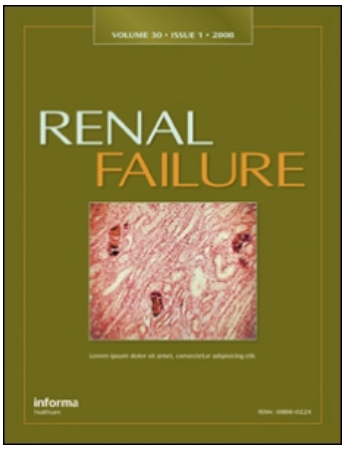

Renal Failure
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597293

The Importance of Serum Albumin and Phosphorous as Predictors of Mortality in ESRD Patients

Paul J. Phelan [a]; Patrick O'Kelly [a]; Joseph J. Walshe [a]; Peter J. Conlon [a]
[a] Department of Nephrology, Beaumont Hospital, Dublin, Ireland

Online Publication Date: 01 May 2008

To cite this Article Phelan, Paul J., O'Kelly, Patrick, Walshe, Joseph J. and Conlon, Peter J.(2008)'The Importance of Serum Albumin and Phosphorous as Predictors of Mortality in ESRD Patients',Renal Failure,30:4,423 — 429
To link to this Article: DOI: 10.1080/08860220801964236
URL: http://dx.doi.org/10.1080/08860220801964236

Renal Failure, 30:423–429, 2008

ISSN: 0886-022X print / 1525-6049 online
DOI: 10.1080/08860220801964236

informa
healthcare

CLINICAL STUDY

The Importance of Serum Albumin and Phosphorous as Predictors of Mortality in ESRD Patients

Paul J. Phelan, Patrick O'Kelly, Joseph J. Walshe, and Peter J. Conlon
Department of Nephrology, Beaumont Hospital, Dublin, Ireland

Secondary hyperparathyroidism and abnormal calcium/phosphate balance are common complications of ESRD and significant cardiovascular risk factors. It has also been demonstrated that malnourished dialysis patients have a much higher mortality than well-nourished patients. There is a lack of research looking at combined mortality with altered mineral metabolism and a low serum albumin.Using our renal database, we analyzed outcomes on 1,007 chronic dialysis patients, commencing dialysis between January 1990 and December 2004. The association between median values of serum phosphate, calcium, albumin (between three and six months post-commencement of dialysis), and long-term survival was examined. Cox proportional hazards models were used to determine the combined effects of these variables on patient outcome. The results showed that 18% of patients had serum phosphorous >1.8 mmol/L (5.5 g/dL), and the five-year survival of these patients was 48.4% compared with 58.6% for those with a serum phosphorous <1.8 mmol/L ($p = 0.047$). For serum albumin, 34.9% had a value <35 g/L, and this group also had a highly significant risk of increased mortality ($p < 0.001$). When combined with corrected calcium, 40.9% of patients reached all three target levels and had the greatest long-term survival (five-year survival of 62.5% for all three targets reached, compared to 30.7% for 0 or 1 targets reached). Poor control of calcium/phosphorous balance appears to have long-term deleterious effects on patient survival in ESRD patients. This risk of death is increased by poor serum albumin levels reflecting inadequate nutrition.

Keywords albumin, ESRD, mineral metabolism, mortality, nutrition

Address correspondence to Dr. Paul J. Phelan, Specialist Registrar in Nephrology, Beaumont Hospital, Dublin 9, Ireland; Tel.: 0035318092747; E-mail: paulphel@gmail.com

INTRODUCTION

Mortality rates among maintenance dialysis patients remain high.[1] Cardiovascular disease accounts for approximately 50% of deaths in patients with ESRD.[2] Many of the identified risk factors for mortality in this population are not modifiable (age, gender, race, co-morbidity). Of those that are, anemia is no longer a major cause of morbidity and mortality due to widespread use of erythropoietin. Hyperphosphatemia and elevated calcium × phosphate product are also potentially modifiable and have been considered risk factors for cardiovascular disease for many years.[3]

Poor nutrition has also been found to confer a worse prognosis in hemodialysis populations.[4] As no single laboratory or anthropomorphic value gives a complete and accurate assessment of nutritional status, several measurements have been studied. Piper et al. analyzed multiple indicators over a six-month period, including BMI, modified subjective global assessment, normalized protein catabolic rate, and serum albumin, creatinine, and bicarbonate.[5]

