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Impact of Kidney Bone Disease and Its Management on Survival of Patients on Dialysis

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Despite the enormous cardiovascular disease epidemic and poor survival among individuals with chronic kidney disease (CKD), traditional risk factors such as hypercholesterolemia, hypertension, and obesity appear not as relevant as was previously thought, nor would their management improve survival in patients with CKD who are undergoing dialysis. On the contrary, kidney disease wasting (KDW) (also known as the malnutrition–inflammation complex), renal anemia, and kidney bone disease (KBD) appear to be the 3 most important nontraditional risk factors associated with cardiovascular disease in CKD. KBD-associated hyperparathyroidism may contribute to worsening refractory anemia and KDW/inflammation. The main cause of secondary hyperparathyroidism is active vitamin D deficiency. Hence, treatment of patients with KBD with vitamin D analogs, especially those with lesser effects on calcium and phosphorus such as paricalcitol, may be the most promising option for improving CKD outcomes. By conducting survival analyses in a 2-year (7/2001 to 6/2003) cohort of 58,058 patients on hemodialysis, we recently found that associations between high serum parathyroid hormone and increased death risk were masked by the demographic and clinical characteristics of patients, and that alkaline phosphatase had an incremental association with mortality. Administration of paricalcitol was associated with improved survival in time-varying models. We now present additional subgroup analyses that show that administration of any dose of paricalcitol, when compared with no paricalcitol, is associated with better likelihood of survival in virtually all subgroups of patients on hemodialysis. Because these associations may be secondary to bias by indication, randomized clinical trials are necessary to verify the findings of this and similar observational studies.

IN THE UNITED STATES today, more than 350,000 individuals with chronic kidney disease stage 5 (CKD-5) undergo renal replacement therapy in the form of maintenance hemodialysis (MHD; >90%) or long-term peritoneal dialysis (<10%).[1] The number of maintenance dialysis outpatients will surpass ½ million by 2010 and 1 million by 2018 or even earlier.[1,2] The death rate among these individuals is high, currently >20% per year in the United States and 12% to 15% in Europe, despite many recent improvements in dialysis treatment and techniques.[1,2] Almost half of all dialysis deaths are due to cardiovascular disease.[2]

Extrapolation of findings from the general population has led to decades of focus on the treatment of patients on dialysis for such conventional cardiovascular risk factors as hypertension,

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hypercholesterolemia, obesity, and hyperhomocysteinemia. However, survival has not improved substantially in the past 2 decades. In the recently conducted Die Deutsche Diabetes Dialyse (4D) Study,[3] cardiovascular outcomes did not improve in diabetic patients on dialysis who received atorvastatin for up to 4 years. Clinical trials in which folic acid was used to correct hyperhomocysteinemia in patients on dialysis have reported negative findings.[4–6] Additional efforts at targeting dialysis dose or membrane have failed to show any significant survival impact.[7,8] Hence, other prevailing risk factors must contribute to this substantial and persistent mortality risk.

Reverse Epidemiology in Patients With CKD-5

In industrialized and affluent nations, malnutrition (undernutrition) is an uncommon cause of poor outcomes in the general population, whereas overnutrition is associated with a greater risk of cardiovascular disease and shortened survival. In contrast, in patients on MHD, an "obesity paradox" exists, in that obesity is associated with enhanced survival.[9] This so-called reverse epidemiology also relates to other indicators of overnutrition and metabolic syndrome, including hypertension and hypercholesterolemia, which are paradoxically associated with improved survival.[10,11] Indeed, in addition to those on MHD, more than 20 million Americans, including those with chronic heart failure (CHF), AIDS, rheumatoid arthritis, or malignancy, and many elderly individuals exhibit similar paradoxes.[11] Hence, the keys to improving survival in patients on MHD and other, similar populations may be an enhanced understanding of the mechanisms that lead to these alterations and recognition of so-called "nontraditional" risk factors.

