National Institute for Health and Clinical Excellence

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Hyperphosphataemia in chronic kidney disease

Management of hyperphosphataemia in patients with stage 4 or 5 chronic kidney disease

This guideline was updated and merged with NICE guidelines on managing chronic kidney disease (CG182) and managing anaemia in CKD (NG8) in 2021. This document preserves evidence reviews and committee discussions for areas of the guideline that were not updated in 2021.

See the chronic kidney disease guideline on the NICE website for the guideline recommendations.

NICE clinical guideline 157
Developed by the Centre for Clinical Practice at NICE

NICE clinical guideline 157
Hyperphosphataemia in chronic kidney disease

Ordering information
You can download the following documents from
www.nice.org.uk/guidance/CG157

- The NICE guideline – all the recommendations.
- The NICE pathway – a set of online diagrams that brings together all NICE guidance and support tools.
- Information for the public – a summary for patients and carers.
- The full guideline (this document) – all the recommendations, details of how they were developed, and reviews of the evidence they were based on.

NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the NHS in England and Wales.

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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Appendices C, D, E, F and G are in separate files.

Introduction

Hyperphosphataemia

Chronic kidney disease (CKD) describes abnormal kidney function and/or structure. It is common and often exists together with other conditions, such as cardiovascular disease and diabetes.

The 'National service framework for renal services' adopted the US 'National Kidney Foundation kidney disease outcomes quality initiative' (NKF-KDOQI) classification of CKD. This classification divides CKD into 5 stages according to the extent of a person's loss of renal function. Stage 4 CKD is defined by a glomerular filtration rate (GFR) of 15–29 ml/min/1.73 m^2, and stage 5 by a GFR of less than 15 ml/min/1.73 m^2.[1]

CKD progresses to these more advanced stages in a small, but significant percentage of people. In 2010, the Health Survey for England reported a prevalence of moderate to severe CKD (stages 3 to 5) of 6% in men and 7% in women, as a percentage of the total population in England. CKD stages 4 and 5 were reported at a prevalence of 1% or less. Although this figure might seem small, it translates to a prevalence of up to 520,000 people in England alone.

When CKD stage 5 advances to end-stage renal disease (ESRD), some people progress to renal replacement therapy (RRT)[2]. The UK Renal Registry reported that 49,080 adult patients were receiving RRT in the UK at the end of 2009. Of these, 25,796 were receiving RRT in the form of dialysis (a population sometimes classified CKD stage 5D).

As kidney dysfunction advances, there is a higher risk of mortality and some comorbidities become more severe. Hyperphosphataemia is one example of

[1] A GFR of over 90 ml/min/1.73 m^2 is considered normal unless there is other evidence of kidney disease.
[2] Note: in this guideline, those who choose not to participate in an active treatment programme for their ESRD (which would generally include RRT, diet, pain management etc), instead opting for 'conservative management', are considered to be a subset of the stage 5 population who are not on dialysis.

this, and occurs because of insufficient filtering of phosphate from the blood by poorly functioning kidneys. This means that a certain amount of the phosphate does not leave the body in the urine, instead remaining in the blood at abnormally elevated levels.

High serum phosphate levels can directly and indirectly increase parathyroid hormone secretion, leading to the development of secondary hyperparathyroidism. Left untreated, secondary hyperparathyroidism increases morbidity and mortality and may lead to renal bone disease, with people experiencing bone and muscular pain, increased incidence of fracture, abnormalities of bone and joint morphology, and vascular and soft tissue calcification.

For adults with stage 4 or 5 CKD who are not on dialysis, the UK Renal Association guidelines recommend that serum phosphate be maintained at between 0.9 and 1.5 mmol/l. For adults with stage 5 CKD who are on dialysis, it is recommended that serum phosphate levels be maintained at between 1.1 and 1.7 mmol/l. Because of the improved removal of phosphate from the blood through dialysis, adults on dialysis have different recommended levels to those with stage 4 or 5 CKD who are not on dialysis.

For children and young people with stage 4 CKD, the NKF-KDOQI guidelines and European guidelines on the prevention and treatment of renal osteodystrophy recommend that serum phosphate be maintained within age-appropriate limits. For those with stage 5 CKD, including those on dialysis, it is recommended that serum phosphate levels be maintained at between 1.3 and 1.9 mmol/l for those aged 1–12 years, and between 1.1 and 1.8 mmol/l during adolescence.

Standard management of hyperphosphataemia involves the use of both pharmacological and non-pharmacological interventions, as well as the provision of education and support. However, there is wide variation between units and practices across the UK in how these interventions are used. At the end of 2009, data from the UK Renal Registry showed that only 61% of patients receiving haemodialysis and 70% of patients receiving peritoneal

dialysis achieved serum phosphate levels within the recommended range. This, together with a rising prevalence of CKD, led to the development of this clinical guideline on the management of hyperphosphataemia.

The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or those with authority to give consent on their behalf) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information. Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), these drugs are marked with a footnote in the recommendations.

