnormalities at initiation of dialysis remains undetermined. Only recently have CMS guidelines mandated monitoring of CKD-MBD markers in ESRD patients.

To our knowledge, ours is the first study reporting the status of mineral and bone metabolism markers and achievement of target values in minority incident ESRD patients. Dialysis Outcomes and Practice Patterns Study (DOPPS) data reported on the achievement of target values for CKD-MBD in prevalent ESRD patients only (Mahdavi-Mazdeh et al., 2007).

According to DOPPS II data, target calcium, phosphorus, calcium-phosphorus product, and iPTH values were met in 42.5%, 44.4%, 61.4%, and 26.2% of prevalent ESRD patients, respectively, in the United States. These targets were met in 34%, 42%, 72%, and 31% of incident ESRD patients, respectively, in our study population. All four targets were met in only 5.5% of DOPPS II prevalent ESRD and 6% of our incident ESRD patients. It should be noted that these comparisons are not among similar patient populations, as these similar proportions of patients achieving target CKD-MBD marker values represent widely heterogeneous ESRD subsets in each study group.

Major features of deranged mineral and bone metabolism include hypocalcaemia, hyperphosphatemia, secondary hyperparathyroidism, altered Vitamin D metabolism, bone disease, soft-tissue calcification (including coronary artery and cardiac valves), pruritus, proximal myopathy, calciphylaxis, skin ulceration, and soft-tissue necrosis (*K/DOQI Clinical Practice Guidelines,* 2003). Abnormalities in arterial stiffness have been shown to be important mediators of cardiovascular events in patients with CKD (Block & Port, 2003). Hyperphosphatemia is associated with higher fracture risk (Block et al., 2004), increased pulse pressure (Klassen et al., 2002), increased risk of all-cause mortality (Ganesh et al., 2001; Wald et al., 2008; Block et al., 2004), cardiovascular mortality (Block et al., 1998; Ganesh et al.,

