

Nutritional management of hypophosphataemia in adult kidney transplant recipients

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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)

- Physicians should be aware that phosphate supplementation has the potential to worsen hyperparathyroidism and may mask phosphorus deficiency beyond 3 months post-transplant. (Level IV)
- Kidney transplant recipients should be advised to consume phosphate-rich foods as early as possible after transplantation, once good graft function is achieved.
- Supplementation may be considered if hypophosphataemia persists despite an adequate dietary phosphate intake. The serum phosphate level at which supplementation may be considered and the dose of replacement to be given are unclear and clinical judgement is required.

BACKGROUND

Hypophosphataemia has been found to affect up to 93% of kidney transplant recipients in the first 4 months after transplantation.¹

In this early post-transplant period, hypophosphataemia is related to tubular dysfunction and increased urinary loss, as well as persistent hyperparathyroidism. The effects are exacerbated by immunosuppressive medications. Late post-transplant hypophosphataemia is mainly related to persistent hyperparathyroidism.²

The clinical significance of hypophosphataemia varies depending on whether it develops in the early or late post-transplant period. In the short-term, the effects include muscle weakness and osteomalacia. In severe phosphate depletion, haemolytic anaemia, rhabdomyolysis, decreased myocardial contractility and respiratory failure may occur. Long-term hypophosphataemia is associated with post-transplantation osteodystrophy.^{3,4}

This review set out to explore and collate the evidence for the efficacy of nutrition interventions in the prevention and management of hypophosphataemia in adult kidney

transplant recipients, based on the best evidence up to and including September 2006.

SEARCH STRATEGY

Relevant reviews and studies were obtained from the sources below and reference lists of nephrology textbooks, review articles and relevant trials were also used to locate studies. Searches were limited to human studies on adult transplant recipients and to studies published in English.

Databases searched: MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for both hypophosphataemia and dietary interventions. MEDLINE – 1966 to week 1 September 2006; EMBASE – 1980 to week 1 September 2006; the Cochrane Renal Group Specialised Register of Randomised Controlled Trials.

Date of searches: 22 September 2006.

WHAT IS THE EVIDENCE?

Level I/II: There are no randomized controlled trials investigating the efficacy of nutritional interventions for treating hypophosphataemia in kidney transplant recipients.

Level III: There is weak evidence from one pseudo-randomized controlled study that oral phosphate supplementation in the early post-transplant period helps to normalize serum phosphate concentration and muscle phosphate content after transplantation without affecting calcium or parathyroid hormone (PTH) metabolism. Oral phosphate supplementation appears to prolong phosphaturia, increasing renal net acid excretion thus helping to correct metabolic acidosis.¹

Level IV: There is level IV evidence from one study that oral phosphate supplementation in the late post-transplant period (mean time since transplantation, 41 months) may increase PTH levels, potentially worsening hyperparathyroidism.⁵

Oral phosphate supplementation in the early post-transplantation period

In a pseudo-randomized, controlled study, Ambuhl *et al.*¹ investigated the effect of oral neutral phosphate supplementation on serum muscle phosphate concentration, mineral metabolism, parathyroid hormone and acid/base homeostasis, in adult kidney transplant recipients with mild, early post-transplant hypophosphataemia.

Twenty-eight kidney transplant recipients with stable renal function and serum phosphate levels of 0.3–0.75 mmol/L were randomly assigned to receive either neutral sodium phosphate or sodium chloride for 12 weeks. The dose was adjusted according to serum phosphate concentration. Subjects were enrolled in the study immediately if all inclusion criteria were met. Mean time since transplantation was 1 month. Diet was unrestricted but all patients were encouraged to consume products rich in phosphorus, such as meat and dairy.

After 12 weeks, mean serum phosphate concentration had normalized in both groups. It was found that muscular phosphate content did not correlate with serum phosphate concentrations, though was restored in both groups after 12 weeks. However, the mean proportion of muscular adenosine triphosphate was significantly higher in the treatment group compared with the control group ($P < 0.03$) after 12 weeks. Metabolic acidosis improved significantly in subjects in the treatment group compared with those in the control group.

This study provides level III evidence that oral neutral phosphate supplements may normalize serum phosphate concentration and muscle phosphate content after transplantation safely. Such supplementation appears effective in prolonging phosphaturia and promoting recovery from latent metabolic acidosis observed in kidney transplant recipients early after transplantation. Oral phosphate supplementation does not seem to affect calcium or parathyroid hormone (PTH) metabolism in the early post-transplant period.¹

Oral phosphate supplementation in the late post-transplantation period

Caravaca *et al.*⁵ undertook a prospective study to evaluate the effects of oral phosphorus supplementation on the mineral metabolism of kidney transplant recipients with well-functioning grafts.