Who this guideline is for

This document is for healthcare professionals and other staff who care for people with stage 4 or 5 CKD, including those with stage 5 CKD who are on dialysis. This includes primary, secondary and tertiary care settings. Where it refers to children and young people, this applies to all people younger than 18 years. Where it refers to adults, this applies to all people 18 years or older.

Patient-centred care

This guideline offers best practice advice on the care of adults, children and young people with stage 4 or 5 CKD who have, or are at risk of, hyperphosphataemia.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If someone does not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent, the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

If the patient is under 16, healthcare professionals should follow the guidelines in the Department of Health's Seeking consent: working with children. Families and carers should also be given the information and support they need to help the child or young person in making decisions about their treatment.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

If a young person is moving between paediatric and adult services, care should be planned and managed according to the best practice guidance described in the Department of Health's Transition: getting it right for young people.

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with hyperphosphataemia. Diagnosis and management should be reviewed throughout the transition

process, and there should be clarity about who is the lead clinician to ensure continuity of care.

Strength of recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Guideline Development Group is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Interventions that must (or must not) be used

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions that should (or should not) be used – a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that an intervention will not be of benefit for most patients.

Interventions that could be used

We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values

and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

1 Recommendations

1.1 List of all recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203.

Summary pathway

The current algorithms can be found at www.nice.org.uk/guidance/ng203.

2 Evidence review and recommendations

For details of how this guideline was developed see appendix D.

2.1 Dietary management for people with stage 4 or 5 CKD who are not on dialysis

2.1.1 Review question

For people with stage 4 or 5 CKD who are not on dialysis, is the dietary management of phosphate effective compared to placebo or other treatments in managing serum phosphate and its associated outcomes? Which dietary methods are most effective?

2.1.2 Evidence review

This review question focused on the use of dietary interventions in the prevention and treatment of hyperphosphataemia in patients with stage 4 or 5 CKD who are not on dialysis. These interventions are based on varying degrees of restriction in the intake of phosphate and/or protein, with or without supplementation with keto and amino acids.

For this review question, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials and the Centre for Reviews and Dissemination) using a broad search strategy, pulling in all papers relating to the dietary management of hyperphosphataemia in CKD. Only randomised controlled trials (RCTs) that

compared a dietary intervention with either a placebo or another comparator in patients with stage 4 or 5 CKD who are not on dialysis were considered for inclusion (appendix E).

Trials were excluded if:

- the population included people with CKD stages 1 to 3 **or**
- the population included people on dialysis.

From a database of 3026 abstracts, 244 full-text articles were ordered (including 107 identified through review of relevant bibliographies) and 13 papers describing 11 primary studies met the inclusion criteria (Cianciaruso et al., 2008; Cianciaruso et al., 2008; Di Iorio et al., 2003; European Study Group for the Conservative Management of Chronic Renal Failure, 1992; Feiten et al., 2005; Ihle et al., 1989; Jungers et al., 1987; Klahr et al., 1994; Kopple et al., 1997; Lindenau et al., 1990; Malvy et al., 1999; Mircescu et al., 2007; Snetselaar et al., 1994). No paediatric studies meeting the inclusion criteria were found. Table 1 lists the details of the included studies.

In order to define the interventions covered and aid an overarching analysis of the dietary management of hyperphosphataemia, protein levels in interventions that included protein restriction were categorised (through review of the available literature, as well as discussion with and an informal consensus among the Guideline Development Group [GDG]) as follows:

- less than or equal to 0.4 g of protein per kilogram of bodyweight per day: very-low-protein diet
- more than 0.4 g to less than or equal to 0.75 g of protein per kilogram of bodyweight per day: low-protein diet
- more than 0.75 g to less than or equal to 1.2 g of protein per kilogram of bodyweight per day: moderate-protein diet
- more than 1.2 g of protein per kilogram of bodyweight per day: high-protein diet.

There was some pooling of studies, although this was limited because of the presence of considerable heterogeneity. A prominent cause of such heterogeneity was the widespread use of a number of concurrent interventions that are known to impact the outcomes of interest. Additionally, many studies were powered for purposes other than the management of hyperphosphataemia, such as the preservation of renal function or patient responsiveness to erythropoietin, further contributing to the heterogeneity observed across the included studies.

Many papers did not report adherence, an outcome considered critical to decision-making by the GDG, in a binary manner. Rather than defining a patient as 'adherent' or 'non-adherent' with the dietary prescriptions, authors often provided mean actual intakes for protein, energy and/or phosphate. In order to use these continuous measures as indicators of adherence that could be compared across studies and interventions, the reviewer converted these mean actual intake levels into a percentage of the prescribed level. For example:

Prescribed protein intake	**Reported mean actual protein intake**	**Actual protein intake expressed as a percentage of the prescribed level**
0.3 g/kg of body weight/day	0.42 g/kg of body weight/day	140% of prescription that is, actual intake exceeded prescription by 40%

This method was confirmed as suitable through discussion with and, again, an informal consensus among the GDG.