Elevated serum calcium, phosphate, and calcium-phosphate product (Ca × P) have been associated with increased all-cause and cardiovascular mortality in ESRD patients.[6,7] There have been some limitations to previous studies that examined the association between mineral metabolism and mortality. These have included the use of only one value for serum calcium and phosphate at a single point in time, and most of the larger studies have been exclusive to hemodialysis patients.[6,7]

Data from DOPPS has shown us that only a very small proportion of dialysis patients achieve bone and nutritional parameters within K-DOQI guidelines.[8] There has been little data on which markers of abnormal mineral metabolism are most strongly associated with mortality. As it is frequently difficult to control for all of these values, it would be beneficial to know which markers should

be primarily targeted. We hypothesized that serum albumin and phosphorous are most closely associated with mortality, and that the effects of each was cumulative.

PATIENTS AND METHODS

Data Source

The study patients were drawn from a dedicated renal database at Beaumont Hospital, which represents the largest dialysis unit in Ireland. All patients commencing maintenance hemodialysis (HD) and peritoneal dialysis (PD) between January 1990 and December 2004 were considered for inclusion in the study. Actual follow-up of patients commenced 90 days after commencing renal replacement therapy (RRT) to exclude patients with acute renal failure. Patients were followed up until death or till the end of the study period, which was June 2006. Patients transferred to other dialysis units were censored at time of transfer. Renal transplant recipients were not censored at time of transplantation unless the post-transplant follow-up was at a center other than Beaumont Hospital.

Demographic information was contained in the database and was used in the analysis, namely, age at commencement RRT and gender.

Measurements of serum calcium, phosphorous and albumin were taken between three and six months after commencing dialysis.

Serum phosphorous, albumin, and corrected calcium levels were allocated into categories according to U.K. Renal Association guidelines.[9] (Calcium levels were corrected for serum albumin as follows: For albumin <40 g/L, corrected calcium = calcium + (0.02) × (40–albumin).) The guidelines stipulate that phosphorous levels be less than 1.8 mmol/L, serum albumin levels equal or above 35 g/L, and corrected calcium levels of between 2.2 and 2.6 mmol/L. The analysis of the above variables focuses on two approaches. The first looks at the sum of the guidelines achieved for each patient between three and six months and whether the attainment of a maximum numbers of guidelines accrues a significant benefit to patients. The second approach examines the individual variables in a collective model with the addition of possible confounder variables. This approach tests for independent significance of the various predictors on outcome.

Statistical Methods

Log rank tests were used to compare survival between groups for univariate tests. Kaplan-Meier survivor functions were used to construct survival graphs. Cox proportional hazard ratio methods were used to assess the various risk factors on patient outcome in a single model. Adjustments were made for age, gender, and mode of dialysis treatment. Software used in the analysis was Stata (version 8, College Station, Texas, USA). A p value of the predictor variables of less than 0.05 was deemed significant.

RESULTS

Clinical data and follow-up times were available for 1,007 patients. Baseline demographic characteristics at three months after commencement of dialysis showed a mean age of 55.9 years (SD = 18.1 years) and a 61/39 percent male-to-female ratio, and the intention to treat RRT was 70% HD with the remainder commencing on PD. Mean follow-up time was 4.5 years (maximum follow up 16.7 years).

There were a mean of 10.1 measurements available for calcium, 9.8 for phosphorous, and 5.75 for albumin in the three- to six-month period after commencing dialysis. Median values of these were used.

Table 1 details the number and percent of patients who achieved the individual guideline targets. Approximately 84% of patients achieved two or more targets. The benefit of reaching the greatest number of target guidelines at three months is illustrated in Figure 1. Five-year survival for those reaching 0 or 1 guidelines is 30.7% (95% CI 22.9–38.7%), 49.7% (95% CI 44.4–54.8%) for two guidelines reached, and 64.4% (95% CI 57.0–67.4%) for all three targets achieved. This result is confirmed as significant with a log rank test ($p < 0.001$).

A Cox proportional hazards model (see Table 2) details the benefits of attaining both serum phosphorous and albumin guidelines on outcome. Albumin is highly significant in this model, with phosphorous achieving a less significant result. Notably, PD technique and lower age are also significant predictors of improved outcome.

