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

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ABSTRACT

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. As Medical Evidence Form 2728 by the Centers for Medicare and Medicaid Services for incident 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 dialysis 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 KDOQI guidelines.

Results: A total of 174 patients were studied, with a mean age of 53.7±16.1 years, mean body mass index of 26.67±5.98 kg/m², and mean estimated GFR of 6.7±4.03 mL/min/1.73m². 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 mg²/dL², 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 patients, respectively, while only 6% of 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 US, with a rate of 16.8% in adults over the age of 20 (MMWR Weekly, 2007). CKD has been associated with significantly increased all cause and cardiovascular mortality (Tonelli et al., 2006). CKD 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 CKD progresses (Kevin 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 et al., 1998; Ganesh et al., 2001; Tentori et al., 2008; Wald et al., 2008). Studies conducted so far primarily focused on prevalent ESRD patients (Table 1) regarding MBD markers and
achievement of Kidney Disease Outcome Quality Initiative (KDOQI) targets (Block et al., 1998; Young et al., 2004; Yokoyama et al., 2004; Al Aly et al., 2004; Maduell et al., 2005; Madhavi-Mazdeh et al., 2007). Only a few studies on CKD-MBD markers have targeted the incident ESRD population (Tangri et al., 2011; Danese et al., 2008; Melamed et al., 2006), but data on minority patients is lacking. Minorities receive less pre-ESRD care and are more likely to be initiated on maintenance dialysis at more advanced stages of CKD. As 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 remains unearthed. Hence, 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 (LMMHC) hemodialysis unit between January 2000 and September 2008. Our hemodialysis unit, serving a predominantly minority population, is an inner-city, hospital-based unit; hence, all patients were started on dialysis in the hospital. Patients’ baseline data was 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 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 (MDRD) formula (Levey et al., 1999). Target values of MBD markers for CKD stage 5 were established as per KDOQI guidelines (calcium 8.4-9.5 mg/dL, phosphorus 3.5-5.5 mg/dL, calcium-phosphorus product less than 55 mg²/dL², and intact parathyroid hormone (iPTH) 150-300 pg/mL) (KDOQI Clinical Practice Guidelines, 2003).

Statistical Analysis

Data was analyzed using a two-tailed Student t-test, chi square test, logistic regression analysis, and 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 time intervals. We attempted to assess impact of the KDOQI 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

A total of 174 patients were included in the study with a mean age of 53.7±16.1 years, mean BMI of 26.67±5.98 kg/m², and mean estimated GFR of 6.7±4.03 mL/min/1.73m². Hispanic, African American, and Asian ethnicity comprised 66.7%, 28.1%, and 5.2% of studied patients, respectively. Table 2 summarizes patients’ baseline characteristics in comparison 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%, others 3%. 32% 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 $46.7\pm18.5$ mg$^2$/dL$^2$. The impact of KDOQI 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 Oct 2003) and found no difference aside from higher iPTH levels in the post-KDOQI 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 65-77% of patients, whereas the other CKD-MBD marker targets were met in 28-45% of patients only. Logistic regression analysis showed trends to be non-significant for all values. Similarly, trends of CKD-MBD marker mean values over the years were non-significant as analyzed by ANOVA (Figure 2A-C).

The target calcium value was met in 34% of patients, while 45% of patients had calcium less than 8.4 mg/dL, and 21% of patients had calcium greater than 9.5 mg/dL. The target value of phosphorus was met in 42% of patients, while 16% of patients had phosphorus less than 3.5 mg/dL, and 42% of patients had phosphorus greater than 5.5 mg/dL. 72% patients had calcium-phosphorus product in target range, while 28% of patients had an elevated calcium-phosphorus product of greater than 55 mg$^2$/dL$^2$. Target iPTH level was met in 31% patients, while iPTH level of greater than 150 pg/mL was seen in 17% of patients. Elevated iPTH level of greater than 300 pg/mL was seen in 52% of patients.

