

Serum phosphate

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GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

General comments in relation to bone mineral metabolism:

- **In Stage 5 kidney disease, serum phosphate, serum calcium, calcium x phosphate product and parathyroid hormone (PTH) level need to be considered simultaneously when assessing the bone mineral status of a patient: a combination of high calcium, high phosphate and low PTH level being associated with the worst outcome. (Level III evidence – cohort)**
- **Ideal targets for bone mineral metabolism parameters are unlikely to be met with conventional dialysis methods and available phosphate binders in the majority of patients. (Level III evidence - cohort)**

Serum phosphate:

- **In Stage 5 kidney disease, a predialysis serum phosphate level of 0.8–1.60 mmol/L is recommended as higher levels of serum phosphate have been shown to be associated with an increase in mortality. (Level III evidence – 8 cohort studies including 2 recent large studies) with robust analyses and good quality, strong association, consistent effect seen).**
- **For Stages 3 and 4 kidney disease, serum phosphate should be kept within the normal laboratory reference range. (Opinion)**
- **It is unclear whether using high doses of phosphate binders, using the newer phosphate binders and/or whether performing longer dialysis to improve the bone mineral metabolism status of patients will translate into improvement in the mortality of patients with chronic kidney disease. (Opinion)**
- **For patients on haemodialysis, a fasting predialysis blood sample should be used. For other patients, a fasting blood sample should be used. (Level III evidence)**

Background

For many years, parameters of bone mineral metabolism (BMM) were followed as a means of monitoring the status of metabolic bone disease in patients with kidney disease.

However, with the publication of observational studies demonstrating a link between serum phosphate and mortality in 1998, (Block et al 1998) the spotlight has moved to exploring the link between these parameters (particularly phosphate and calcium x phosphate product) and mortality. This publication and others fuelled investigations at both the basic and clinical science levels to explore the role of hyperphosphataemia as a putative factor in the high cardiovascular disease risk seen in patients with renal impairment.

However, there are no data involving randomised controlled trials (RCT's) with the aim being to target specific levels of BMM parameters, with mortality as the outcome.

This review set out to explore and collate the evidence to support an appropriate target range for serum phosphate in patients with renal impairment, looking at the outcomes of bone disease, all-cause mortality and disease-specific mortality, based on the best evidence up to and including April 2005.

Search strategy

Databases searched: MeSH terms and text words for kidney dialysis were combined with MeSH terms and text words for serum phosphates. This search was carried out in Medline (1966 to April Week 3, 2005). The Cochrane Renal Group Trials Register was also searched for phosphate trials not indexed in Medline. A further Medline search was carried out for the period 1 Feb 2004 to 30 Apr 2005.

Date of searches: 3 March 2004; 30 April 2005.

What is the evidence?

There are no available randomised controlled trials (RCT's) – all data is at Level III or lower.

However, the literature to date demonstrates a strong association between serum phosphate and all-cause mortality, cardiovascular mortality and fracture rates. There is also data linking serum phosphate to vascular calcification which has been shown to be associated with mortality.

Summary of the evidence

1. Is there a relationship between indices of bone mineral metabolism and extra-skeletal outcomes?

All-cause mortality

There have been 8 key observational studies exploring the relationship between indices of bone mineral metabolism (serum phosphate, serum calcium, calcium x phosphate product and PTH) and mortality in Stage 5 disease (Lowrie and Lew, 1990, Foley et al 1996, Leggat et al 1998, Block et al 1998, Ganesh et al 2001, Block et al 2004, Stevens et al 2004, Young 2005) and 1 study exploring this in patients with kidney disease before Stage 5 (Kestenbaum B et al 2005).

A strong association between serum phosphate and all-cause mortality has been consistently demonstrated, including a dose response.

Disease-specific mortality

A number of studies have explored specific extra-skeletal outcomes other than all-cause mortality, cardiovascular disease being the most studied. Ganesh et al (2001) looked at sudden death, death from coronary artery disease, and infectious deaths. Block et al (2004) explored the risk of hospitalisation for cardiovascular disease and Young et al (2005) looked at cardiovascular mortality.

A strong association between serum phosphate and cardiovascular mortality has been consistently demonstrated, including a dose response.

Importantly, the majority of publications have related to the haemodialysis cohort. There is very little data relating to peritoneal dialysis (PD) patients.