Table 1
Sum of guidelines reached at three months after start RRT

Number of guidelines reached	Number of patients meeting guidelines (%)
0	17 (2)
1	143 (14)
2	435 (43)
3	412 (41)

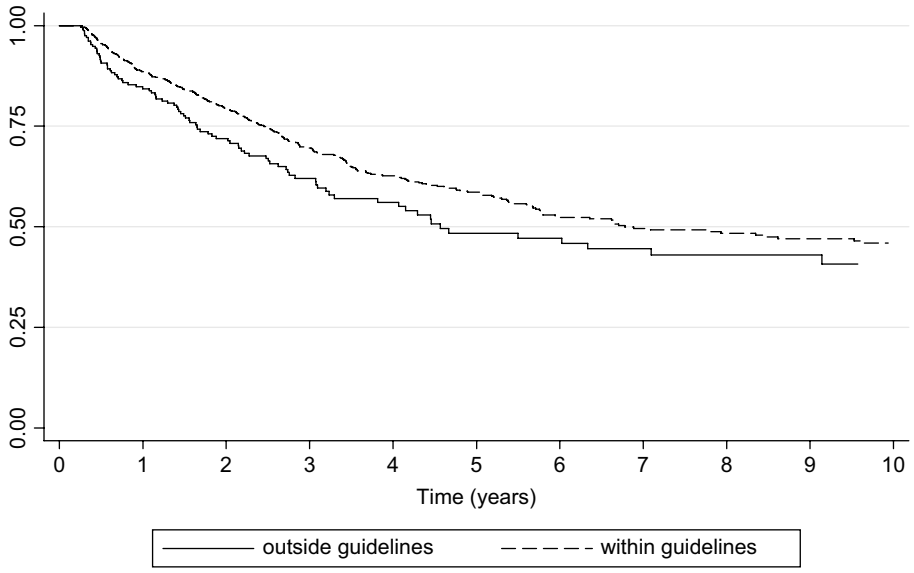

Figure 1. Age-adjusted Kaplan-Meier survival curves for the two categories of serum phosphorous.

Table 2
Cox model detailing mortality outcome for guidelines achieved

Variable	Percent meeting guidelines	Hazard ratio	95% CI	*p*
Phosphorous <1.8 mmol/L	82.1	0.781	0.616 – 0.992	0.043
Albumin ≥35 g/L	65.1	0.412	0.340 – 0.501	<0.001
Corrected calcium 2.2–2.6 mmol/L	76.1	1.158	0.932 – 1.439	0.185
Age at 90 days after start RRT	—	1.048	1.041 – 1.055	<0.001
Gender	—	0.956	0.793 – 1.154	0.644
Peritoneal dialysis technique	—	0.709	0.573 – 0.879	0.002

The one- and five-year age-adjusted patient survival for those reaching phosphorous guidelines was 88.6% and 58.6%, respectively, compared to those outside the guidelines of 84.3% and 48.4%, respectively (see Figure 1). Log rank test *p* value = 0.047.

For serum albumin, the corresponding patient survival for those achieving the guidelines versus those who did not at one and five years was 93.9% and 65.1% versus 73.4% and 37.2%, respectively (see Figure 2). Log rank test *p* value was <0.001.

Corrected calcium guidelines did not have the same influential effect on mortality outcome with similar one- and five-year patient survival rates of 86.6% and 56.0% for those within the guidelines compared to 88.6% and 57.4% for those outside the guidelines (see Figure 3). Log Rank test *p* value = 0.452.

Combining the above data, 17% of patients achieved zero or one target guideline, and more than 40% achieved two or all three targets (see Figure 4). Survival for those achieving three targets was consistently better than the two-target group, which itself was better than those achieving zero or one targets. This was across the full follow-up from 1 to 10 years (see Figures 5 and 6).