Only 6% of 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 ($57.5\pm17.9$ years vs. $51.3\pm14.9$ 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 KDOQI guidelines also did not result in significant improvement in mean values of CKD-MBD markers; in fact, we found significantly higher iPTH values after the publication of the guidelines.

Our patients were significantly younger compared to 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 co-morbidities 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 US population with Hispanic being the largest minority group. Minority populations tend to be poorer and have a lesser education, and they are more likely to lack health insurance coverage and to suffer from severe disease burden. Hence, these factors could be significant barriers to obtaining appropriate health care in our patient population. According to 2011 US Census Bureau data, 30.1% of Hispanics and 19.5% of Blacks were without health insurance (U.S. Census Bureau, 2011). 82% of our patients were unemployed, while 32% of patients were without any medical coverage. As per USRDS in 2005-2007, 20.2% of incident ESRD patients, were currently 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 the CMS Medical Evidence Report (2728 form) upon initiation of maintenance dialysis. The requested information includes all demographic data, co-morbid conditions and laboratory values, except for 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. DOPPS data reported on the achievement of target values for CKD-MBD in prevalent ESRD patients only (Mahdavi-Mazdeh et al., 2007).

As per 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 US. These targets were met in in 34%, 42%, 72%, and 31% of incident ESRD patients, respectively, in our study population. All 4 targets were only met in 5.5% of DOPPS II prevalent ESRD and 6% of our incident ESRD patients. It should be noted that these comparisons are not in similar patient populations, as these similar proportions of patients achieving targets CKD-MBD marker values in fact 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 (KDOQI Clinical Practice Guidelines, 2003). Abnormalities in arterial stiffness have been shown to be important mediators of cardiovascular events in patients with CKD (Block et al., 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., 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 Jan 2002 and Dec 2004 showed target achievement among patients for calcium (43-46%), phosphorus (54-62%), and iPTH (27-23%) and did not find a benefit of achievement of KDOQI 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 as a strong predictor of survival.

Block et al. (1998) showed population attributable risk of all-cause mortality in CKD stage 5 to be 17.5% for MM 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 than11 gm/dL), and 5.1% for insufficient dialysis (urea reduction ratio less than65%). Their study highlights the impact of mineral and bone metabolism disorders on mortality in advanced CKD compared to anemia and inadequate dialysis which was the main focus until recently. Presently, the beneficial effect of achieving CKD-MBD markers is demonstrated by observational studies only. Various organizations around the world had set forth guidelines for MBD in advanced CKD that were most recently updated by KDIGO (Kidney Disease: Improving Global Outcome) 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 of complications in terms 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 CKD-MBD markers target achievement. 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 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 initiation of dialysis and inclusion of MBD indicators in the CMS medical evidence form will assist in ascertaining the magnitude of MBD in ESRD patients. Early referral to nephrology and early recognition and management of CKD-MBD as per guidelines may impact morbidity and mortality related to these disorders.

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**Author Contributions:** Study concept and design- I Gnansekaran. Acquisition of data, analysis and interpretation of data- N Goel, H Pokharna. Drafting of the manuscript-N Goel, H Pokharna. Critical revision of the manuscript-M Abramowitz, I Gnansekaran. Statistical analysis- M Abramowitz.

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

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**Previous Presentation:** The paper was presented at National Kidney Foundation Clinical Spring Meet, Nashville, TN, April 2009.

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MMWR Weekly March 2, 2007/ 56(08): 161-165 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5608a2.htm


Table 1. National and international experiences in prevalent ESRD patients regarding CKD-MBD markers.