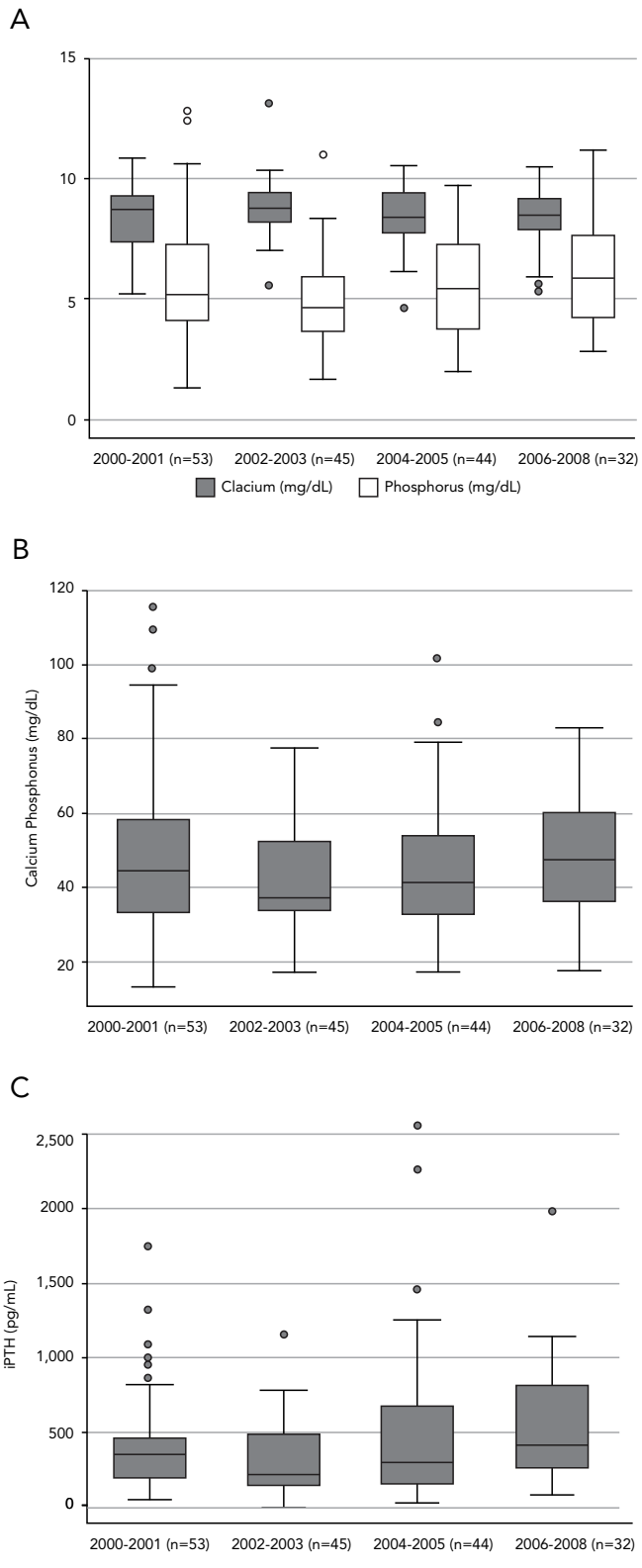

Figure 2 | Trends of levels of CKD-MBD markers. (A) Trends of levels of calcium and phosphorus. (A-C) P > 0.05 (nonsignificant) for all trends. (B) Trends of levels of calcium x phosphorus product . (C) Trends of levels of iPTH.

2001; Young et al., 2005), infection-related mortality, and sudden death (Ganesh et al., 2001).

An analysis of the United Kingdom Renal Registry by Tangri et al. (2011) including incident ESRD patients between January 2002 and December 2004 showed target achievement among patients for calcium (43–47%), phosphorus (54–62%), and iPTH (23-26%), and did not find a benefit of achievement of K/DOQI targets in decreasing all-cause mortality. In contrast, the study by Danese et al. (2008) of incident ESRD patients between July 2000 and June 2002 showed consistent achievement of CKD-MBD targets to be a strong predictor of survival.

Block et al. (2004) showed population-attributable risk of all-cause mortality in CKD stage 5 to be 17.5% for MM mineral metabolism abnormalities (phosphorus greater than 5.0 mg/dL, calcium greater than 10 mg/dL, iPTH greater than 600 pg/mL), 11.3% for anemia (hemoglobin less than 11 gm/dL), and 5.1% for insufficient dialysis (urea reduction ratio less than 65%). Their study highlights the impact of mineral and bone metabolism disorders on mortality in advanced CKD compared with anemia and inadequate dialysis, which was the main focus until recently. Presently, the beneficial effect of achieving CKD-MBD markers is demonstrated only by observational studies. Various organizations around the world set forth guidelines for MBD in advanced CKD that were most recently updated by KDIGO (Kidney Disease: Improving Global Outcomes) in 2009.

Our study cohort differs in racial and ethnic makeup from the overall ESRD population of the United States. However, this difference has the potential to highlight disparities in care among those at greatest risk for complications because of socioeconomic factors. Our study had a small sample size and we lacked data on pre-ESRD care and outcomes such as mortality, which would have improved our understanding of the impact of achieving target CKD-MBD markers. We also lack information on the use of phosphate binders and vitamin D analogues in our study population.

CONCLUSION

Our study demonstrated that mineral and bone metabolism abnormalities are widely prevalent in minority incident ESRD patients, and only 6% of the patients achieved target values for all MBD markers at the time of initiation of dialysis. This finding may be explained by lack of pre-ESRD care in our minority population. Estimating CKD-MBD status at the initiation of dialysis and including MBD indicators on the CMS medical evidence form will help ascertain the magnitude of MBD in ESRD patients. Early referral to nephrology and early recognition and management of CKD-MBD as per the guidelines may affect morbidity and mortality related to these disorders.

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Conflict of Interest Disclosure: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No conflicts were noted.

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