Nontraditional Risk Factors

It has been noted that 3 nontraditional risk factors appear to play major roles in the outcomes of patients with CKD. The malnutrition–inflammation complex (or cachexia) syndrome (MICS), which has recently begun to be referred to as kidney disease wasting (KDW), is probably one of the strongest risk factors for poor survival in patients with CKD.[12] The impact of KDW on survival is enormous, to the extent that it even reverses associations between traditional risk factors and survival, as was discussed earlier.[11] Anemia associated with CKD is another important risk factor in patients with CKD, including those in early stages of the disease[13] and those undergoing maintenance dialysis.[14] Finally, renal osteodystrophy, also known as kidney bone disease (KBD), is a somewhat underappreciated risk factor for cardiovascular mortality in patients with CKD.[15] To counter obsession with such traditional risk factors as obesity, hypercholesterolemia, or hypertension, we have advanced the hypothesis that improved survival of patients with CKD may be achieved if the 3 previously mentioned nontraditional risk factors are targeted effectively. In this article, we focus on renal osteodystrophy and present data that suggest an association between treatment of patients with osteodystrophy with vitamin D analogs and improved survival in patients with CKD-5.

Kidney Bone Disease

The KBD is a common complication of CKD stages 3 to 5. It is associated with disorders of mineral metabolism such as hyperphosphatemia, hypocalcemia, and hypercalcemia.[15] Achieving optimal control of serum phosphorus without worsening hypercalecmia is a major challenge in the management of KBD. A randomized controlled trial known as Treat to Goal[16] showed that in comparison with calcium-based phosphate binders, sevelamer hydrochloride (HCl) was less likely to cause hypercalcemia or progressive coronary and aortic calcification in patients on MHD. In another study by the same investigators,[17] the sevelamer HCl led to favorable changes in lipids and inflammatory markers with potentially useful antiatherogenic effects. Preliminary results of the recently conducted Dialysis Clinical Outcomes Revisited (DCOR) trial[18] demonstrated mortality and morbidity benefits for those given sevelamer HCl in some but not all subgroups of patients with CKD-5.

Administration of active vitamin D analogs compensates for the dysfunctional 1-hydroxylation of vitamin D that is inherent to KBD pathophysiology. However, resultant elevations in levels of calcium and phosphorus may accelerate vascular disease and hasten death in patients with CKD. Paricalcitol, a newer vitamin D analogue, appears to lessen elevations in levels of serum calcium and

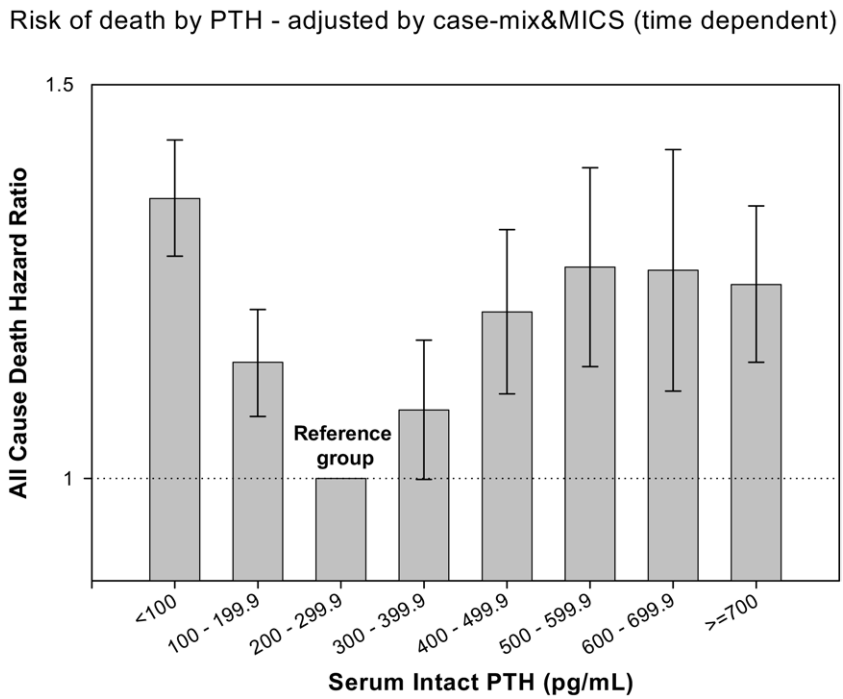

Figure 1. Association between time-varying serum intact parathyroid hormone and relative risk of death in 58,058 patients on MHD over a 2-year interval (7/2001 to 6/2003). Time-dependent Cox models with time-varying repeated measures were used after adjustment was made for case mix and surrogates of the malnutrition–inflammation complex (re-created on the basis of data presented by Kalantar-Zadeh et al[24]).