Mean differences (MDs) were calculated for continuous outcomes and odds ratios (ORs) for binary outcomes, as well as the corresponding 95% confidence intervals (CI) where sufficient data were available. Where meta-analysis was possible, a forest plot is also presented.

Table 1 Summary of included studies for dietary management for adults with stage 4 or 5 CKD who are not on dialysis

Study	Population	Intervention	Control	Follow-up
Low-protein diet (+ ad-hoc binders + vitamin D) compared with moderate-protein diet (+ ad-hoc binders + vitamin D)				
Cianciaruso et al, 2008 RCT Naples, Italy	n = 423 (392 analysed) Basal eGFR ≤ 30 ml/min/1.73 m^2 Aged 18 years or older note: same population as Cianciaruso et al, 2009[1] Baseline serum phosphate (mean±SD): Intervention = 1.4±0.3 mmol/l Control = 1.2±0.2 mmol/l	0.55 g protein/kg/day At least 30 kcal/kg/day, reduced to a minimum of 25 kcal/kg/day in overweight patients, or if hypertension and hyperlipidaemia are present Calcium supplemented at 1000–1500 mg/day as calcium carbonate Further binders (calcium carbonate/sevelamer) prescribed where needed to treat hyperphosphataemia Ad-hoc prescription of vitamin D analogues when required	0.8 g protein/kg/day At least 30 kcal/kg/day, reduced to a minimum of 25 kcal/kg/day in overweight patients, or if hypertension and hyperlipidaemia are present Calcium supplemented at 1000–1500 mg/day as calcium carbonate Further binders (calcium carbonate/sevelamer) prescribed where needed to treat hyperphosphataemia Ad-hoc prescription of vitamin D analogues when required	18 months Monitored every 3 months
Cianciaruso et al, 2009 RCT Naples, Italy	n = 423 (392 analysed) Basal eGFR ≤ 30 ml/min/1.73 m^2 Aged 18 years or older note: same population as Cianciaruso et al, 2008[1] Baseline serum phosphate (mean±SD): Intervention = 1.4±0.3 mmol/l Control = 1.2±0.2 mmol/l	0.55 g protein/kg/day At least 30 kcal/kg/day, reduced to a minimum of 25 kcal/kg/day in overweight patients, or if hypertension and hyperlipidaemia are present Calcium supplemented at 1000–1500 mg/day as calcium carbonate Further binders (calcium carbonate/sevelamer) prescribed where needed to treat hyperphosphataemia Ad-hoc prescription of vitamin D analogues when required	0.8 g protein/kg/day At least 30 kcal/kg/day, reduced to a minimum of 25 kcal/kg/day in overweight patients, or if hypertension and hyperlipidaemia are present Calcium supplemented at 1000–1500 mg/day as calcium carbonate Further binders (calcium carbonate/sevelamer) prescribed where needed to treat hyperphosphataemia Ad-hoc prescription of vitamin D analogues when required	48 months Monitored every 3 months
Low-protein diet (+ ad-hoc binders) compared with ad libitum diet (moderate-protein intake as baseline) (+ ad-hoc binders)				
Ihle et al, 1989 RCT Melbourne, Australia	n = 72 (64 analysed) Mean Cr-EDTA clearance at baseline was 13.8±2.4 ml/min in the LPD group and 15 (±1.8) ml/min in the control group Baseline serum phosphate (mean±SD):	0.4 g of protein/kg body weight/day provided by foods of 75–80% biologic value 700 mg of phosphorus/day (30–40% less than conventional diet) 35–40 kcal/kg/day	Ad libitum food intake with at least 0.75 g of protein/kg body weight/day 35–40 kcal/kg/day 'When-required' phosphate binder use (calcium carbonate or aluminium hydroxide) to control phosphate levels	18 months Monitored monthly, although data provided for every 3 months

	Intervention = 1.29±0.40 mmol/l Control = 1.35±0.21 mmol/l See evidence tables in appendix E for full inclusion/exclusion criteria	'When-required' phosphate binder use (calcium carbonate or aluminium hydroxide) to control phosphate levels		
Supplemented very-low-protein diet compared with low-protein diet				
European Study Group for the Conservative Management of Chronic Renal Failure, 1992 (only those with poor renal function) RCT	n = 202 GFR < 20 ml/min Progressive renal failure during the 3 month run-in period Baseline serum phosphate (mean±SD): Intervention = no data available Control = no data available	0.3 g protein/kg/day Keto/amino acid mixture ≥ 35 kcal/kg ideal body weight/day	0.6 g/kg/day of protein ≥ 35 kcal/kg ideal body weight/day	1 year
Supplemented very-low-protein diet (+ Ca supplementation) compared with low-protein diet (+ Ca supplementation)				
Snetselaar et al, 1994 (MDRD pilot study B) RCT USA	n = 66 (58 analysed) Patients with advanced renal disease GFR 7.5–24 ml/min/1.73 m^2 Progressive increase in serum creatinine Aged 18 to 75 years Baseline serum phosphate (mean±SD): Intervention = no data available Control = no data available See evidence tables in appendix E for full inclusion/exclusion criteria	0.28 g protein/kg/day 4–9 mg phosphorus/kg/day 0.28 g keto acid/amino acid mixture (Cetolog)/kg/day or 0.22 g amino acid mixture (Aminess Novum)/kg/day 1500 mg calcium/day	0.575 g protein/kg/day – > 0.35 g/kg/day high biologic value dietary protein 5–10 mg phosphorus/kg/day 1500 mg calcium/day	2 years Monitored monthly
Supplemented very-low-protein diet (+ vitamin D) compared with low-protein diet (+ Ca-based binders/supplements + vitamin D)				
Lindenau et al, 1990 RCT	n = 40 Patients with advanced renal failure C_{Cr} < 15 ml/min	0.4 g protein/kg body weight/day Mixture of KAs and AAs (Ketosteril) 20,000–40,000 U vitamin D/day	0.6 g protein/kg body weight/day 750 mg calcium (as calcium carbonate or lactate) 20,000–40,000 U vitamin D/day	12 months

