

DIALYSIS

Is the road to survival paved with good mineral management?

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A recent observational study from the UK raises questions over the control of mineral metabolism parameters to within target levels defined by the KDOQI clinical practice guidelines. Data from this study highlight the need for a randomized controlled trial to determine whether optimal management of bone mineral metabolism actually provides any survival benefit.

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Disorders of mineral metabolism affect the majority of dialysis patients and are increasingly being recognized as risk factors for mortality. Early studies, including the first observational study by Block *et al.*,¹ found associations between baseline parameters of mineral metabolism and increased mortality; however, most of these studies did not account for variation in the clinical and laboratory parameters of mineral metabolism and other covariates over time. Subsequent studies used time-dependent models and showed that biochemical values of mineral metabolism that closely preceded outcomes of interest were associated with subsequent mortality.² A more recent study used cumulative time-dependent approaches and demonstrated that accumulated effects of disordered mineral metabolism were associated with heightened mortality and cardiovascular morbidity.³ Although these observational studies reported minor differences in the cut-off points for an increased risk of mortality, they consistently showed that altered bone mineral metabolism was associated with adverse outcomes in patients receiving dialysis therapy. Based on these findings, several national and international clinical practice guidelines recommend the control of serum calcium, phosphorus, and parathyroid hormone (PTH) levels to within specific ranges.⁴

In a new study, published in the *American Journal of Kidney Diseases*,⁵ Tangri and colleagues analyzed data from the UK Renal Registry for 7,076 patients new to hemodialysis or peritoneal dialysis. The investigators examined the associations between achievement of the targets specified in the National Kidney Foundation Kidney



Disease Outcomes Quality Initiative (KDOQI) guidelines (for calcium, phosphorus, and intact PTH levels during the first year on dialysis) and subsequent patient survival. The study's main findings were that achievement of the KDOQI guideline targets during the first year on dialysis was not associated with any survival benefit in the following 2 years. The authors performed several different sensitivity analyses to show that their findings were robust. The different analytic strategies included a subgroup analysis comparing patients on

hemodialysis with those on peritoneal dialysis, and a complete-case analysis without imputation for missing values of calcium, phosphorus, or intact PTH. In additional analyses, the investigators found a trend towards increased mortality with calcium levels >2.6 mmol/l (>10.4 mg/dl) and a substantially increased risk of mortality with phosphorus levels >2.1 mmol/l (>6.5 mg/dl), both of which are higher than the upper limit of the KDOQI target ranges. No statistically significant relationships were found between intact PTH levels and mortality.

On the basis of these results, Tangri *et al.*⁵ propose more liberal cut-off values for the targets of bone mineral metabolism. However, their study had several limitations that should be considered. Firstly, the authors evaluated the achievement of the guideline targets during the first year of dialysis only, and subsequent changes in mineral management were not included in the analysis. Because parameters of bone mineral metabolism vary greatly over time—presumably due to loss of residual renal function, changes in dietary phosphorus load, variations in medications administered, and progression of secondary hyperparathyroidism—the use of guideline target achievement during the first year as a predictor of long-term survival is the major weakness of the study. Secondly, the study sample was restricted to incident patients who underwent 1 year of dialysis, so the results cannot be generalized to prevalent dialysis patients. Importantly, as the authors acknowledge, their analysis did not adjust for alkaline phosphatase and 25-hydroxyvitamin D concentrations, which have been associated with survival independently

of other mineral parameters.^{2,6} Another important limitation is the lack of information on medications being taken by patients for mineral and bone disorders. Although biochemical parameters of mineral metabolism might be considered to mediate the effects of these medications on patient-level outcomes, recent clinical data indicate that treatment with active vitamin D provides beneficial effects on survival independently of other mineral parameters⁶ and that administration of phosphate binders improves survival even among patients without hyperphosphatemia.⁷ Although these data are still inconclusive, the possibility that the lack of medication data might have confounded the results should be considered.

“...achievement of the KDOQI guideline targets ... was not associated with any survival benefit...”