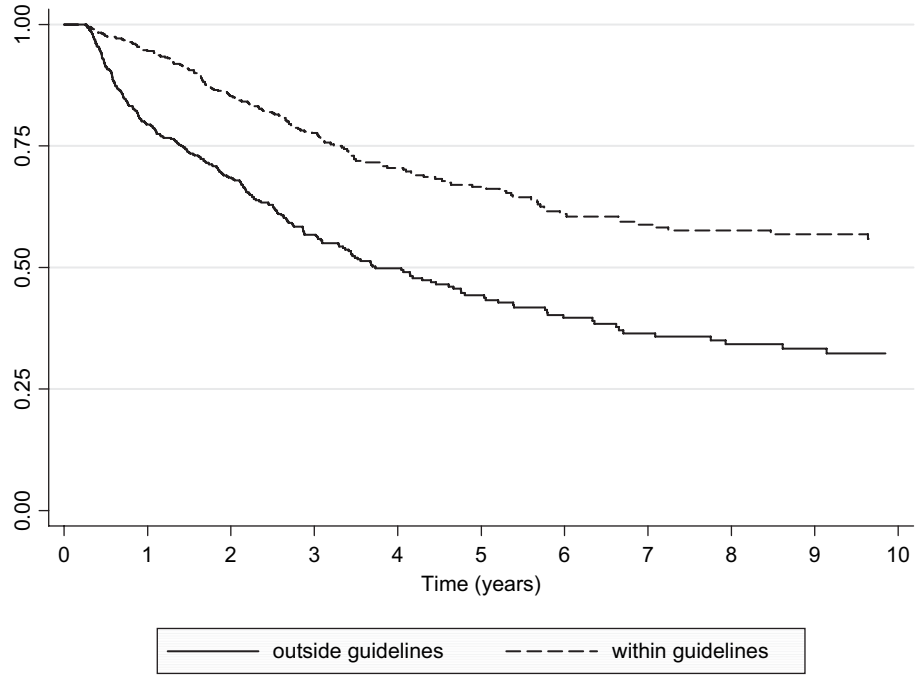

Figure 2. Survival curves for the two categories of serum albumin level.

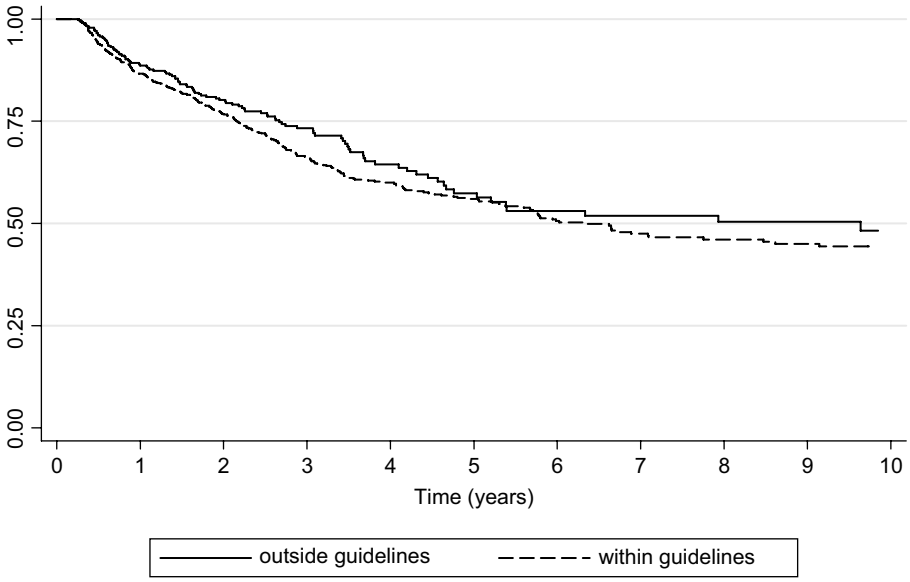

Figure 3. Age-adjusted Kaplan-Meier survival curves for the two categories of corrected calcium.

