**National Quality Forum—Evidence (subcriterion 1a)**

**Measure Number** (*if previously endorsed*)**:** 1454

**Measure Title**: Proportion of patients with hypercalcemia

**IF the measure is a component in a composite performance measure, provide the title of the Composite Measure here:** Click here to enter composite measure #/ title

**Date of Submission**: 4/2/2019

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| **Instructions**  *Complete 1a.1 and 1a.2 for all measures. If instrument-based measure, complete 1a.3.*  *Complete* ***EITHER 1a.2, 1a.3 or 1a.4*** *as applicable for the type of measure and evidence.*  *For composite performance measures:*  *A separate evidence form is required for each component measure unless several components were studied together.*  *If a component measure is submitted as an individual performance measure, attach the evidence form to the individual measure submission.*   * All information needed to demonstrate meeting the evidence subcriterion (1a) must be in this form. An appendix of *supplemental* materials may be submitted, but there is no guarantee it will be reviewed. * If you are unable to check a box, please highlight or shade the box for your response. * Contact NQF staff regarding questions. Check for resources at [Submitting Standards webpage](http://www.qualityforum.org/Measuring_Performance/Submitting_Standards.aspx). |

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| **Note: The information provided in this form is intended to aid the Standing Committee and other stakeholders in understanding to what degree the evidence for this measure meets NQF’s evaluation criteria.**   1a. Evidence to Support the Measure Focus The measure focus is evidence-based, demonstrated as follows:   * Outcome: [**3**](#Note3) Empirical data demonstrate a relationship between the outcome and at least one healthcare structure, process, intervention, or service. If not available, wide variation in performance can be used as evidence, assuming the data are from a robust number of providers and results are not subject to systematic bias. * Intermediate clinical outcome: a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence [**4**](#Note4)that the measured intermediate clinical outcome leads to a desired health outcome. * Process: [**5**](#Note5) a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence [**4**](#Note4) that the measured process leads to a desired health outcome. * Structure: a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence [**4**](#Note4) that the measured structure leads to a desired health outcome. * Efficiency: [**6**](#Note6) evidence not required for the resource use component. * For measures derived from patient reports, evidence should demonstrate that the target population values the measured outcome, process, or structure and finds it meaningful. * Process measures incorporating Appropriate Use Criteria: See NQF’s guidance for evidence for measures, in general; guidance for measures specifically based on clinical practice guidelines apply as well.   **Notes**  **3.** Generally, rare event outcomes do not provide adequate information for improvement or discrimination; however, serious reportable events that are compared to zero are appropriate outcomes for public reporting and quality improvement.  **4.** The preferred systems for grading the evidence are the Grading of Recommendations, Assessment, Development and Evaluation [(GRADE) guidelines](http://www.gradeworkinggroup.org) and/or modified GRADE.  **5.** Clinical care processes typically include multiple steps: assess → identify problem/potential problem → choose/plan intervention (with patient input) → provide intervention → evaluate impact on health status. If the measure focus is one step in such a multistep process, the step with the strongest evidence for the link to the desired outcome should be selected as the focus of measurement. Note: A measure focused only on collecting PROM data is not a PRO-PM.  **6.** Measures of efficiency combine the concepts of resource use and quality (see NQF’s [Measurement Framework: Evaluating Efficiency Across Episodes of Care](http://www.qualityforum.org/Publications/2010/01/Measurement_Framework__Evaluating_Efficiency_Across_Patient-Focused_Episodes_of_Care.aspx); [AQA Principles of Efficiency Measures](http://www.aqaalliance.org/files/PrinciplesofEfficiencyMeasurementApril2006.doc)). |

**1a.1.This is a measure of**: (*should be consistent with type of measure entered in De.1*)

Outcome

Outcome: Click here to name the health outcome

Patient-reported outcome (PRO): Click here to name the PRO

*PROs include HRQoL/functional status, symptom/symptom burden, experience with care, health-related behaviors.* (*A PRO-based performance measure is not a survey instrument. Data may be collected using a survey instrument to construct a PRO measure.)*

Intermediate clinical outcome (*e.g., lab value*): Serum or Plasma calcium >10.2 (3-mo. rolling average)

Process: Click here to name what is being measured

Appropriate use measure: Click here to name what is being measured

Structure: Click here to name the structure

Composite: Click here to name what is being measured

**1a.2** **LOGIC MODEL** Diagram or briefly describe the steps between the healthcare structures and processes (e.g., interventions, or services) and the patient’s health outcome(s). The relationships in the diagram should be easily understood by general, non-technical audiences. Indicate the structure, process or outcome being measured.

Numerous studies have demonstrated the association of prolonged calcium and phosphorus dysregulation on patient morbidity and mortality (KDOQI 2003; KDIGO 2009; KDIGO Update 2017). Observational cohort studies show a consistent adverse association of hypercalcemia with cardiovascular events and all-cause mortality [1-9]. Clinical data demonstrate the association of increased serum calcium with vascular [10,11] and valvular calcifications [12]. The basic science also supports a pathological role of high calcium in promoting soft tissue and vascular calcification [13-15]. Although there are no interventional studies demonstrating the benefit of correcting hypercalcemia, the current available evidence indicates that serum calcium concentrations >10.2 mg/dL place the patient at increased risk of poor outcomes.

(Citations included at the end of this document, with newly added citations in red).

**1a.3** **Value and Meaningfulness:**  **IF** this measure is derived from patient report, provide evidence that the target population values the measured ***outcome, process, or structure*** and finds it meaningful. (Describe how and from whom their input was obtained.)