	Baseline serum phosphate (mean±SD): Intervention = 1.63±0.47 mmol/l Control = 1.41±0.25 mmol/l			
Supplemented very-low-protein diet (+ ad-hoc binders) compared with low-protein diet (+ ad-hoc binders)				
Feiten et al, 2005 RCT Sao Paulo, Brasil	n = 24 $C_{Cr} \leq 25$ ml/min/1.73 m^2 Aged 18 years or older Absence of catabolic illnesses, diabetes mellitus, auto-immune disease and malignant hypertension Baseline serum phosphate (mean±SD): Intervention = 1.5±0.2 mmol/l Control = 1.5±0.3 mmol/l	0.3 g/kg/day of vegetable origin protein diet 1 tablet/5 kg ideal body weight/day, divided into 3 doses taken during meals, of keto acids and amino acids (Ketosteril) 30–35 kcal/kg ideal body weight/day 'When-required' phosphate binder use to control phosphate levels	0.6 g/kg/day of protein (50% of high biological value) 30–35 kcal/kg ideal body weight/day 'When-required' phosphate binder use to control phosphate levels	4 months All outcomes monitored monthly, except for iPTH which was measured at 2-month intervals
Mircescu et al, 2007 RCT Bucharest, Romania	n = 53 (47 analysed) Non-diabetic adult patients with CKD eGFR <30 ml/min/1.73 m^2 Stable renal function at least 12 weeks before enrolment (i.e. a reduction in eGFR < 4 ml/min/year and well-controlled arterial BP) Good nutritional status (i.e. Subjective Global Assessment Score A/B and serum albumin >35 g/l) Baseline serum phosphate (mean±SD): Intervention = 1.9±0.7 mmol/l Control = 1.8±0.7 mmol/l See evidence tables in appendix E for full inclusion/exclusion criteria	0.3 g/kg/day of vegetable proteins 1 capsule/5 kg ideal body weight/day of ketoanalogues of essential amino acids (Ketosteril) Total recommended energy intake of 30 kcal/kg/day 'When-required' prescription of calcium carbonate to maintain serum calcium and serum phosphate within the recommended range	Continued conventional low-protein diet with 0.6 g/kg/day (including high biological value proteins) Total recommended energy intake of 30 kcal/kg/day 'When-required' prescription of calcium carbonate to maintain serum calcium and serum phosphate within the recommended range	48 weeks Monitored monthly
Di Iorio et al, 2003 RCT	n = 20 (19 completed the study period) Patients with $C_{Cr} \leq 25$ ml/min/1.73 m^2	0.3 g/kg body weight/day of protein of vegetable origin Supplemented with a mixture of ketoanalogues and essential amino acids	0.6 g/kg body weight/day of protein 35 kcal/kg body weight/day	18 months (although data were also available at 24