phosphorus, as compared with calcitriol, which is the classical form of active vitamin D.[19] Recent epidemiologic analyses of historical data in more than 65,000 patients on MHD showed that patients who received paricalcitol had a significant survival advantage over those who were given calcitriol.[20]

Cinacalcet, a calcimimetic that modulates the calcium-sensing receptor, reduces parathyroid hormone (PTH) secretion and lowers concentrations of serum calcium and PTH in patients with CKD who also have KBD. Recently, Cunningham et al[21] combined the results from 4 clinical trials and showed that randomization to cinacalcet led to significant reductions in the risks of parathyroidectomy, fracture, and cardiovascular hospitalization, along with improvements in self-reported physical function and diminished pain in patients with CKD. These data suggest that, in addition to its effects on PTH and mineral metabolism, cinacalcet may have favorable effects on important clinical outcomes.

Several observational studies, including 2 large epidemiologic studies by Block et al[22] and Teng et al,[23] showed significant associations between surrogates of KBD and mortality in patients on dialysis. However, the epidemiologic study recently reported by Block et al[22] examined survival in a cohort before initiation of the routine use of sevelamer HCl and paricalcitol—the 2 medications most commonly used at the dawn of the 21st century in the management of osteodystrophy in patients on dialysis. Similarly, in the past, the default dialysate calcium concentration was 3.5 mEq/L. Since the early 2000s, the standard dialysate calcium concentration has been reduced to 2.5 mEq/L in most US dialysis facilities. In addition, a number of important questions about renal osteodystrophy have remained unanswered. It is not clear whether a fall or a rise in serum calcium or phosphorus over time has any association with subsequent survival, independent of baseline values for calcium and phosphorus. The association between time-varying minerals and survival is also unclear.

To address these questions, some coauthors of this manuscript recently studied a large and contemporary national cohort (7/2001 to 6/2003) of patients on MHD across the United States with repeated measures and dialysate calcium concen-

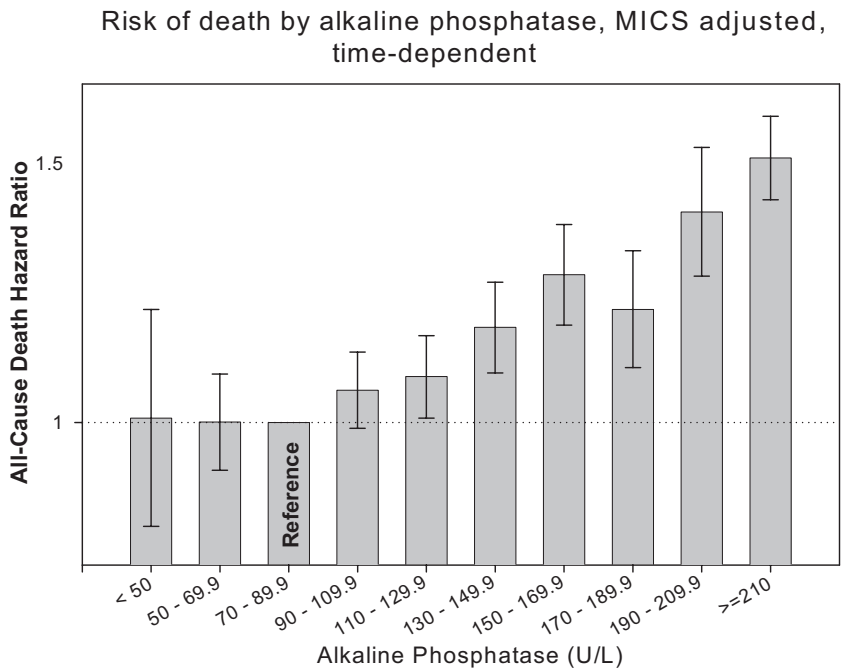

Figure 2. Association between time-varying serum alkaline phosphatase values and relative risk of death in 58,058 patients on MHD over a 2-year interval (7/2001 to 6/2003). Time-dependent Cox models with time-varying repeated measures were used after adjustment was made for case mix and surrogates of the malnutrition–inflammation complex (re-created on the basis of data presented by Kalantar-Zadeh et al[24]).