N/A

**\*\*RESPOND TO ONLY ONE SECTION BELOW -EITHER 1a.2, 1a.3 or 1a.4) \*\***

**1a.2** **FOR OUTCOME MEASURES including PATIENT REPORTED OUTCOMES - Provide empirical data demonstrating the relationship between the outcome (or PRO) to at least one healthcare structure, process, intervention, or service.**

N/A

**1a.3.****SYSTEMATIC REVIEW(SR) OF THE EVIDENCE (for intermediate outcome, PROCESS, or STRUCTURE PERFORMANCE measures, including those that are instrument-based) If the evidence is not based on a systematic review go to section 1a.4) If you wish to include more than one systematic review, add additional tables.**

**What is the source of the systematic review of the body of evidence that supports the performance measure? A systematic review is a scientific investigation that focuses on a specific question and uses explicit, prespecified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. It may include a quantitative synthesis (meta-analysis), depending on the available data. (IOM)**

X Clinical Practice Guideline recommendation (with evidence review)

☐ US Preventive Services Task Force Recommendation

☐ Other systematic review and grading of the body of evidence (*e.g., Cochrane Collaboration, AHRQ Evidence Practice Center*)

☐ Other

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| **Source of Systematic Review:**   * **Title** * **Author** * **Date** * **Citation, including page number** * **URL** | 1) Kidney Disease: Improving Global Outcomes (KDIGO) CKDMBD Work Group: KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney International 2009 76 (Suppl 113): S1-S130.  2) National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. American Journal of Kidney Disease 2003 42:S1-S202 (suppl 3).  3) KDIGO 2017 Clinical Practice Guidelines Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney International Supplements 2017 7(1):1-59. |
| Quote the guideline or recommendation verbatim about the process, structure or intermediate outcome being measured. If not a guideline, summarize the conclusions from the SR. | 1) KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD): 4.1.2. In patients with CKD stages 3-5D, we suggest maintaining serum calcium in the normal range (2D).  2) KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease: Guideline 6.2.In CKD Patients With Kidney Failure (Stage 5): Serum levels of corrected total calcium should be maintained within the normal range for the laboratory used, preferably toward the lower end (8.4 to 9.5 mg/dL [2.10 to 2.37 mmol/L]). (OPINION)  3) KDIGO 2017 Clinical Practice Guidelines Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD): 4.1.3 In adult patients with CKD G3a-G5D, we suggest avoiding hypercalcemia (2c). In children with CKD G3a-G5D, we suggest maintaining serum calcium in the age-appropriate normal range (2c). |
| Grade assigned to the **evidence** associated with the recommendation with the definition of the grade | The 2009 KDIGO guideline recommendation was graded 2D. The KDOQI recommendation was not graded.  The 2017 KDIGO guideline recommendation was graded 2C.  Grade C: Low quality of evidence. The true effect may be substantially different from the estimate of the effect. |
| Provide all other grades and definitions from the evidence grading system | The rating system defined in the KDOQI Guidelines was used to grade the strength of the Guideline recommendation. KDOQI defined grades as follows:  A: High quality of evidence. We are confident that the true effect lies close to that of the estimate of the effect.  B: Moderate quality of evidence. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.  C: Low quality of evidence. The true effect may be substantially different from the estimate of the effect.  D: Very low quality of evidence. The estimate of effect is very uncertain and often will be far from the truth. |
| Grade assigned to the **recommendation** with definition of the grade | The 2009 KDIGO guideline recommendation was graded 2D. The KDOQI recommendation was not graded.  The 2017 KDIGO guideline recommendation was graded 2C.  Level 2 (conditional recommendation/suggestion): “We Suggest”. Implications:   * Patients: The majority of people in your situation would want the recommended course of action, but many would not. * Clinicians: Different choices will be appropriate for different patients. Each patient needs help to arrive at a management   decision consistent with her or his values and preferences.  Policy: The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined. |
| Provide all other grades and definitions from the recommendation grading system | Level 1 (strong recommendation): “We Recommend”.  Implications   * Patients: Most people in your situation would want the recommended course of action and only a small proportion would not. * Clinicians: Most patients should receive the recommended course of action.   Policy: The recommendation can be adopted as policy in most situations. |
| Body of evidence:   * Quantity – how many studies? * Quality – what type of studies? | N/A |
| Estimates of benefit and consistency across studies | N/A |
| What harms were identified? | N/A |
| Identify any new studies conducted since the SR. Do the new studies change the conclusions from the SR? | See below for a list of new studies (and their abstracts) that have been published in recent years. These studies support the SR’s cited above. |

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**1a.4 OTHER SOURCE OF EVIDENCE**

*If source of evidence is NOT from a clinical practice guideline, USPSTF, or systematic review, please describe the evidence on which you are basing the performance measure.*

**1a.4.1** **Briefly SYNTHESIZE the evidence that supports the measure.** A list of references without a summary is not acceptable.

N/A

**1a.4.2 What process was used to identify the evidence?**  
N/A

**1a.4.3.** **Provide the citation(s) for the evidence.**

N/A

1. Kim Y, Yoo KD, Kim HJ et al. Association of serum mineral parameters with mortality in hemodialysis patients: Data from the Korean end-stage renal disease registry. Kidney Res Clin Pract. 2018 Sep;37(3):266-276. doi: 10.23876/j.krcp.2018.37.3.266. Epub 2018 Sep 30.

BACKGROUND:  
We investigated the associations between mineral metabolism parameters and mortality to identify optimal targets in Korean hemodialysis patients.

METHODS:  
Among hemodialysis patients registered in the end-stage renal disease registry of the Korean Society of Nephrology between March 2012 and June 2017, those with serum calcium, phosphorus, and intact parathyroid hormone (iPTH) measured at enrollment were included. Association of serum levels of calcium, phosphorus, and iPTH with all-cause mortality was analyzed.