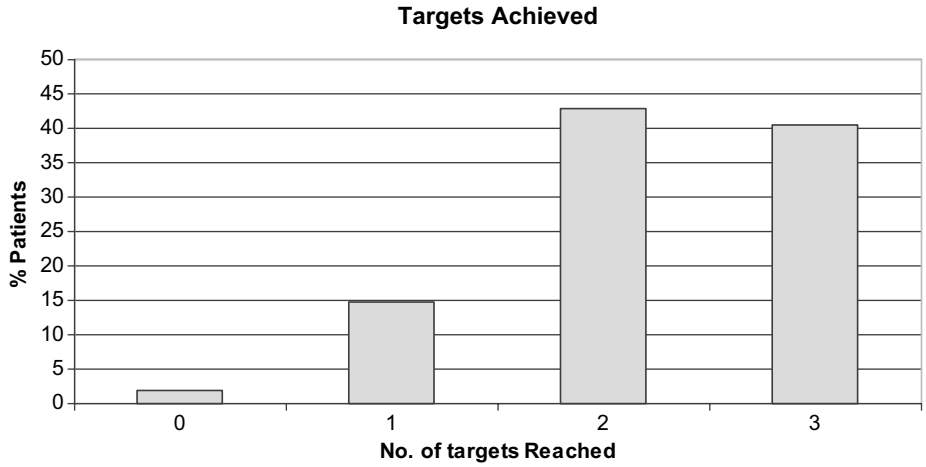

Figure 4. Percentage of patients achieving normal values for serum phosphorous, corrected calcium and albumin.

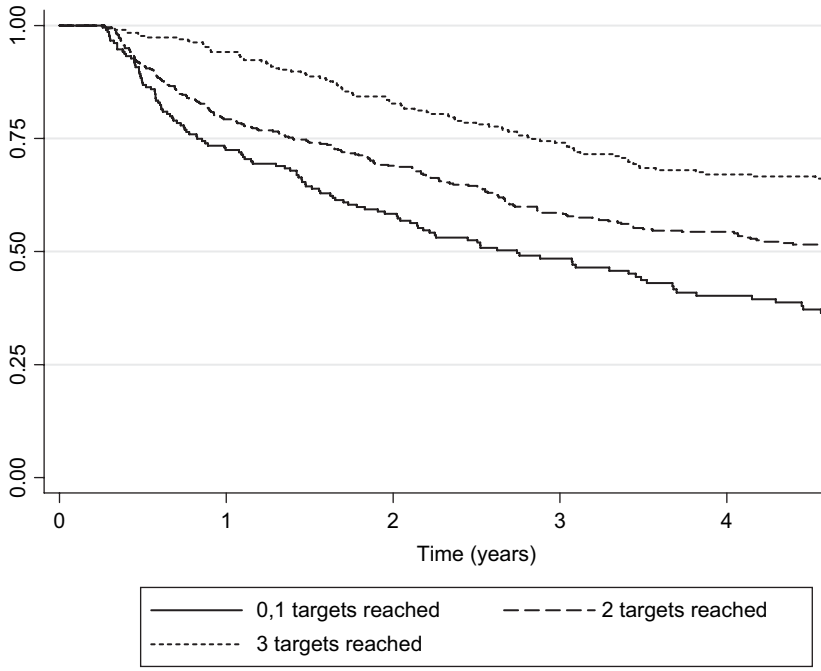

Figure 5. Age-adjusted Kaplan-Meier survival curves for patients achieving the different number of targets.

DISCUSSION

Our study reinforces the association between altered mineral metabolism and mortality in ESRD patients. Increased cardiovascular mortality has been the presumed mechanism, as has been observed in previous studies.[6,10] Goodman et al. showed that young dialysis patients with higher levels of phosphorous and calcium phosphorous product had more extensive coronary calcification.[11] Kawagishi et al. used high-resolution ultrasound to show a strong association between carotid artery calcification and serum phosphorous.[12] Previous studies have also described the transformation of vascular smooth muscle cells into osteoblasts in uremic patients.[13] These observations are consistent with the presumed mechanism of accelerated vascular disease seen in the dialysis population.

Results from DOPPS show how poorly we treat deranged mineral metabolism in our ESRD patients.