Italy	Treated with LPD (0.6 g/kg body weight/day) and EPO for a period of 6 to 12 months Baseline serum phosphate (mean±SD): Intervention = 1.2±0.3 mmol/l Control = 1.2±0.1 mmol/l See evidence tables in appendix E for full inclusion/exclusion criteria	(Alfa Kappa) administered at the dose of 1 tablet/5 kg body weight 35 kcal/kg body weight/day Phosphate binders were administered to maintain serum phosphate levels ≤ 5.5 mg/dl	Phosphate binders were administered to maintain serum phosphate levels ≤ 5.5 mg/dl	months for the sVLPD group only) Data provided for every 6 months
Klahr et al, 1994 (MDRD study B) RCT USA	n = 255 GFR 13-24 ml/min/1.73 m^2 Aged 18 to 70 years Baseline serum phosphate (mean±SD): Intervention = no data available Control = no data available See evidence tables in appendix E for full inclusion/exclusion criteria Note: same population as Kopple et al, 1997 (MDRD study)[2]	0.28 g protein/kg/day 0.28 g keto acid/amino acid mixture 4–9 g phosphorus/kg/day calcium carbonate prescribed for hyperphosphataemia 'as required'	0.58 g protein/kg/day (including ≥ 0.35 g/kg/day in essential AAs) 5–10 g phosphorus/kg/day calcium carbonate prescribed for hyperphosphataemia 'as required'	18 to 45 months
Kopple et al, 1997 (MDRD study B)	n = 255 GFR 13-24 ml/min/1.73 m^2 Aged 18 to 70 years Baseline serum phosphate (mean±SD): Intervention = no data available Control = no data available See evidence tables in appendix E for full inclusion/exclusion criteria Note: same population as Klahr et al, 1994 (MDRD study)[2]	0.28 g protein/kg/day 0.28 g keto acid/amino acid mixture 4–9 g phosphorus/kg/day calcium carbonate prescribed for hyperphosphataemia 'as required'	0.58 g protein/kg/day (including ≥0.35 g/kg/day in essential AAs) 5–10 g phosphorus/kg/day calcium carbonate prescribed for hyperphosphataemia 'as required'	18 to 45 months Information on hospitalisation was obtained 'routinely' during study visits or if a study visit was missed
Supplemented very-low-protein diet (+ ad-hoc binders + vitamin D) compared with low-protein diet (+ ad-hoc binders + vitamin D)				
Jungers et al, 1987 RCT	n = 19 (15 analysed)	0.4 g/kg/day of mixed quality proteins < 600 mg/day of phosphates	0.6 g/kg/day of mainly high biological value proteins < 750 mg/day of phosphates	Minimum of 3 months and maximum of 18 months, although

Paris, France	Established advanced chronic renal failure, defined by an S_{Cr} > 600 µmol/l in males or > 500 µmol/l in females, or a C_{Cr} of 5–15 ml/min/1.73 m^2 Slowly progressive rate of decline in renal function for at least 3 months Good general and nutritional condition Motivated to accept a low-protein diet and be available for follow-up Baseline serum phosphate (mean±SD): Intervention = 1.64±0.24 mmol/l Control = 1.58±0.28 mmol/l	1 capsule/6 kg ideal body weight/day of ketoanalogues of essential amino acids (Ketosteril), divided into 3 doses taken during meals (average actual daily dose was 11.3±1.5 tablets/day) Vitamin D (at a dosage of 25–50 µg/day) used to maintain plasma phosphate levels below 1.7 mmol/l Total recommended energy intake of 35–40 kcal/kg/day 'When-required' binders (aluminium hydroxide) used to maintain plasma phosphate levels below 1.7 mmol/l	Ad-hoc/'when-required' calcium carbonate supplementation for hypocalcaemia Vitamin D (at a dosage of 50 µg/day) used to maintain plasma phosphate levels below 1.7 mmol/l Total recommended energy intake of 35–40 kcal/kg/day 'When-required' binders (aluminium hydroxide) used to maintain plasma phosphate levels below 1.7 mmol/l	data given for 'the end of the study period' Monitored monthly
Malvy et al, 1999 RCT Bordeaux, France	n = 50 (38 analysed) C_{Cr} < 19 ml/min/1.73 m^2 Baseline serum phosphate (mean±SD): Intervention = 1.50±0.20 mmol/l Control = 1.62±0.35 mmol/l See evidence tables in appendix E for full inclusion/exclusion criteria	0.3 g/kg/day of protein Supplement of ketoanalogues and hydroxyanalogues of amino acids (Ketosteril) Daily supplement of vitamin D3 (25–50 mg) and nicotinic acid (25 mg) Calcium (1–4 g per day), and aluminium hydroxide were added depending on calcium and phosphate plasma levels	0.65 g/kg/day of protein Daily supplement of vitamin D3 (25–50 mg) and nicotinic acid (25 mg) Calcium (1–4 g per day), and aluminium hydroxide were added depending on calcium and phosphate plasma levels	At least 3 months Monitored at baseline, once a month during the first 3 months, and then every 3 months thereafter

[1] Note: Cianciaruso et al, 2008 and Cianciaruso et al, 2009 are 2 reports of the same study. Individual outcomes were included from only 1 of the 2 papers, to avoid double-counting of the results: serum phosphate, adherence, need for additional phosphate management and serum PTH were extracted from Cianciaruso et al, 2008; malnutrition (adverse event) was extracted from Cianciaruso et al, 2009.

[2] Note: Klahr et al, 1994 and Kopple et al, 1997 are 2 reports of the same study (the MDRD study). Individual outcomes were included from only 1 of the 2 papers to avoid double-counting of the results: adherence was extracted from Klahr et al, 1994; hospitalisation (adverse event) was extracted from Kopple et al, 1997.

Abbreviations: AA, amino acids; Ca, calcium; C_{Cr}, creatinine clearance rate; CKD, chronic kidney disease; CrEDTA, chromium-ethylenediaminetetraacetic acid complex; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; iPTH, intact parathyroid hormone; KA, keto acids; LPD, low-protein diet; PTH, parathyroid hormone; RCT, randomised controlled trial; S_{Cr}, serum creatinine; SD, standard deviation; sVLPD, supplemented very low-protein diet.