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<tbody>
<tr>
<td>Calcium (8.4-9.5 mg/dL)</td>
<td>40.5 %</td>
<td>42.5 %</td>
<td>49 %</td>
<td>49 %</td>
<td>45 %</td>
<td>53.2 %</td>
</tr>
<tr>
<td>Phosphorus (3.5-5.5 mg/dL)</td>
<td>40.8 %</td>
<td>44.4 %</td>
<td>50 %</td>
<td>36 %</td>
<td>55 %</td>
<td>52.2 %</td>
</tr>
<tr>
<td>Calcium x Phosphorus (&lt;55 mg^2/dL^2)</td>
<td>56.5 %</td>
<td>61.4 %</td>
<td>--</td>
<td>57 %</td>
<td>73 %</td>
<td>75.1 %</td>
</tr>
<tr>
<td>iPTH (151-300 pg/mL)</td>
<td>21.4 %</td>
<td>26.2 %</td>
<td>27 %</td>
<td>20 %</td>
<td>26 %</td>
<td>27.7 %</td>
</tr>
<tr>
<td>All 4 target values met</td>
<td>4.6 %</td>
<td>5.5 %</td>
<td>9 %</td>
<td>7 %</td>
<td>7.3 %</td>
<td>1.8 %</td>
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Table 2. Patients’ Baseline Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Our Study Population</th>
<th>USRDS (2000-2006)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td><strong>Total Patients</strong></td>
<td>n=174</td>
<td>n=709,212</td>
<td>----</td>
</tr>
<tr>
<td>Female</td>
<td>89 (51.1%)</td>
<td>45.4%</td>
<td>0.14</td>
</tr>
<tr>
<td>Hispanic</td>
<td>116 (66.7%)</td>
<td>13.2%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>African American</td>
<td>49 (28.1%)</td>
<td>28%</td>
<td>0.96</td>
</tr>
<tr>
<td>Asian</td>
<td>9 (5.2%)</td>
<td>2.6%</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Mean Age (years)</strong></td>
<td>53.7±16.1</td>
<td>62.8</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Mean eGFR (mL/min/1.73m²)</strong></td>
<td>6.7±4.03</td>
<td>9.9</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Mean BMI (kg/m²)</strong></td>
<td>26.67±5.98</td>
<td>27.7</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>ESRD Etiology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>39.1%</td>
<td>44.8%</td>
<td>0.14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20.1%</td>
<td>27.4%</td>
<td>0.03</td>
</tr>
<tr>
<td>Chronic Glomerulonephritis</td>
<td>19.5%</td>
<td>9.9%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HIV Nephropathy</td>
<td>3.4%</td>
<td>0.8%</td>
<td>0.0005</td>
</tr>
<tr>
<td>Polycystic Kidney Disease</td>
<td>2.3%</td>
<td>2.2%</td>
<td>0.9</td>
</tr>
<tr>
<td>Obstructive Uropathy</td>
<td>2.3%</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Others</td>
<td>13.3%</td>
<td>14.9%</td>
<td>0.6</td>
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### Table 3. Mean Values of CKD-MBD markers in Pre-and-Post-KDOQI guidelines

<table>
<thead>
<tr>
<th>MBD Markers</th>
<th>Pre-KDOQI</th>
<th>Post-KDOQI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dL)</td>
<td>8.6±1.2</td>
<td>8.4±1.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>5.4±2.2</td>
<td>5.7±2.1</td>
<td>0.28</td>
</tr>
<tr>
<td>iPTH (pg/mL)</td>
<td>377±307</td>
<td>523±480</td>
<td>0.01</td>
</tr>
<tr>
<td>Calcium x Phosphorus (mg²/dL²)</td>
<td>45.7±19</td>
<td>47.4±17.8</td>
<td>0.55</td>
</tr>
</tbody>
</table>
Figure 1. Percentage of patients achieving CKD-MBD targets.*

*p-value: non-significant (p >0.05) for all trends
Figure 2. Trends of levels of CKD-MBD markers. (A) Trends of level of calcium and phosphorus [p-value: non-significant (p >0.05)]. (B) Trends of level of calcium x phosphorus product [p-value: non-significant (p >0.05)]. (C) Trends of level of iPTH [p-value: non-significant (p >0.05)].