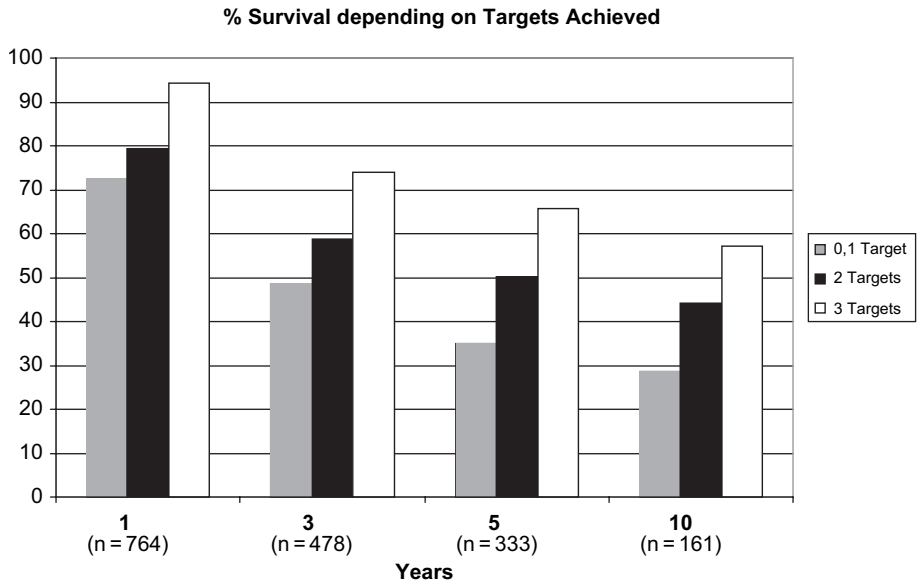

Figure 6. Percentage survival at 1, 3, 5, and 10 years, depending on number of targets achieved for corrected calcium, phosphorous, and albumin.

In DOPPS II, only 44.4% of patients had serum phosphorous within K-DOQI guidelines, 42.5% for calcium, 61.4% for Ca × P product, 26.2% for iPTH, and a mere 5.5% achieving all four targets.[8] Similarly abysmal results are reproduced in other studies.[14,15] It is not yet known how new therapies such as calcimimetic and newer activated vitamin D treatments will affect survival.

We examined the association between mortality and hyperphosphatasemia in all patients requiring maintenance peritoneal and hemodialysis over a fifteen-year period. We divided patients into groups above and below a serum phosphorous of 1.8 mmol/L. Only 18% of patients had average values above this level, which compares well internationally.[8] Serum phosphorous and particularly albumin were independently associated with increased mortality. This difference was seen as early as the first year.

A direct relationship was not seen between corrected calcium values and relative risk of death. There have been contradictory findings in the literature regarding calcium concentrations and mortality in ESRD patients. Foley et al. reported an association between calcium levels <8.8 mg/dL and death in 433 hemodialysis patients followed for 41 months.[16] However, Block et al. described a direct relationship between calcium and RR of death across the full spectrum of serum calcium concentrations.[6] Despite no identified relationship between calcium and mortality, patients achieving normal values for phosphorous, albumin, and calcium did better than those only achieving two normal variables.

Previous observations by Block et al., among others, have shown an association between high PTH and all-cause mortality.[6,17] It was a weaker association than that between phosphorous and mortality, and the RR was driven primarily by patients with very high values (>900 pg/mL). We examined a model including iPTH in which values above and below 300 pg/mL were compared. No effect on mortality was observed in our study, possibly due to the fewer patients with available iPTH values. Another potential reason is that the effects of very high PTH levels may have been cancelled out by the very low levels. These low levels of iPTH may be just as harmful as the high levels.[18]

Good nutritional status in both hemodialysis and peritoneal dialysis patients confers a better prognosis. This has been shown using high body and muscle mass as measures of nutrition.[19,20] Conversely, signs of under-nutrition such as low body mass, low blood urea nitrogen, and low serum albumin have been associated with decreased survival.[21] Hypoalbuminemia has been consistently shown to be an independent risk for mortality in ESRD. This may be due to increased cardiovascular risk as suggested by Cooper et al., who demonstrated that low serum albumin when commencing dialysis predicted new vascular events during follow-up.[22] There has been little evidence examining the cumulative effect of poor nutrition with abnormal

bone mineral metabolism. Patients with low serum albumin are frequently expected also have low serum phosphorous levels due to poor nutrition. However, a large proportion of our patients had a low serum albumin and high phosphorous, and it conferred a worse prognosis.

We acknowledge the inherent limitations of observational studies in evaluating the outcome of this study. Also, our sample size is not as great as in other studies. However, we obtained several values for phosphate, calcium, and albumin over a three-month period, in comparison with other larger studies where a single measurement was used.

In summary, this study of maintenance dialysis patients identifies hyperphosphatemia and hypoalbuminemia as strong risk factors for all-cause mortality. These results support the hypothesis that altered mineral metabolism is a major cardiovascular risk factor in dialysis patients, and this risk is significantly worsened by inadequate nutrition. It also highlights the need for new therapies to control renal bone disease and the importance of dietetic support in the ESRD population.