Summary GRADE profile 1 Low-protein diet (+ ad-hoc binders + vitamin D) compared with moderate-protein diet (+ ad-hoc binders + vitamin D) in adults with stage 4 or 5 CKD who are not on dialysis

Outcome	Number of Studies	Number of patients		Effect	Quality
		Low protein (+ ad-hoc binders + vitamin D)	Moderate protein (+ ad-hoc binders + vitamin D)		
Serum phosphate 18-month follow-up	1 RCT Cianciaruso et al, 2008	200	192	*Absolute effect* MD = 0.1 mmol/l higher (95% CI: 0 to 0.2 higher)	Very low
Adherence to protein prescription (% of patients adherent to dietary prescription) 18-month follow-up	1 RCT Cianciaruso et al, 2008	56/212 (26.4%)	103/211 (48.8%)	*Relative effect* OR = 0.38 (95%CI: 0.25 to 0.57) *Absolute effect* 22 fewer per 100 (14 to 30 fewer)	Moderate
Adherence to protein prescription (% of prescription, calculated from urinary urea nitrogen) 18-month follow-up	1 RCT Cianciaruso et al, 2008	200	192	*Absolute effect* MD = 21.6% higher (95% CI: 18.4 to 24.8 higher)	Very low
Adverse events – malnutrition (% of patients reaching pre-defined malnutrition point) 48-month follow-up	1 RCT Cianciaruso et al, 2009	2/212 (0.94%)	1/211 (0.47%)	*Relative effect* OR = 2 (95%CI: 0.18 to 22.23) *Absolute effect* 0 more per 100 (0 fewer to 9 more)	Very low
Need for additional phosphate management (% of patients who received phosphate binders [serum phosphate > 0.85–1.85 mmol/l]) 18-month follow-up	1 RCT Cianciaruso et al, 2008	27%	36%	*Relative effect* OR = 0.66 (95% CI: 0.36 to 1.2) *Absolute effect* 9 fewer per 100 (19 fewer to 4 more)	Very low
Serum PTH 18-month follow-up	1 RCT Cianciaruso et al, 2008	200	192	*Absolute effect* MD =3.4 pmol/l lower (7.3 lower to 0.5 higher)	Very low
Abbreviations: CI, confidence interval; MD, mean difference; OR, odds ratio; RCT, randomised controlled trial.					

Summary GRADE profile 2 Low-protein low-phosphate diet (+ ad-hoc binders) compared with ad libitum diet (minimum: moderate-protein) (+ ad-hoc binders) in adults with stage 4 or 5 CKD who are not on dialysis

Outcome	Number of Studies	Number of patients		Effect	Quality
		Low-protein low-phosphate diet (+ ad-hoc binders)	Ad libitum diet (minimum: moderate-protein) (+ ad-hoc binders)		
Serum phosphate 18-month follow-up	1 RCT Ihle et al, 1989	31	33	*Absolute effect* MD = 0.05 mmol/l lower (95% CI: 0.28 lower to 0.18 higher)	Very low
Serum PTH (C-terminal radioimmunoassay) 18-month follow-up	1 RCT Ihle et al, 1989	31	33	*Absolute effect* MD = 5.9 pmol/l lower (95% CI: 10.9 to 0.9 lower)	Very low
Abbreviations: CI, confidence interval; MD, mean difference; RCT, randomised controlled trial					

Summary GRADE profile 3 Supplemented very-low-protein diet compared with low-protein diet in adults with stage 4 or 5 CKD who are not on dialysis

Outcome	Number of Studies	Number of patients		Effect	Quality
		Supplemented very-low-protein diet	Low-protein diet		
Adherence to protein prescription (% of prescription, calculated from urinary urea nitrogen) 12 months follow-up	1 RCT European Study Group for the Conservative Management of Chronic Renal Failure, 1992[1]	99	103	*Absolute effect* Difference in medians = 23.4% higher	Very low
[1]Data were only extracted for those with 'poor renal function' Abbreviations: RCT, randomised controlled trial.					

Summary GRADE profile 4 Supplemented very-low-protein low-phosphate diet with (+ calcium) compared with low-protein low-phosphate diet (+ calcium)

Outcome	Number of Studies	Number of patients		Effect	Quality
		Supplemented very-low-protein low-phosphate diet (+ Ca supplement)	Low-protein low-phosphate diet (+ Ca supplement)		
Adherence to protein prescription (% of prescription, calculated from urinary urea nitrogen) 12-month follow-up[1]	1 RCT Snetselaar et al, 1994[2]	36[3]	22	*Absolute effect* MD = 64.1% higher (95% CI: 47.2 to 81.0 higher)	Very low
Adherence to protein prescription (% of prescription, calculated from 3-day diet diary) 12-month follow-up[1]	1 RCT Snetselaar et al, 1994[2]	36[3]	22	*Absolute effect* MD = 29.9% higher	Very low
Adherence to phosphate prescription (% of prescription, calculated from 3-day diet diary) 12-month follow-up[1]	1 RCT Snetselaar et al, 1994[2]	36[3]	22	*Absolute effect* MD = 1% lower	Very low

[1] Data provided are the weighted means of follow-up data collected throughout the 12-month study period

[2] Data were only extracted for 'Study B'

[3] Study is a 3-arm trial; reviewer combined data for 2 arms (both VLPDs, but 1 supplemented with KAs, the other with essential AAs) into a weighted mean and, where possible, pooled standard deviation, producing a pairwise comparison of sVLPD versus LPD

Abbreviations: AAs, amino acids; CI, confidence interval; LPD, low-protein diet; MD, mean difference; RCT, randomised controlled trial; sVLPD, supplemented very-low-protein diet; VLPD, very-low-protein diet.