RESULTS:  
Among 21,433 enrolled patients, 3,135 (14.6%) died during 24.8 ± 14.5 months of follow-up. After multivariable adjustment, patients in the first quintile of corrected calcium were associated with lower mortality (hazard ratio [HR], 0.84; 95% confidence interval [95% CI], 0.71-0.99; P = 0.003), while those in the fifth quintile were associated with higher mortality (HR, 1.39; 95% CI, 1.20-1.61; P < 0.001) compared with those in the third quintile. For phosphorus, only the lowest quintile was significantly associated with increased mortality (HR, 1.24; 95% CI, 1.08-1.43; P = 0.003). The lowest (HR, 1.18; 95% CI, 1.02-1.36; P = 0.026) and highest quintiles of iPTH (HR, 1.24; 95% CI, 1.05-1.46; P = 0.013) were associated with increased mortality. For target counts achieved according to the Kidney Disease Outcomes Quality Initiative guideline, patients who did not achieve any mineral parameter targets hadhigher mortality than those who achieved all three targets (HR, 1.37; 95% CI, 1.12-1.67; P = 0.003).

CONCLUSION:  
In Korean hemodialysis patients, high serum calcium, low phosphorus, and high and low iPTH levels were associated with increased all-cause mortality.

1. Wang M, Obi Y, Streja E et al. Association of Parameters of Mineral Bone Disorder with Mortality in Patients on Hemodialysis according to Level of Residual Kidney Function. Clin J Am Soc Nephrol. 2017 Jul 7;12(7):1118-1127. doi: 10.2215/CJN.11931116. Epub 2017 May 9.

BACKGROUND AND OBJECTIVES:  
The relationship between mineral and bone disorders and survival according to residual kidney function status has not been previously studied in patients on hemodialysis. We hypothesized that residual kidney function, defined by renal urea clearance, modifies the association between mineral and bone disorder parameters and mortality.

DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS:  
The associations of serum phosphorus, albumin-corrected calcium, intact parathyroid hormone, and alkaline phosphatase with all-cause mortality were examined across three strata (<1.5, 1.5 to <3.0, and ≥3.0 ml/min per 1.73 m2) of baseline residual renal urea clearance using Cox models adjusted for clinical characteristics and laboratory measurements in 35,114 incident hemodialysis patients from a large United States dialysis organization over the period of 2007-2011.

RESULTS:  
A total of 8102 (23%) patients died during the median follow-up of 1.3 years (interquartile range, 0.6-2.3 years). There was an incremental mortality risk across higher serum phosphorus concentrations, which was pronounced among patients with higher residual renal urea clearance (Pinteraction=0.001). Lower concentrations of serum intact parathyroid hormone were associated with higher mortality among patients with low residual renal urea clearance (i.e., <1.5 ml/min per 1.73 m2), whereas higher concentrations showed a higher mortality risk among patients with greater residual renal urea clearance (i.e., ≥1.5 ml/min per 1.73 m2; Pinteraction<0.001). Higher serum corrected total calcium and higher alkaline phosphatase concentrations consistently showed higher mortality risk (Ptrend<0.001 for both) irrespective of residual renal urea clearance strata (Pinteraction=0.34 and Pinteraction=0.53, respectively).

CONCLUSIONS:  
Residual kidney function modified the mortality risk associated with serum phosphorus and intact parathyroid hormone among incident hemodialysis patients. Future studies are needed to examine whether taking account for residual kidney function into the assessment of mortality risk associated with serum phosphorus and intact parathyroid hormone improves patient management and clinical outcomes in the hemodialysis population.

1. Liu CT, Lin YC, Lin YC et al. Roles of Serum Calcium, Phosphorus, PTH and ALP on Mortality in Peritoneal Dialysis Patients: A Nationwide, Population-based Longitudinal Study Using TWRDS 2005-2012. Sci Rep. 2017 Feb 24;7(1):33. doi: 10.1038/s41598-017-00080-4.

Biomarkers of chronic kidney disease-mineral and bone disorder (CKD-MBD) correlate with morbidity and mortality in dialysis patients. However, the comparative roles of each CKD-MBD biomarker remained undetermined on long-term peritoneal dialysis (PD) patients. This retrospective study, employing a population-based database, aimed to evaluate the performance and provide the best evidence of each biomarker of CKD-MBD as predictor of all-cause mortality. Throughout the 8-year study period, total 12,116 PD patients were included in this study. Cox proportional regression and Kaplan-Meier method were used for survival analysis. For Cox regression model, baseline measurements and time-varying covariates were used for analysis. In Cox regression model using time-dependent covariates, serum calcium level of ≧9.5 mg/dL was associated with increased mortality. For phosphorus, serum levels of either ≧6.5 mg/dL or <3.5 mg/dL were associated with increased mortality. For parathyroid hormone (PTH), higher serum levels were not associated increased mortality. For alkaline phosphatase (ALP), mortality increased at levels ≧100 IU/L. Our findings suggested that the detrimental effect of ALP on survival was more consistent, while serum calcium, phosphorus and PTH may have a less prominent effect on mortality. This study provided additional information for manipulating CKD-MBD biomarkers in PD patients.

1. Soohoo M, Feng M, Obi Y et al. Changes in Markers of Mineral and Bone Disorders and Mortality in Incident Hemodialysis Patients.Am J Nephrol. 2016;43(2):85-96. doi: 10.1159/000444890. Epub 2016 Mar 8.

BACKGROUND:  
Abnormalities in mineral and bone disorder (MBD) markers are common in patients with chronic kidney disease. However, previous studies have not accounted for their changes over time, and it is unclear whether these changes are associated with survival.