Despite these limitations, the study by Tangri *et al.*⁵ generates an important discussion about the validity of controlling bone mineral parameters to within specific ranges. A number of observational studies, including this one, have consistently shown associations between elevations in mineral metabolism parameters and an increased risk of mortality, albeit with varying magnitudes. Substantial biological plausibility exists to support these observations, and it is, therefore, well-accepted that biochemical parameters of mineral metabolism should be managed in an effort to improve patient outcomes. Indeed, in contrast to the findings from the study by Tangri *et al.*, other research indicates that sustained control of bone mineral parameters within the target ranges recommended by the KDOQI guidelines is associated with improved survival.⁸ Thus, the results of the study by Tangri *et al.* should not be interpreted in isolation to justify neglecting control of bone mineral metabolism. Rather, this study highlights the need for robust evidence from randomized controlled trials (RCTs) to support the recommendations of the KDOQI guidelines for the management of mineral and bone disorders. One could argue that conducting a placebo-controlled RCT would be unethical in patients with apparent elevations in biochemical parameters of mineral metabolism. Although this notion is a matter of discussion, it is likely that randomly assigning patients to receive either ‘intensive’ or

‘standard’ mineral metabolism control would be more ethically feasible, given the lack of hard evidence for optimal target ranges. To date, RCTs using this approach have made relevant contributions to the determination of the optimal targets for treating various diseases, including diabetes mellitus, renal anemia,⁹ and hypertension.¹⁰ The new study by Tangri *et al.*⁵ should be welcomed because it provides additional rationale for conducting such RCTs in the field of mineral and bone disorders. We are being challenged with the task of determining whether optimal management of bone mineral parameters provides survival benefit for patients who are undergoing dialysis.

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Competing interests

H. Komaba declares associations with the following companies: Chugai Pharmaceutical, Kyowa Hakko Kirin. M. Fukagawa declares associations with the following companies: Bayer Yakuin, Chugai Pharmaceutical, Kyowa Hakko Kirin. See the article online for full details of the relationships.

1. Block, G. A., Hulbert-Shearon, T. E., Levin, N. W. & Port, F. K. Association of serum phosphorus

- and calcium × phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am. J. Kidney Dis.* **31**, 607–617 (1998).
2. Kalantar-Zadeh, K. *et al.* Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int.* **70**, 771–780 (2006).
3. Wald, R. *et al.* Disordered mineral metabolism in hemodialysis patients: an analysis of cumulative effects in the Hemodialysis (HEMO) study. *Am. J. Kidney Dis.* **52**, 531–540 (2008).
4. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease—mineral and bone disorder (CKD-MBD). *Kidney Int. Suppl.* **113**, S1–S130 (2009).
5. Tangri, N. *et al.* Effect of bone mineral guideline target achievement on mortality in incident dialysis patients: an analysis of the United Kingdom renal registry. *Am. J. Kidney Dis.* doi:10.1053/j.ajkd.2010.08.037.
6. Wolf, M. *et al.* Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int.* **72**, 1004–1013 (2007).
7. Isakova, T. *et al.* Phosphorus binders and survival on hemodialysis. *J. Am. Soc. Nephrol.* **20**, 388–396 (2009).
8. Danese, M. D., Belozeroff, V., Smirnakis, K. & Rothman, K. J. Consistent control of mineral and bone disorder in incident hemodialysis patients. *Clin. J. Am. Soc. Nephrol.* **3**, 1423–1429 (2008).
9. Drüeke, T. B. *et al.* Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N. Engl. J. Med.* **355**, 2071–2084 (2006).
10. Appel, L. J. *et al.* Intensive blood-pressure control in hypertensive chronic kidney disease. *N. Engl. J. Med.* **363**, 918–929 (2010).

BIOMARKERS

Kidney markers predict mortality in patients with HIV disease

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Individuals with HIV disease frequently experience kidney dysfunction, which is accompanied by an increased risk of cardiovascular disease and death. Choi *et al.* have found that albuminuria and an estimated glomerular filtration rate of <60 ml/min/1.73 m², estimated using serum cystatin C level, accounted for 17% of the population-attributable 5-year mortality risk in a cohort of patients with HIV infection.

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In developed countries, access to combined antiretroviral therapy has meant that, for most individuals, HIV disease has shifted from being a rapidly fatal disease to being a chronic condition. Similarly, as the HIV epidemic has evolved over the past three decades, the causes of death have changed. Before the availability of antiretroviral therapy, most deaths were the result of opportunistic infections and AIDS-defining

cancers. Currently, the major causes of death are similar to those in the general population, including cardiovascular disease and non-AIDS-defining cancers, although these deaths usually occur at an earlier age than in the general population.¹ Inflammation is increased in patients with HIV disease, promoting end-organ damage, including kidney dysfunction, which is far more prevalent in this patient population than