Summary GRADE profile 5 Supplemented very-low-protein diet (+ vitamin D) compared with low-protein diet (+ calcium + vitamin D) in adults with stage 4 or 5 CKD who are not on dialysis

Outcome	Number of Studies	Number of patients		Effect	Quality
		Supplemented very-low-protein diet (+ vitamin D)	Low-protein diet (+ calcium + vitamin D)		
Serum phosphate 12-month follow-up	1 RCT Lindenau et al, 1990	22	18	*Absolute effect* MD = 0.04 mmol/l lower (95% CI: 0.25 lower to 0.17 higher)	Very low
Serum iPTH 12-month follow-up	1 RCT Lindenau et al, 1990	22	18	*Absolute effect* MD = 9.8 pmol/l lower (95% CI: 15.8 to 3.8 lower)	Very low
Abbreviations: CI, confidence interval; iPTH, intact parathyroid hormone; MD, mean difference; RCT, randomised controlled trial.					

Summary GRADE profile 6 Supplemented very-low-protein diet (+ ad-hoc binders) compared with low-protein diet (+ ad-hoc binders) in adults with stage 4 or 5 CKD who are not on dialysis

Outcome	Number of Studies	Number of patients		Effect	Quality
		Supplemented very-low-protein diet (+ ad-hoc binders)	Low-protein diet (+ ad-hoc binders)		
Serum phosphate (pooled) 48.5-week follow-up (mean)	3 RCTs Feiten et al, 2005 Mircescu et al, 2007 Di Iorio et al, 2003	47	40	*Absolute effect* MD = 0.30 mmol/l lower (95% CI: 0.53 to 0.18 lower)	Very low
Adherence to protein prescription (% of prescription, calculated from 3-day diet diary) 4-month follow-up	1 RCT Feiten et al, 2005	10	12	*Absolute effect* MD = 28.3% higher (95% CI: 1.7 lower to 58.3 higher)	Very low
Adherence to protein prescription (% of prescription, calculated from urinary urea nitrogen)[1] 4-month follow-up	1 RCT Feiten et al, 2005	11	12	*Absolute effect* MD = 80/0% higher (95% CI: 56.1 to 103.9 higher)	Very low
Adherence to protein prescription (% of prescription, calculated from urinary urea nitrogen)[1] 48-week follow-up	1 RCT Mircescu et al, 2007	26	19	*Absolute effect* MD = 8.4% higher (95% CI: 2.4 lower to 19.2 higher)	Very low
Adherence to protein prescription (% of prescription, calculated from urinary urea nitrogen)[1] 36-month follow-up	1 RCT Klahr et al, 1994[2,3]	21	23	*Absolute effect* Difference in medians = 27.7% higher	Very low
Adherence to energy prescription (% of prescription, calculated from 3-day diet diary)[1]	1 RCT Feiten et al, 2005	12	12	*Absolute effect* MD = 3.7% lower	Very low

4-month follow-up					
Adherence to energy prescription (% of prescription, calculated from 3-day diet diary)[1] 48-week follow-up	1 RCT Mircescu et al, 2007	26	19	*Absolute effect* MD = 2.7% higher (95% CI: 1.2 lower to 6.6 higher)	Very low
Adverse events – malnutrition (% of patients defined as malnourished according to SGA) 48-week follow-up	1 RCT Mircescu et al, 2007	13%[4]	10%[4]	*Relative effect* OR = 1.34 (95% CI: 0.56 to 3.23) *Absolute effect* 3 more per 100 (4 fewer to 16 more)	Very low
Adverse events – hospitalisation (number of patients to undergo first hospitalisation during study) 34-month follow-up	1 RCT Kopple et al, 1997[3,5]	28/126 (22.2%)	32/129 (24.8%)	*Relative effect* OR = 0.87 (95% CI: 0.49 to 1.55) *Absolute effect* 3 fewer per 100 (11 fewer to 9 more)	Very low
Need for additional phosphate management (pooled) (number of patients who received phosphate binders) 33-week follow-up (mean)	2 RCTs Feiten et al, 2005 Mircescu et al	5/39 (12.8%)	25/38 (65.8%)	*Relative effect* OR = 0.07 (95% CI: 0.01 to 0.59) *Absolute effect* 54 fewer per 100 (13 to 64 fewer)	Very low
Serum PTH (pooled) (immunofluorometric assay/radioimmunoassay) 11-month follow-up (mean)	2 RCTs Feiten et al, 2005 Di Iorio et al, 2003	20	21	*Absolute effect* MD = 9.88 pmol/l (95% CI: 12.73 to 7.03 lower)	Very low