METHODS:  
We examined the association of change in MBD markers (serum phosphorus (Phos), albumin-corrected calcium (Ca(Alb)), intact parathyroid hormone (iPTH) and alkaline phosphatase (ALP)) during the first 6 months of hemodialysis (HD) with all-cause mortality across baseline MBD strata using survival models adjusted for clinical characteristics and laboratory measurements in 102,754 incident HD patients treated in a large dialysis organization between 2007 and 2011.

RESULTS:  
Across all MBD markers (Phos, Ca(Alb), iPTH and ALP), among patients whose baseline MBD levels were higher than the reference range, increase in MBD levels was associated with higher mortality (reference group: MBD level within reference range at baseline and no change at 6 months follow-up). Conversely, decrease in Phos and iPTH, among baseline Phos and iPTH levels lower than the reference range, respectively, were associated with higher mortality. An increase in ALP was associated with higher mortality across baseline strata of ALP ≥80 U/l. However, patients with baseline ALP <80 U/l trended towards a lower risk of mortality irrespective of the direction of change at 6 months follow-up.

CONCLUSIONS:  
 There is a differential association between changes in MBD markers with mortality across varying baseline levels in HD patients. Further study is needed to determine if consideration of both baseline and longitudinal changes in the management of MBD derangements improves outcomes in this population.

1. Fernandez-Martin JL, Martinez-Camblor P, Dionisi MP et al. Improvement of mineral and bone metabolism markers is associated with better survival in haemodialysis patients: the COSMOS study. Nephrol Dial Transplant. 2015 Sep;30(9):1542-51. doi: 10.1093/ndt/gfv099. Epub 2015 Apr 28.

BACKGROUND:  
Abnormalities in serum phosphorus, calcium and parathyroid hormone (PTH) have been associated with poor survival in haemodialysis patients. This COSMOS (Current management Of Secondary hyperparathyroidism: a Multicentre Observational Study) analysis assesses the association of high and low serum phosphorus, calcium and PTH with a relative risk of mortality. Furthermore, the impact of changes in these parameters on the relative risk of mortality throughout the 3-year follow-up has been investigated.

METHODS:  
COSMOS is a 3-year, multicentre, open-cohort, prospective study carried out in 6797 adult chronic haemodialysis patients randomly selected from 20 European countries.

RESULTS:  
Using Cox proportional hazard regression models and penalized splines analysis, it was found that both high and low serum phosphorus, calcium and PTH were associated with a higher risk of mortality. The serum values associated with the minimum relative risk of mortality were 4.4 mg/dL for serum phosphorus, 8.8 mg/dL for serum calcium and 398 pg/mL for serum PTH. The lowest mortality risk ranges obtained using as base the previous values were 3.6-5.2 mg/dL for serum phosphorus, 7.9-9.5 mg/dL for serum calcium and 168-674 pg/mL for serum PTH. Decreases in serum phosphorus and calcium and increases in serum PTH in patients with baseline values of >5.2 mg/dL (phosphorus), >9.5 mg/dL (calcium) and <168 pg/mL (PTH), respectively, were associated with improved survival.

CONCLUSIONS:  
COSMOS provides evidence of the association of serum phosphorus, calcium and PTH and mortality, and suggests survival benefits of controlling chronic kidney disease-mineral and bone disorder biochemical parameters in CKD5D patients.

1. Rivara MB, Ravel V, Kalantar-Zadeh K et al. Uncorrected and Albumin-Corrected Calcium, Phosphorus, and Mortality in Patients Undergoing Maintenance Dialysis. J Am Soc Nephrol. 2015 Jul;26(7):1671-81. doi: 10.1681/ASN.2014050472. Epub 2015 Jan 22.

Uncorrected serum calcium concentration is the first mineral metabolism metric planned for use as a quality measure in the United States ESRD population. Few studies in patients undergoing either peritoneal dialysis (PD) or hemodialysis (HD) have assessed the association of uncorrected serum calcium concentration with clinical outcomes. We obtained data from 129,076 patients on dialysis (PD, 10,066; HD, 119,010) treated in DaVita, Inc. facilities between July 1, 2001, and June 30, 2006. After adjustment for potential confounders, uncorrected serum calcium <8.5 and ≥10.2 mg/dl were associated with excess mortality in patients on PD or HD (comparison group uncorrected calcium 9.0 to <9.5 mg/dl). Additional adjustment for serum albumin concentration substantially attenuated the all-cause mortality hazard ratios (HRs) associated with uncorrected calcium <8.5 mg/dl (HR, 1.29; 95% confidence interval [95% CI], 1.16 to 1.44 for PD; HR, 1.17; 95% CI, 1.13 to 1.20 for HD) and amplified the HRs associated with calcium ≥10.2 mg/dl (HR, 1.65; 95% CI, 1.42 to 1.91 for PD; HR, 1.59; 95% CI, 1.53 to 1.65 for HD). Albumin-corrected calcium ≥10.2 mg/dl and serum phosphorus ≥6.4 mg/dl were also associated with increased risk for death, irrespective of dialysis modality. In summary, in a large nationally representative cohort of patients on dialysis, abnormalities in markers of mineral metabolism, particularly high concentrations of serum calcium and phosphorus, were associated with increased mortality risk. Additional studies are needed to investigate whether control of hypercalcemia and hyperphosphatemia in patients undergoing dialysis results in improved clinical outcomes.

1. Block GA, Klassen PS, Lazarus JM, et al. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. Journal of the American Society of Nephrology : JASN 2004 15:2208-18.