tration of 2.5 in more than 80% of patients.[24] In the foregoing study, the following hypotheses were examined: (1) A significant number of associations between indices of bone disease management and mortality in patients on MHD is due to the confounding effects of time-varying MICS/KDW; (2) a fall or rise in serum calcium, phosphorus, or calcium-phosphorus product over time to below or above National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI)–recommended targets[15] is associated with increased death risk; and (3) in any given calendar quarter, administration of the vitamin D analog paricalcitol is associated with greater survival in patients on MHD. In particular, findings of the DaVita study[24] were compared with those reported by Block et al[22] and Teng et al[23]; these latter 2 are based on Fresenius databases.

Is Kidney Bone Disease Associated With Higher Death Risk?

In a 2-year (7/2001 to 6/2003) cohort of 58,058 patients on MHD in the United States, survival models, including time-dependent Cox proportional hazard regressions, were recently examined.[24] The goal was to investigate time-varying predictors of survival among surrogates of KBD, including quarterly (13-week averaged) laboratory values and administered paricalcitol.[24] Associations between low levels of serum calcium and phosphorus and mortality were mostly due to the confounding effects of MICS, whereas hypercalcemia and hyperphosphatemia were robust predictors of higher death risk.[24] Changes in baseline values for calcium and phosphorus beyond K/DOQI-recommended targets were associated with increased mortality.

Another important finding was the positive association between high serum PTH and increased death risk, which was originally masked by the case mix characteristics of patients on MHD but was disclosed after control was provided for these confounders (Fig 1).[24] In other words, the unadjusted model showed no appreciable association between serum PTH and death risk. However, after multivariate adjustment was made for patient demographics (eg, age, sex, race, diabetes mellitus, vintage), a strong and strictly