Thirty-two kidney transplant recipients with stable graft function and serum phosphate levels of < 3.5 mg/dL were included in the study. The mean time since transplantation was 41 ± 18 months.

After a one-month wash-out period, in which oral phosphate supplements were withdrawn, baseline blood samples were taken and analysed for creatinine, uric acid total calcium corrected to albumin, phosphate, alkaline phosphatase, bicarbonate, PTH, 25-hydroxycholecalciferol and 1,25-dihydroxycholecalciferol. In a 24 h urine sample, baseline urinary creatinine, calcium and phosphate excretions

were determined. Patients then received 1.5 g oral neutral phosphate for 15 days and were advised to continue with their usual diets.

After 15 days of treatment serum concentrations of calcium and 1,25-dihydroxycholecalciferol concentrations for the whole group were significantly reduced ($P < 0.0003$ and $P < 0.0006$, respectively). There were also significant reductions in urinary calcium excretion ($P < 0.0001$). However, there was a significant increase in serum phosphorus; PTH levels; and urinary phosphorus excretion ($P < 0.0001$; $P < 0.0001$; and $P < 0.0001$, respectively).

The study provides level IV evidence that phosphate supplements can potentially worsen hyperparathyroidism in the late post-transplantation period.

SUMMARY OF THE EVIDENCE

There is currently limited evidence for the efficacy of nutrition interventions in the prevention and management of hypophosphataemia in adult kidney transplant recipients.

One small pseudo-randomized controlled study indicates that oral phosphate supplementation in the early post-transplant period may help to normalize serum phosphate concentration and muscle phosphate content after transplantation without affecting calcium or parathyroid hormone (PTH) metabolism. Oral phosphate supplementation appears to prolong phosphaturia, increasing renal net acid excretion thus helping to correct metabolic acidosis.¹

One small before and after trial suggests that oral phosphate supplementation in the late post-transplant period (mean time since transplantation, 41 months) may increase PTH levels, potentially worsening hyperparathyroidism.⁵

In the absence of additional studies it is not possible to determine whether or not increased dietary phosphate intake may have a role in prevention or treatment of hypophosphataemia.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendations.

SUGGESTIONS FOR FUTURE RESEARCH

1 Prospective, controlled studies are required to answer whether or not particular increased dietary phosphate intake is effective in preventing or treating hypophosphataemia in adult kidney transplant recipients.

2 Well-designed studies on phosphate supplementation after kidney transplantation are required to guide starting point, dosage, side-effect profile or likely response rate.

CONFLICT OF INTEREST

Steven Chadban, Maria Chan, Karen Fry, Aditi Patwardhan, Catherine Ryan, Paul Trevillian, Fidy Westgarth have no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDIX

Table A1 Characteristics of included studies

Study ID (author, year)	n	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Ambuhl <i>et al.</i> 1999	28	Pseudo-randomized trial	Switzerland	28 kidney transplant recipients	Na ₂ HPO ₄ : NaH ₂ PO ₄ (ratio 4:1) (100 mg)	NaCl (182 mg)	12 weeks	Co-intervention – diet was unrestricted but all patients were encouraged to consumer products rich in phosphorus (e.g. meat and dairy)
Caravaca <i>et al.</i> 1998	32	Prospective before and after study	Spain	Kidney transplant recipients with stable graft function	1 month washout (supplements withdrawn) 1.5 g PO (750 mg Phosphorus Sandoz™ bd, after meals) for 15 days	No patient received vitamin D, antacids, anticonvulsants, allopurinol or other medications known to affect bone mineral metabolism	15 days after supplementation	Suggests potentially negative effect of phosphate supplements

Table A2 Quality of randomized trials

Study ID (author, year)	Method of allocation concealment*	Blinding			Intention-to-treat analysis†	Loss to follow up (%)
		Participants	Investigators	Outcome assessors		
Ambuhl 1999	None	Not stated	Not stated	Not stated	No	4.4

*Choose between: central; third party (e.g. pharmacy); sequentially labelled opaque sealed envelopes; alternation; not specified.

†Choose between: yes; no; unclear.

Table A3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean (SD))	Control group (mean (SD))	Difference in means [95% CI]
Ambuhl <i>et al.</i> 1999	U-phosphate (mmol) at 12 weeks	32.3 (9.35)	20.5 (6.36)	11.80 (95% CI: 5.88, 17.72)
	FE phosphate (%) at 12 weeks	40.0 (11.22)	35 (14.97)	5.00 (95% CI: -4.80, 14.80)
	S-Ca (mmol/L) at 12 weeks	1.30 (0.07)	1.30 (0.07)	0.00 (95% CI: -0.05, 0.05)
	PTH (pg/mL) at 12 weeks	53 (18.71)	58 (26.19)	-5.00 (95% CI: -21.86, 11.86)