Mortality rates in ESRD are unacceptably high. Disorders of mineral metabolism (hyperphosphatemia, hypercalcemia, and secondary hyperparathyroidism) are potentially modifiable. For determining associations among disorders of mineral metabolism, mortality, and morbidity in hemodialysis patients, data on 40,538 hemodialysis patients with at least one determination of serum phosphorus and calcium during the last 3 mo of 1997 were analyzed. Unadjusted, case mix-adjusted, and multivariable-adjusted relative risks of death were calculated for categories of serum phosphorus, calcium, calcium x phosphorus product, and intact parathyroid hormone (PTH) using proportional hazards regression. Also determined was whether disorders of mineral metabolism were associated with all-cause, cardiovascular, infection-related, fracture-related, and vascular access-related hospitalization. After adjustment for case mix and laboratory variables, serum phosphorus concentrations >5.0 mg/dl were associated with an increased relative risk of death (1.07, 1.25, 1.43, 1.67, and 2.02 for serum phosphorus 5.0 to 6.0, 6.0 to 7.0, 7.0 to 8.0, 8.0 to 9.0, and >/=9.0 mg/dl). Higher adjusted serum calcium concentrations were also associated with an increased risk of death, even when examined within narrow ranges of serum phosphorus. Moderate to severe hyperparathyroidism (PTH concentrations >/=600 pg/ml) was associated with an increase in the relative risk of death, whereas more modest increases in PTH were not. When examined collectively, the population attributable risk percentage for disorders of mineral metabolism was 17.5%, owing largely to the high prevalence of hyperphosphatemia. Hyperphosphatemia and hyperparathyroidism were significantly associated with all-cause, cardiovascular, and fracture-related hospitalization. Disorders of mineral metabolism are independently associated with mortality and morbidity associated with cardiovascular disease and fracture in hemodialysis patients.

1. Young EW, Albert JM, Satayathum S, et al. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. Kidney international 2005 67:1179-87.

BACKGROUND:

Altered mineral metabolism contributes to bone disease, cardiovascular disease, and other clinical problems in patients with end-stage renal disease.

METHODS:

This study describes the recent status, significant predictors, and potential consequences of abnormal mineral metabolism in representative groups of hemodialysis facilities (N= 307) and patients (N= 17,236) participating in the Dialysis Outcomes and Practice Patterns Study (DOPPS) in the United States, Europe, and Japan from 1996 to 2001.

RESULTS:

Many patients fell out of the recommended guideline range for serum concentrations of phosphorus (8% of patients below lower target range, 52% of patients above upper target range), albumin-corrected calcium (9% below, 50% above), calcium-phosphorus product (44% above), and intact PTH (51% below, 27% above). All-cause mortality was significantly and independently associated with serum concentrations of phosphorus (RR 1.04 per 1 mg/dL, P= 0.0003), calcium (RR 1.10 per 1 mg/dL, P < 0.0001), calcium-phosphorus product (RR 1.02 per 5 mg(2)/dL(2), P= 0.0001), PTH (1.01 per 100 pg/dL, P= 0.04), and dialysate calcium (RR 1.13 per 1 mEq/L, P= 0.01). Cardiovascular mortality was significantly associated with the serum concentrations of phosphorus (RR 1.09, P < 0.0001), calcium (RR 1.14, P < 0.0001), calcium-phosphorus product (RR 1.05, P < 0.0001), and PTH (RR 1.02, P= 0.03). The adjusted rate of parathyroidectomy varied 4-fold across the DOPPS countries, and was significantly associated with baseline concentrations of phosphorus (RR 1.17, P < 0.0001), calcium (RR 1.58, P < 0.0001), calcium-phosphorus product (RR 1.11, P < 0.0001), PTH (RR 1.07, P < 0.0001), and dialysate calcium concentration (RR 0.57, P= 0.03). Overall, 52% of patients received some form of vitamin D therapy, with parenteral forms almost exclusively restricted to the United States. Vitamin D was potentially underused in up to 34% of patients with high PTH, and overused in up to 46% of patients with low PTH. Phosphorus binders (mostly calcium salts during the study period) were used by 81% of patients, with potential overuse in up to 77% patients with low serum phosphorus concentration, and potential underuse in up to 18% of patients with a high serum phosphorus concentration.

CONCLUSION:

This study expands our understanding of the relationship between altered mineral metabolism and outcomes and identifies several potential opportunities for improved practice in this area.

1. Kalantar-Zadeh K, Kuwae N, Regidor DL, et al. Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. Kidney international 2006 70:771-80.

Although renal osteodystrophy and vitamin D analogs may be related to survival in maintenance hemodialysis (MHD) patients, most studies have examined associations between baseline values and survival without accounting for variations in clinical and laboratory measures over time. We examined associations between survival and quarterly laboratory values and administered paricalcitol in a 2-year (July 2001-June 2003) cohort of 58,058 MHD patients from all DaVita dialysis clinics in USA using both time-dependent Cox models with repeated measures and fixed-covariate Cox models with only baseline values. Whereas hypercalcemia and hyperphosphatemia were robust predictors of higher death risk in all models, the association between serum calcium and mortality was different in time-varying models. Changes in baseline calcium and phosphorus values beyond the Kidney Disease Outcome Quality Initiative recommended targets were associated with increased mortality. Associations between high serum parathyroid hormone and increased death risk were masked by case-mix characteristics of MHD patients. Time-varying serum alkaline phosphatase had an incremental association with mortality. Administration of any dose of paricalcitol was associated with improved survival in time-varying models. Controlling for nutritional markers may introduce overadjustment bias owing to their strong collinearity with osteodystrophy surrogates. Whereas both time-dependent and fixed-covariate Cox models result in similar associations between osteodystrophy indicators and survival, subtle but potentially clinically relevant differences between the two models exist, probably because fixed models do not account for variations of osteodystrophy indices and changes in medication dose over time.