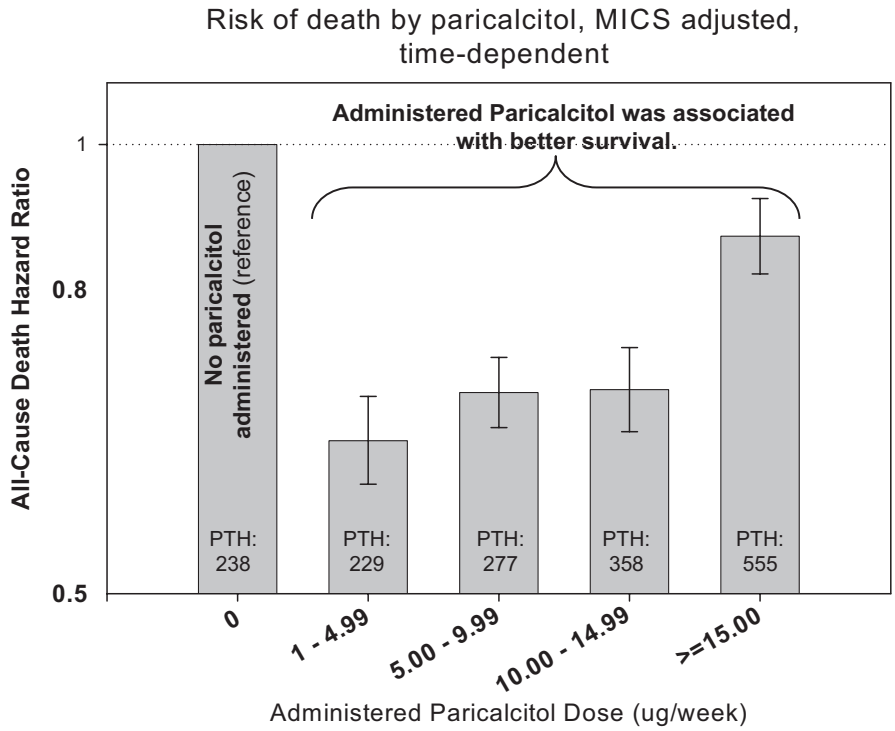

Figure 3. Association between time-varying administered doses of paricalcitol and relative risk of death in 58,058 patients on maintenance hemodialysis over a 2-year interval (7/2001 to 6/2003). Time-dependent Cox models with time-varying repeated measures were used after adjustment was made for case mix and surrogates of the malnutrition–inflammation complex (based on data presented by Kalantar-Zadeh et al[24]).

increasing association was noted between serum PTH levels >300 pg/mL and increased death risk. Further multivariate adjustment for MICS surrogates only slightly decreased these associations (see Fig 1). A low PTH level (<200 pg/mL) was also found to be associated with increased death risk, probably because these patients rarely, if ever, receive active vitamin D products due to the K/DOQI guidelines. Hence, high turnover bone disease is associated with higher death rates among patients on dialysis.[24]

Time-varying serum alkaline phosphatase had linear association with higher mortality (Fig 2).[24] This monotonic and almost strictly increasing association independent of the level of multivariate adjustment contrasted sharply with associations between minerals or PTH and survival, which are U or J shaped.[22] The K/DOQI guidelines state that the deleterious effects of high serum PTH levels may be manifested by elevated bone alkaline phosphatase activity due to associated bone resorption.[15] It is important to note that alkaline phosphatase measured routinely in patients on dialysis is not bone specific. Liver disease may be associated with increased serum alkaline phosphatase levels. However, even though liver diseases such as hepatitis C are associated with elevated liver enzymes and with increased death risk in patients on MHD,[25] a large proportion of the mortality predictability of alkaline phosphatase is likely due to its association with renal osteodystrophy.

Is Paricalcitol Administration Associated With Better Survival?

The DaVita database study[24] also confirmed the recently reported association between administration of any dose of active vitamin D and improved survival in patients on MHD in the Fresenius database as reported by Teng et al.[23] The former study[24] found that among those who received paricalcitol, the requirement for higher doses was associated with a trend toward greater death risk (Fig 3); however, this trend is probably due to a much higher baseline serum PTH level (555 pg/mL) among those who were subsequently given the highest paricalcitol dose as