2. Is there a proven relationship between indices of BMM and bone disease outcomes?

Elevated serum phosphate directly influences the development of hyperparathyroidism. Hyperphosphataemia influences the efficacy of vitamin D analogues to suppress PTH secretion (Slatopolsky and Delmez 1996). Block et al (2004) demonstrated that serum phosphate (> 1.63 mmol/L) is associated with increased risk of hospitalisation with fracture.

It has been clearly demonstrated that hyperphosphataemia influences the development of hyperparathyroidism and hyperphosphataemia has been associated with fractures requiring hospitalisation in Stage 5 kidney disease.

Additional summary comments

Phosphate as a predictor of surrogate indicators of cardiovascular disease: Serum phosphate has been linked in a number of studies to vascular calcification (Blacher et al, Goodman et al, Raggi et al, and Rufino et al), congestive heart failure (Stack et al 2001) and valvular calcification requiring intervention (Rubel et al 2003). Vascular calcification has been associated with mortality in a number of studies (Blacher et al 2001, Goodman et al 2000, Raggi et al 2002, Rebel et al 2003, Rufino et al 2003).

Difficulty achieving guideline targets

Young et al (2004) and other smaller studies (not listed in this guideline) have demonstrated that only a relatively modest percentage of patients fell within the guideline range in relation to control of serum phosphate and other parameters of bone mineral metabolism.

The studies listed above are described in detail below

Lowrie and Lew (1990) found a 2-fold higher RR of death in chronic haemodialysis patients with serum phosphate between 2.3 and 3.7 mmol/L (7–11 mg/dl) compared with those between 1.7–2.3 mmol/L (5–7 mg/dl) but did not adjust for co-morbid conditions.

Nichols and co-workers (1990) studied 73 dialysis patients following parathyroidectomy. Those with progressive vascular calcification had serum phosphate levels > 1.8 mmol/L and elevated calcium x phosphate products (Nichols et al 1990).

The limitations of these studies were:

- uncertain relevance because of date of publication and date of patient sample,
- small numbers of patients, and
- no adjustment for confounders.

Foley et al (1996) in a prospective study of both haemodialysis and CAPD patients found no independent association between phosphate levels over 2 mmol/L (6 mg/dL) and RR of death. This study was designed in the early 1980s and did not adjust for dialysis dose.

Leggat et al (1998) analysed 6251 haemodialysis patients from the Case Mix Adequacy Study and Dialysis Morbidity and Mortality Study. Serum phosphate > 2.5 mmol/L (7.5 mg/dL) was used as an indicator of dietary and medication non-compliance and correlated with dialysis non-compliance indicators. Compared with phosphates in the 0.9–1.8 mmol/L range (2.6–5.5 mg/dL), the RR of death for patients with phosphate in the 1.9–2.5 mmol/L range (5.6–7.5 mg/dL) was 1.16, $P < 0.007$ and for phosphate over 2.5 mmol/L, RR was 1.22, $P < 0.002$.

Using the same data sources as for the Leggat et al (1998) publication, Block et al (1998) found the RR for death was constant for serum phosphate below 2.2 mmol/L (6.5 mg/dL), increasing above this level (N = 6407). For serum phosphate > 2.2 mmol/L, RR was 1.27 relative to those with serum phosphate of 0.8–2.2 mmol/L (2.4–6.5 mg/dL). Covariate adjustment for dialysis dose, atherosclerotic vascular disease, markers of non-compliance, PTH and serum calcium did not reduce the RR. This study used the data on 6407 patients, of which only 2669 had information on serum calcium.

The limitations of the study were:

- observational nature of the data,
- all North American patients,
- haemodialysis patients only,

- baseline cross-sectional data based on only a single measure of a bone mineral metabolism parameter, and
- serum calcium only available in 2,669 of 6,409 patients.

Ganesh et al (2001) set out to look at whether serum phosphate was associated with specific causes of death in end stage kidney disease (ESKD) patients and in particular, whether the association was with cardiovascular deaths. They published a large study utilising data again from the US renal data system, with data from 2 random samples of 12 833 haemodialysis patients who were followed for 2 years.

This study demonstrated that serum phosphate > 2.12 mmol/L (6.5 mg/dL) was associated with a higher total mortality (RR 1.20, P < 0.01), death from coronary artery disease (RR 1.41, P < 0.0005), sudden death (RR 1.20, P < 0.005) infection (RR 1.20, P < 0.05) and unknown causes (RR 1.25, P < 0.05) compared with serum phosphate < 2.12 mmol/L.