REFERENCES

1. U.S. Department of Health and Human Service. U.S. Renal Data System 2004 Annual Report. *Am J Kidney Dis.* 2005;45 (Suppl. 1):1–280.
2. Wallen MD, Radhakrishnan J, Appel G, Hodgson ME, Pablos-Mendez A. An analysis of cardiac mortality in patients with new-onset end-stage renal disease in New York state. *Clin Nephrol.* 2001 Feb; 55(2):101–108.
3. Lazarus JM, Lowrie EG, Hampers CL, Merrill JP. Cardiovascular disease in uremic patients on haemodialysis. *Kidney Int Suppl.* 1975;167–175.
4. Owen WF Jr, Lew NL, Liu Y, Lowrie EG, Lazarus JM. The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. *N Engl J Med.* 1993 Sep 30;329(14):1001–1006.
5. Pifer TB, McCullough KP, Port FK, et al. Mortality risk in hemodialysis patients and changes in nutritional indicators: DOPPS. *Kidney Int*. 2002 Dec;62(6):2238–2245.
6. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol.* 2004 Aug;15(8):2208–2218.
7. Young EW, Albert JM, Satayathum S, et al. Predictors and consequences of altered mineral metabolism: The Dialysis Outcomes and Practice Patterns Study. *Kidney Int.* 2005 Mar;67(3):1179–1187.
8. Young EW, Akiba T, Albert JM, et al. Magnitude and impact of abnormal mineral metabolism in hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis.* 2004 Nov;44(5 Suppl 2):34–38. Available at http://www.renal.org/Standards/standards.html.
9. *U.K. Renal Association Standards document*, 3rd ed. U.K. Renal Association; 2002.
10. Slinin Y, Foley RN, Collins AJ. Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: The USRDS Waves 1, 3, and 4 Study. *J Am Soc Nephrol.* 2005 Jun;16(6):1788–93. E-pub: 2005 Apr 6.
11. Goodman WG, Goldin J, Kuizon BD, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med.* 2000;342:1478–1483.
12 Kawagishi T, Nishizawa Y, Konishi T, et al. High Resolution B-mode ultrasonography in evaluation of atherosclerosis in uremia. *Kidney Int.* 1995;48: 820–826.
13. Moe SM, Duan D, Doehle BP, O'Neill KD, Chen NX. Uremia induces the osteoblast differentiation factor Cbfa1 in human blood vessels. *Kidney Int.* 2003;63:1003–1011.
14. Maduell F, Gorriz JL, Pallardo LM, Pons R, Santiago C. Multicentric group for the study of the phosphocalcic metabolism in the community of Valencia. Assessment of phosphorus and calcium metabolism and its clinical management in hemodialysis patients in the community of Valencia. *J Nephrol.* 2005 Nov–Dec;18(6):739–748.
15. Aly ZA, González EA, Martin KJ, Gellens ME. Achieving K/DOQI laboratory target values for bone and mineral metabolism: An uphill battle. *Am J Nephrol.* 2004;24:422–426.
16. Foley RN, Parfrey PS, Harnett JD, et al. Hypocalcemia, morbidity, and mortality in end-stage renal disease. *Am J Nephrol.* 1996;16(5):386–393.
17. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO_4, $Ca \times PO_4$ product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol.* 2001;12:2131–2138.
18. Avram MM, Mittman N, Myint MM, Fein P. Importance of low serum intact parathyroid hormone as a predictor of mortality in hemodialysis and peritoneal dialysis patients: 14 years of prospective observation. *Am J Kidney Dis.* 2001 Dec;38(6):1351–1357.
19. Ramkumar N, Pappas LM, Beddhu S. Effect of body size and body composition on survival in peritoneal dialysis patients. *Perit Dial Int*. 2005 Sep–Oct;25(5):461–469.
20. Kakiya R, Shoji T, Tsujimoto Y, et al. Body fat mass and lean mass as predictors of survival in hemodialysis patients. *Kidney Int.* 2006 Aug;70(3):549–556. E-pub: 2006 Jun 21.
21. Owen WF Jr, Lew NL, Liu Y, Lowrie EG, Lazarus JM. The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. *N Engl J Med.* 1993 Sep 30;329(14):1001–1006.
22. Cooper BA, Penne EL, Bartlett LH, Pollock CA. Protein malnutrition and hypoalbuminemia as predictors of vascular events and mortality in ESRD. *Am J Kid Dis.* 2004 Jan;43(1):61–66.