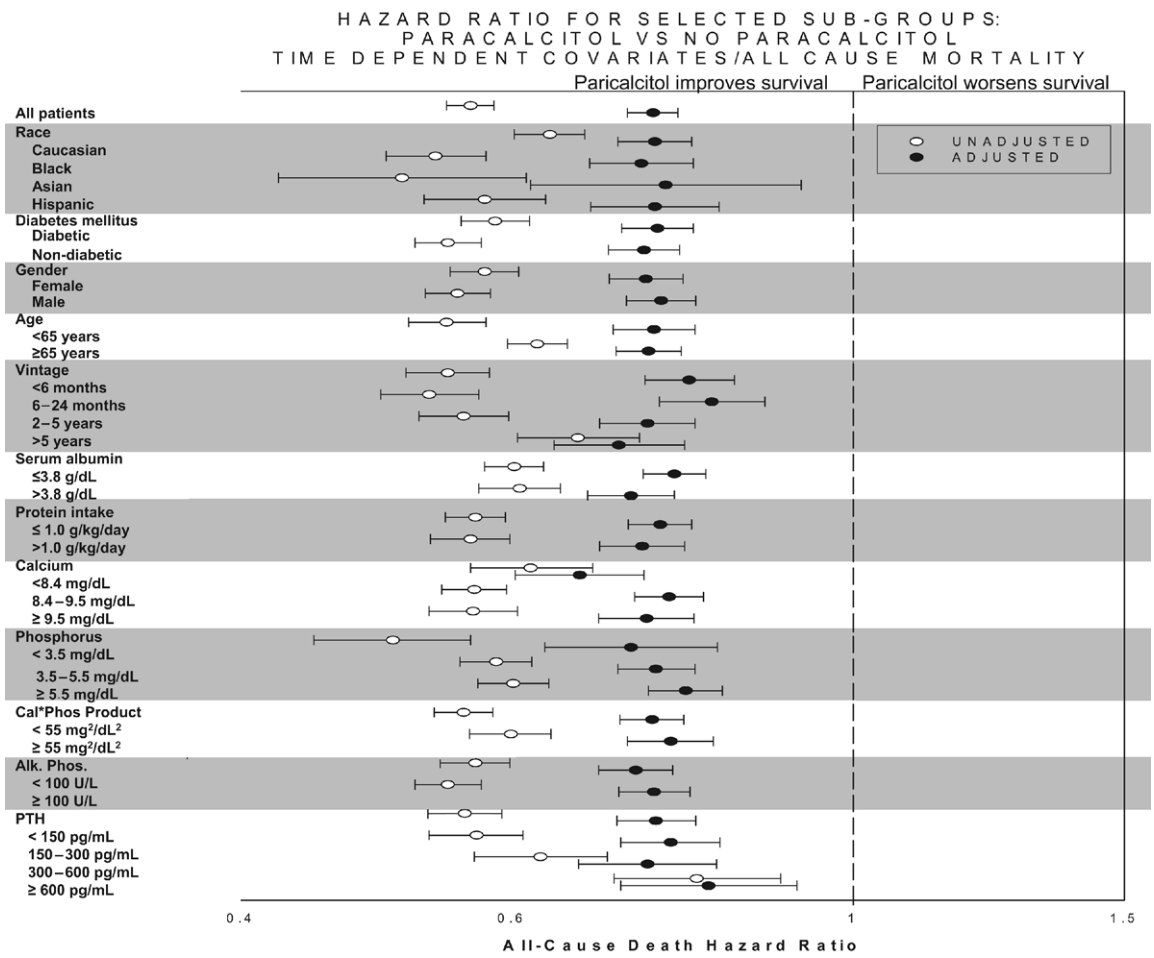

Figure 4. Associations between any administered dose of paricalcitol (yes/no) over a 13-week interval and relative risk of all-cause death in various demographic, clinical, and laboratory subgroups of 58,058 patients on maintenance hemodialysis over a 2-year interval (7/2001 to 6/2003). Empty circles represent unadjusted death hazard ratios, whereas filled circles represent fully multivariate (case mix and MICS) adjusted death hazard ratios.

compared with those who were placed on the lowest paricalcitol dose (PTH 229 pg/mL). This association may be somewhat analogous to what has been described for recombinant human erythropoietin (EPO) in patients on MHD, in whom the requirement for higher doses of EPO appears associated with higher death risk,[26] probably because EPO resistance is a surrogate of MICS, which per se is associated with poor survival.

In the current manuscript, we have included previously unpublished results of subgroup analyses (Fig 4). As shown in Figure 4, the hazard ratio of death in virtually all subgroups of patients on MHD is below 1, indicating significant association between paricalcitol administration at any dose and improved survival. It is important to note that bias by indication may also have led to different approaches to treatment of patients with varying death risk profiles (eg, patients with higher death risk may not have received vitamin D analogs), leading to an apparent association between vitamin D administration and improved survival. Hence, additional studies, including randomized clinical trials, are needed to verify these associations.

Conclusions

Despite the enormous cardiovascular disease epidemic in patients with CKD-5, management of traditional cardiovascular risk factors such as

hypercholesterolemia, hypertension, and obesity does not appear to mitigate the extremely high death rate among patients on dialysis. On the contrary, management of KDW, anemia, and KBD offers the most promising strategies for improving outcomes of CKD. Control of hyperphosphatemia with the use of non–calcium-containing phosphorus binders and treatment of patients with KBD with the use of vitamin D analogs, especially those with lesser effects on calcium and phosphorus such as paricalcitol, may provide the key to improving survival. We have shown that administration of any dose of paricalcitol is associated with improved survival in virtually all subgroups of patients on MHD; however, these associations may be secondary to bias by indication. Further studies, including randomized controlled trials, on the effects of vitamin D analogs and calcimimetics on the pathophysiology of KBD and its clinical outcomes are needed to verify the findings of previous observational studies.

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