As demonstrated, the strongest association of hyperphosphataemia is with cardiac deaths, particularly due to coronary artery disease and sudden death.

The limitations of this study were:

- observational nature of the study,
- prevalent cohort only,
- classification of cause of death – accuracy of the data, and
- North American haemodialysis cohort only.

Block et al (2004) represents the single most important publication in this domain, being a large cohort with detailed rigorous analyses. This study was of retrospective cohort design using the Fresenius Medical Care and North American Patient Statistical profile system and involved 40 538 haemodialysis patients. The study explored the associations between phosphate, calcium, the calcium x phosphate product and PTH with the following outcomes: (1) all-cause mortality; (2) hospitalisation from (i) all causes (ii) CV disease (iii) infection related (iv) vascular access related; and (3) hospitalisation with fracture. Biochemical data was taken during the last 3 months of 1997 and > 1 measurement was available in all patients. Analytical methods included: (1) without adjustment; (2) casemix adjusted: age, gender, race, diabetes, dialysis vintage; (3) multivariable adjusted: casemix indices as well as body weight, dialysis adequacy (Urea reduction ratio), serum albumin, creatinine, urea, bicarbonate, cholesterol, haemoglobin, aluminium, ferritin. In addition, in relation to analyses of phosphate this was done adjusting for the effects of calcium and PTH. This study demonstrated that serum calcium, serum phosphate, calcium x phosphate product and iPTH were associated with mortality.

This study showed an increased in serum phosphate (> 1.60 mmol/L) is associated with: (1) all-cause mortality; (2) increased risk of hospitalisation for CV disease; and (3) increased fracture risk. Serum phosphate of 1.6–1.76 mmol/L was associated with a RR of death of 1.10 (95% CI: 1.02–1.17) compared with the reference group with serum phosphate of 0.96–1.6 mmol/L. A progressive increase in RR of death with increasing serum phosphate was demonstrated. Effect modification was seen with diabetes and serum phosphate.

Phosphate level mg/dl (mmol/L)	RR of death	95% CI
3–5 (0.96–1.6)	1.0 (Referent group)	
5–6 (1.61–1.92)	1.07	
5–5.5 (1.61–1.76)	1.10	1.02–1.17
5.5–6 (1.76–1.92)	1.25	1.18–1.33
6–7 (1.93–2.24)	1.25	
7–8 (2.25–2.56)	1.43	
8–9 (1.57–2.88)	1.67	
> 9 (> 2.88)	2.02	

(Multivariate adjusted)

Limitations of the study were:

- only observational data,
- North American population only, and
- no peritoneal dialysis cohort / haemodialysis only.

Stevens et al (2004) conducted an important study as it demonstrated the importance of examination combinations of BMM parameters. This retrospective cohort study looked at 515 prevalent dialysis patients using the British Columbia Renal Agency provincial database. Patients were on haemodialysis (69%) and peritoneal dialysis. In this study, serum phosphate was predictive of mortality rate as was calcium x phosphate, although calcium was not independently predictive in this study. Importantly, the combination of high serum calcium and phosphate with high iPTH (RR 3.71, 95% CI: 1.53–9.22, P = 0.004) and low iPTH (RR 4.30, 95%CI: 2.01–9.22, P < 0.001) had highest risks for mortality.

Limitations of the study were:

- observational only,
- prevalent cohort only, and
- relatively small study.

Young et al (2004) explored this in a recent publication by DOPPS. Young et al (2004) described the state of bone mineral metabolism from the DOPPS studies including DOPPS I (1996–2001) and DOPPS II (2002–2004). This study demonstrated that a relatively modest percentage of patients fell within the guideline range for phosphate, albumin-corrected calcium and calcium x phosphate product. The proportion of patients whose results fell within the K/DOQI guideline range are as follows:

Markers of bone mineral metabolism	DOPPS I	DOPPS II
Phosphate	40.8%	44.4%
Calcium (albumin-corrected)	40.5%	42.5%
Calcium x phosphate product	56.6%	61.4%
Parathyroid hormone	21.4%	26.2%