10) Kimata N, Albert JM, Akiba T, et al. Association of mineral metabolism factors with all-cause and cardiovascular mortality in hemodialysis patients: the Japan dialysis outcomes and practice patterns study. Hemodialysis international. International Symposium on Home Hemodialysis 2007 11:340-8.

Abnormalities in mineral metabolism have been linked to mortality in hemodialysis (HD) patients. We postulated that these abnormalities would have a particularly large deleterious impact on deaths due to cardiovascular causes in Japan. This study describes the recent status of abnormal mineral metabolism, significant predictors, and potential consequences in the Dialysis Outcomes and Practice Patterns Study (DOPPS), Phases 1 and 2, in Japan. Major predictor variables were patient demographics, comorbidities, and laboratory markers of mineral metabolism such as albumin-adjusted serum calcium (calciumAlb), phosphorus, and intact PTH (iPTH). In a cross section of 3973 Japanese HD patients in DOPPS I and II, a large faction had laboratory values outside of the recommended Kidney Disease Outcomes Quality Initiative (K/DOQI) guideline range for serum concentrations of phosphorus (51% of patients above upper target range), calciumAlb (43.7% above), calcium-phosphorus (Ca x P) product (41.1% above), and iPTH (18.6% above). All-cause mortality was significantly and independently associated with calciumAlb (relative risk [RR]=1.22 per 1 mg/dL, p=0.0005) and iPTH (RR=1.04 per 100 pg/mL, p=0.04). Cardiovascular mortality was significantly associated with calciumAlb (RR=1.28, p=0.02), phosphorus (RR=1.13 per 1 mg/dL, p=0.008), Ca x P product (RR=1.07 per 2 mg(2)/dL(2), p=0.002), and PTH (RR=1.08, p=0.0001). This study expands our understanding of the relationship between altered mineral metabolism and mortality outcomes, showing slightly stronger associations with cardiovascular causes than observed for all-cause mortality. These findings have important therapeutic implications for Japanese HD patients.

11) Tentori F, Blayney MJ, Albert JM, et al. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). American journal of kidney diseases : the official journal of the National Kidney Foundation 2008 52:519-30.

BACKGROUND:

Abnormalities in serum calcium, phosphorus, and parathyroid hormone (PTH) concentrations are common in patients with chronic kidney disease and have been associated with increased morbidity and mortality. No clinical trials have been conducted to clearly identify categories of calcium, phosphorus, and PTH levels associated with the lowest mortality risk. Current clinical practice guidelines are based largely on expert opinions, and clinically relevant differences exist among guidelines across countries. We sought to describe international trends in calcium, phosphorus, and PTH levels during 10 years and identify mortality risk categories in the Dialysis Outcomes and Practice Patterns Study (DOPPS), an international study of hemodialysis practices and associated outcomes.

STUDY DESIGN:

Prospective cohort study.

PARTICIPANTS:

25,588 patients with end-stage renal disease on hemodialysis therapy for longer than 180 days at 925 facilities in DOPPS I (1996-2001), DOPPS II (2002-2004), or DOPPS III (2005-2007).

PREDICTORS:

Serum calcium, albumin-corrected calcium (Ca(Alb)), phosphorus, and PTH levels.

OUTCOMES:

Adjusted hazard ratios for all-cause and cardiovascular mortality calculated using Cox models.

RESULTS:

Distributions of mineral metabolism markers differed across DOPPS countries and phases, with lower calcium and phosphorus levels observed in the most recent phase of DOPPS. Survival models identified categories with the lowest mortality risk for calcium (8.6 to 10.0 mg/dL), Ca(Alb) (7.6 to 9.5 mg/dL), phosphorus (3.6 to 5.0 mg/dL), and PTH (101 to 300 pg/mL). The greatest risk of mortality was found for calcium or Ca(Alb) levels greater than 10.0 mg/dL, phosphorus levels greater than 7.0 mg/dL, and PTH levels greater than 600 pg/mL and in patients with combinations of high-risk categories of calcium, phosphorus, and PTH.

LIMITATIONS:

Because of the observational nature of DOPPS, this study can only indicate an association between mineral metabolism categories and mortality.

CONCLUSIONS:

Our results provide important information about mineral metabolism trends in hemodialysis patients in 12 countries during a decade. The risk categories identified in the DOPPS cohort may be relevant to efforts at international harmonization of existing clinical guidelines for mineral metabolism.

12) Chertow G.M., Raggi P., Chasan-Taber S., Bommer J., Holzer H., Burke S.K. Determinants of progressive vascular calcification in haemodialysis patients. Nephrology Dialysis Transplantation 2004 19 (6), pp. 1489- 1496.

BACKGROUND:

We determined recently that targeted treatment with calcium-based phosphate binders (calcium acetate and carbonate) led to progressive coronary artery and aortic calcification by electron beam tomography (EBT), while treatment with the non-calcium-containing phosphate binder, sevelamer, did not. Aside from the provision of calcium, we hypothesized that other factors might be related to the likelihood of progressive calcification in both or either treatment groups.

METHODS:

We explored potential determinants of progressive vascular calcification in 150 randomized study subjects who underwent EBT at baseline and at least once during follow-up (week 26 or 52).

RESULTS:

Among calcium-treated subjects, higher time-averaged concentrations of calcium, phosphorus and the calcium-phosphorus product were associated with more pronounced increases in EBT scores; no such associations were demonstrated in sevelamer-treated subjects. The relation between parathyroid hormone (PTH) and the progression of calcification was more complex. Lower PTH was associated with more extensive calcification in calcium-treated subjects, whereas higher PTH was associated with calcification in sevelamer-treated subjects. Serum albumin was inversely correlated with progression in aortic calcification. Sevelamer was associated with favourable effects on lipids, although the link between these effects and the observed attenuation in vascular calcification remains to be elucidated.

CONCLUSION:

Calcium-based phosphate binders are associated with progressive coronary artery and aortic calcification, especially when mineral metabolism is not well controlled. Calcium may directly or indirectly (via PTH) adversely influence the balance of skeletal and extraskeletal calcification in haemodialysis patients.

13) Dhingra R, Sullivan LM, Fox CS, Wang TJ, D´Agostino RB Sr, Gaziano JM, Vasan RS: Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. Arch Intern Med 2007 167: 879–885.

BACKGROUND:

Higher levels of serum phosphorus and the calcium-phosphorus product are associated with increased mortality from cardiovascular disease (CVD) in patients with chronic kidney disease (CKD) or prior CVD. However, it is unknown if serum phosphorus levels influence vascular risk in individuals without CKD or CVD.

METHODS:

We prospectively evaluated 3368 Framingham Offspring study participants (mean age, 44 years; 51% were women) free of CVD and CKD. We used multivariable Cox models to relate serum phosphorus and calcium levels to CVD incidence.

RESULTS:

On follow-up (mean duration, 16.1 years), there were 524 incident CVD events (159 in women). In multivariable analyses and adjusting for established risk factors and additionally for glomerular filtration rate and for hemoglobin, serum albumin, proteinuria, and C-reactive protein levels, a higher level of serum phosphorus was associated with an increased CVD risk in a continuous fashion (adjusted hazard ratio per increment of milligrams per deciliter, 1.31; 95% confidence interval, 1.05-1.63; P=.02; P value for trend across quartiles = .004). Individuals in the highest serum phosphorus quartile experienced a multivariable-adjusted 1.55-fold CVD risk (95% confidence interval, 1.16%-2.07%; P=.004) compared with those in the lowest quartile. These findings remained robust in time-dependent models that updated CVD risk factors every 4 years and in analyses restricted to individuals without proteinuria and an estimated glomerular filtration rate greater than 90 mL/min per 1.73 m(2). Serum calcium was not related to CVD risk.

CONCLUSION:

Higher serum phosphorus levels are associated with an increased CVD risk in individuals free of CKD and CVD in the community. These observations emphasize the need for additional research to elucidate the potential link between phosphorus homeostasis and vascular risk.

14) Wang AY, Lam CW, Wang M, Chan IH, Lui SF, Sanderson JE. Is valvular calcification a part of the missing link between residual kidney function and cardiac hypertrophy in peritoneal dialysis patients? Clinical journal of the American Society of Nephrology 2009 4:1629-36.

BACKGROUND AND OBJECTIVES:

Residual renal function (RRF) predicts survival and shows an important inverse relation with cardiac hypertrophy in peritoneal dialysis (PD) patients. We hypothesized that valvular calcification and the calcification milieu may be part of the process linking loss of RRF and cardiac hypertrophy.

DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS:

A cross-sectional study was conducted by performing two-dimensional echocardiography on 230 PD patients to assess valvular calcification and left ventricular (LV) mass and collecting 24-h urine for estimation of RRF.

RESULTS:

Patients having valvular calcification had lower RRF than those without. Patients with no RRF showed higher calcium-phosphorus product (Ca x P) and C-reactive protein (CRP). Using multiple logistic regression analysis, every 1-ml/min per 1.73 m(2) increase in residual GFR was associated with a 28% reduction in the risk for valvular calcification. The association was lost after additional adjustment for Ca x P and CRP. Using multiple linear regression analysis, loss of RRF showed significant association with increased LV mass index, but this association was lost after additional adjustment for CRP, Ca x P, and valvular calcification. Patients with all three calcification risk factors, namely inflammation, high CaxP, and no RRF, showed the highest prevalence of valvular calcification and had the most severe cardiac hypertrophy.

CONCLUSIONS:

The association among loss of RRF, valvular calcification, and cardiac hypertrophy was closely linked to increased inflammation and high Ca x P in PD patients. These data suggest that valvular calcification and the calcification milieu are part of the processes linking loss of RRF and worsening cardiac hypertrophy in PD.

15) Ketteler M, Schlieper G, Floege J. Calcification and cardiovascular health: new insights into an old phenomenon. Hypertension 2006 47:1027–1034.  
Abstract:

Uremic cardiovascular disease is characterized by accelerated calcifying atherosclerosis and valvular heart disease. Vascular calcification develops at different sites within the vessel wall. Although intimal plaque calcification is a feature of genuine atherosclerosis, medial calcification is restricted to the smooth muscle cell layer and especially to the elastic laminae of arterial vessels (Figure 1). Both entities can be frequently observed in chronic kidney disease (CKD) patients. Dialysis patients with intimal calcifications are elderly and characterized by a history of “traditional” risk factors (eg, smoking and dyslipidemia) before the start of dialysis, whereas those with medial calcifications are, on average, 20 years younger and characterized by a longer time on dialysis treatment and a higher incidence of derangements in their calcium (Ca) phosphate (P) balance. Another recent study in incident dialysis patients showed that those with rapid arterial calcification progress already had calcified coronary arteries before reaching the dialysis stage. This emphasizes that diagnostic, preventive, and therapeutic measures need to be initiated in early CKD stages. The clinical importance of this notion is stressed by a number of reports demonstrating that coronary artery and valvular calcifications occur prematurely and are very prevalent in dialysis patients and that they are independent risk factors of cardiovascular death in this patient group. Such calcifications can, therefore, serve to at least partially explain why cardiovascular mortality is dramatically increased in the uremic as compared with a normal population and why it is not appropriately explained by the traditional Framingham risk factors. One of the mechanisms by which medial vascular calcification feeds into cardiovascular mortality may be via the associated increase in aortic pulse wave velocity. Calcified arteries become stiffer, causing quicker return of the systolic pulse wave from the periphery, thereby increasing left ventricular afterload. Through this mechanism, a high aortic pulse wave velocity is associated with increased left ventricular mass.