Young et al (2005) reported the results of observational retrospective cohort data from units in the United States, Europe (Germany, Italy and Spain), and Japan, as part of the Dialysis Outcomes and Practice Patterns Study (DOPPS), including 307

dialysis facilities and 17 236 patients. Data was collected between 1996 and 2001. Altogether, 17 236 patients were studied – 8 615 at the start and 8 621 replacement patients. The study set out to explore whether indices of bone mineral metabolism were predictive of all-cause mortality, cardiovascular mortality, and parathyroidectomy rate. Analyses included standard regression models – with various models adjusting for patient and laboratory variables with adjustment for clustering factor. All-cause mortality was significantly and independently associated with serum concentrations of phosphorus (RR 1.04 per 1 mg/dL, (0.32 mmol/L P = 0.0003), calcium (RR 1.10 per 1 mg/dL, P < 0.0001), calcium x phosphorus product (RR 1.02 per 5 mg²/dL² (0.4 mmol²/L²), P = 0.0001), PTH (RR 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 x phosphorus product (RR 1.05, P < 0.0001), and PTH (RR 1.02, P = 0.03).

Limitations of the study included:

- observational design,
- prevalent cohort only, and
- HD patients only.

Important strengths:

- includes populations other than north American (includes European and Japanese cohorts).

Kestenbaum et al (2005) explored in an observational retrospective cohort study, the impact of serum phosphate in the pre-dialysis population in relation to mortality and cardiac events. This study included 6 730 patients from 95 619 patients from 8 Veteran's Affairs' Medical Centres in the Pacific North-West (only 3 490 with serum phosphate were measured within 18 months). Chronic Kidney Disease (CKD) was defined by two abnormal serum creatinine measures > 6 months apart between 1999 and 2002; Stage 5 was excluded.

Study outcomes were: 1. all-cause mortality; and 2. (ii) acute myocardial infarction (MI); and (ii) composite end-point: MI or death. Analysis included: (1) adjustments for – age, race, gender, previous medical conditions, total calcium intake, haemoglobin, calcium and baseline serum creatinine; (2) adjustments for time-averaged creatinine, rate of change of creatinine, maximum value for creatinine during the baseline period; and (3) BP, BMI, CV medications, serum albumin, serum bicarbonate and serum triglycerides.

The conclusion was that serum phosphate > 1.12 mmol/L is associated with increased RR of death.

Limitations of the study were:

The risk of elevated serum phosphate found in the study was greater than for Stage 5, which is not thought to be biologically plausible. How can we know enough was done to adjust for level of renal function? (see editorial by Chertow & Moe 2005). Although there was an adjustment made for level of renal function in the multivariate analysis, residual confounding by the “renal dysfunction” is still a concern.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: In CKD patients (Stages 3 and 4), the serum level of phosphorus should be maintained at or above 2.7 mg/dL (0.87 mmol/L) (EVIDENCE) and no higher than 4.6 mg/dL (1.49 mmol/L). (OPINION)

3.2: In CKD patients with kidney failure (Stage 5) and those treated with hemodialysis or peritoneal dialysis, the serum levels of phosphorus should be maintained between 3.5 and 5.5 mg/dL (1.13 and 1.78 mmol/L). (EVIDENCE)

UK Renal Association: Recommended standards for haemodialysis (5.38): phosphate 1.2–1.7 mmol/L. Recommended standards for peritoneal dialysis (6.12): phosphate 1.1–1.6 mmol/L.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines:

Dieticians' Special Interest Group of the European Dialysis & Transplant Nurses Association, European Renal Care Association:

2.3 Phosphorous: The dietitian/nutrition advisor will advise the haemodialysis patient on a phosphorus intake of 1000–1400 mg/day (32–45 mmol/day) (Evidence & Agreed Best Practice).

3.3 Phosphorous: The dietitian/nutrition advisor will advise the peritoneal dialysis patient on a phosphorus intake of 1000–1400 mg/day (32–45 mmol/day) (Evidence & Agreed Best Practice).

4.3 Phosphorous: The dietitian/nutrition advisor will advise the predialysis patient on a phosphorus intake of 600–1000 mg/day (19–32 mmol/day) (Evidence & Agreed Best Practice).

Implementation and audit

Audit of phosphate values for dialysis patients together with PTH, adjusted calcium and calcium x phosphate product. What serum phosphate is currently achieved in the Australian and New Zealand dialysis population?

Suggestions for future research

1. In the peritoneal dialysis cohort, does serum phosphate predict patient outcomes, particularly all-cause mortality?
2. An RCT using the newer phosphate binders (non-calcium non-aluminium) with all-cause mortality as the primary outcome and cardiovascular mortality as the main secondary outcome.

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