16) Giachelli CM. Vascular calcification mechanisms. Journal of the American Society of Nephrology : JASN 2004 15:2959–2964.  
Abstract:

Vascular calcification is highly correlated with cardiovascular disease mortality, especially in patients with ESRD or diabetes. In addition to the devastating effects of inappropriate biomineralization seen in cardiac valvulopathies, calciphylaxis, and idiopathic arterial calcification, vascular calcification is now recognized as a marker of atherosclerotic plaque burden as well as a major contributor to loss of arterial compliance and increased pulse pressure seen with age, diabetes, and renal insufficiency. In recent years, several mechanisms to explain vascular calcification have been identified including (1) loss of inhibition, (2) induction of bone formation, (3) circulating nucleational complexes, and (4) cell death. Alterations in calcium (Ca) and phosphorus (P) balance as seen in patients with ESRD promotes vascular calcification via multiple mechanisms and may explain the alarmingly high levels of cardiovascular disease deaths in these patients. Strategies to control Ca and P levels in patients with ESRD have met with early success in preventing progression of vascular calcification. Whether or not vascular calcification can be reversed is not yet known, but exciting new studies suggest that this may be possible in the future.

17) Yang H, Curinga G, Giachelli CM. Elevated extracellular calcium levels induce smooth muscle cell matrix mineralization in vitro. Kidney Int. 2004;66(6):2293–2299.

Hyperphosphatemia, elevated calcium x phosphorus product (Ca x P), and calcium burden, major causes of vascular calcification, are correlated with increased cardiovascular morbidity and mortality in dialysis patients.

METHODS:  
To address the underlying mechanisms responsible for these findings, we have utilized an in vitro human smooth muscle cell (HSMC) model of vascular calcification. Previous studies using this system demonstrated enhanced calcification of HSMC cultures treated with phosphorus levels in the hyperphosphatemic range, and implicated a sodium-dependent phosphate cotransport-dependent mechanism in this effect. In the present study, we examine the effect of increasing calcium concentrations on HSMC calcification in vitro.

RESULTS:  
Increasing calcium to levels observed in hypercalcemic individuals increased mineralization of HSMC cultures under normal phosphorus conditions. Importantly, at these total calcium concentrations, ionized calcium levels increased from 1.2 mmol/L to 1.7 mmol/L, consistent with levels observed physiologically in normocalcemic and hypercalcemic individuals, respectively. Furthermore, increasing both calcium and phosphorus levels led to accelerated and increased mineralization in the cultures. Calcium-induced mineralization was dependent on the function of a sodium-dependent phosphate cotransporter, since it was inhibited by phosphonoformic acid (PFA). While elevated calcium did not affect short-term phosphorus transport kinetics, long-term elevated calcium treatment of HSMCs induced expression of the sodium-dependent phosphate cotransporter, Pit-1.

CONCLUSION:  
These studies suggest that elevated calcium may stimulate HSMC mineralization by elevating Ca x P product and enhancing the sodium-dependent phosphate cotransporter-dependent mineralization pathway previously observed in HSMCs.

18) Foley RN, Parfrey PS, Harnett JD, et al. Hypocalcemia, morbidity, and mortality in end-stage renal disease. American journal of nephrology 1996 16:386-93.

BACKGROUND:

Hypocalcemia and hyperphosphatemia with secondary hyper-parathyroidism are characteristic of end-stage renal disease (ESRD). Although calcium levels critically affect almost all cellular processes, the impact of chronic hypocalcemia and other abnormalities of calcium-phosphate homeostasis on the prognosis of ESRD patients is unknown.

METHODS:

An inception cohort of 433 patients starting ESRD therapy was followed prospectively for an average of 41 months. Serum calcium and other parameters were measured monthly. The mean calcium levels were 9.4 +/- 0.7 mg/dl. 23% of the patients had mean calcium levels < 8.8 mg/dl. After adjusting for baseline age, diabetes mellitus, ischemic heart disease, smoking and cholesterol levels, as well as serial albumin, hemoglobin, mean arterial blood pressure, phosphate and alkaline phosphatase levels, chronic hypocalcemia was strongly associated with mortality (RR 2.10, p = 0.006 for a mean calcium level < 8.8 mg/dl). The association with mortality was similar in hemodialysis (RR 2.10, p = 0.006) and peritoneal dialysis patients (2.67, p = 0.034). Using similar covariate adjustment, chronic hypocalcemia was associated with de novo ischemic heart disease (RR 5.23, p < 0.001), recurrent ischemic heart disease (RR 2.46, p = 0.006), de novo cardiac failure (RR 2.64, p < 0.001), and recurrent cardiac failure (RR 3.30, p < 0.001). Hypocalcemia retained its independent impact on morbidity and mortality when analyzed as a time-dependent covariate.

CONCLUSIONS:

Chronic hypocalcemia, a very common, reversible feature of chronic uremia, is independently associated with morbidity and mortality in ESRD patients.

19) Koch M, Lund R, Oldemeyer B, Meares AJ, Dunlay R. Refeeding hypophosphatemia in a chronically hyperphosphatemic hemodialysis patient. Nephron 2000;86(4):552.  
Abstract:

Hyperphosphatemia is a common problem in dialysis patients and is usually due to inadequate adherence to dietary phosphate restrictions and noncompliance with pre- scribed phosphate binders. We report an unusual case of refeeding hypophosphatemia in a dialysis patient with an eating disorder and chronic hyperphosphatemia.