[1] Data available for outcome inappropriate for meta-analysis across studies

[2] Same population as Kopple et al, 1997

[3] Data only extracted from 'Study B'

[4] Note: values were unchanged from baseline

[5] Same population as Klahr et al, 1994

Abbreviations: CI, confidence interval; MD, mean difference; OR, odds ratio; PTH, parathyroid hormone; RCT, randomised controlled trial; SGA, subjective global assessment of nutrition.

Summary GRADE profile 7 Supplemented very-low-protein diet (+ ad-hoc binders + vitamin D) compared with low-protein diet (+ ad-hoc binders + vitamin D) in adults with stage 4 or 5 CKD who are not on dialysis

Outcome	Number of Studies	Number of patients		Effect	Quality
		Supplemented very-low-protein diet (+ ad-hoc binders + vitamin D)	Low-protein diet (+ ad-hoc binders + vitamin D)		
Serum phosphate (pooled) Follow-up unclear	2 RCTs Jungers et al, 1987 Malvy et al, 1999	26	31	*Absolute effect* MD = 0.30 mmol/l (95% CI: 0.58 to 0.01 lower)	Very low
Adherence to protein prescription (% of prescription, calculated from urinary urea nitrogen) Follow-up unclear	1 RCT Jungers et al, 1987	7	8	*Absolute effect* MD = 45.0% higher (95% CI: 25.9 lower to 115.9 higher)[1]	Very low
Adverse events - need for additional calcium supplementation (number of patients who received calcium supplementation for hypocalcaemia) Follow-up unclear	1 RCT Jungers et al, 1987	0/10	3/9	*Absolute effect* 33 fewer per 100	Very low
Need for additional phosphate management (number of patients who received phosphate binders) Follow-up unclear	1 RCT Jungers et al, 1987	0/10	3/9	*Absolute effect* 33 fewer per 100	Very low
Serum PTH Follow-up unclear	1 RCT Malvy et al, 1999	19	23	*Absolute effect* MD = 33.9 pmol/l lower (95% CI: 43.5 to 24.3 lower)	Very low

[1] Actual intake in the intervention group falls in the 'low-protein' rather than the 'very-low-protein' range; actual protein intake in the intervention group was 0.66 g/kg/day and 0.72 g/kg/day in the control group (MD 0.06 lower [95% CI 0.43 lower to 0.31 higher i.e. not statistically significant])

Abbreviations: CI, confidence interval; MD, mean difference; PTH, parathyroid hormone; RCT, randomised controlled trial.

See appendix E for the evidence tables and GRADE profiles in full.

2.1.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual'.

Dietary management for people with stage 4 or 5 CKD who are not on dialysis

A low-protein diet (+ ad-hoc binders) compared with a moderate-protein diet (+ ad-hoc binders)

Critical outcomes

2.1.3.1 Very-low-quality evidence from 1 RCT of 392 patients showed a low-protein diet with ad-hoc phosphate binder use to be associated with a mean serum phosphate level 0.1 mmol/l higher (95% confidence interval [CI] 0.0 to 0.2, i.e. statistically significant) than a moderate-protein diet with ad-hoc phosphate binder use at 18 months.

2.1.3.2 Moderate-quality evidence from 1 RCT of 423 patients showed that a low-protein diet with ad-hoc phosphate binder use was associated with a smaller proportion of patients adherent to protein prescription than a moderate-protein diet with ad-hoc phosphate binder use (odds ratio [OR] 0.38 [95% CI 0.25 to 0.57, i.e. statistically significant]).

2.1.3.3 Very low-quality evidence from the RCT of 392 patients showed that, as a percentage of the prescribed protein intake, those on a low-protein diet with ad-hoc phosphate binder use exceeded the relevant prescription to a greater extent than those on a moderate-protein diet with ad-hoc phosphate binder use (mean difference [MD] 21.6% more [95% CI 18.4 to 24.8, i.e. statistically significant]).

2.1.3.4 Very-low-quality evidence from 1 RCT of 423 patients did not show a statistically significant difference in the incidence of malnutrition over 48 months between those on a low-protein diet with ad-hoc

phosphate binder use and those on a moderate-protein diet with ad-hoc phosphate binder use (OR 2 [95% CI 0.18 to 22.23]).

Important outcomes

2.1.3.5 *Very-low-quality evidence from 1 RCT of 392 patients did not show a statistically significant difference in the number of patients that required/were prescribed phosphate binders between those on a low-protein diet and those on a moderate-protein diet (OR 0.66 [95% CI 0.36 to1.20]).*

2.1.3.6 *Very-low-quality evidence from 1 RCT of 392 patients did not show a statistically significant difference in mean serum parathyroid hormone (PTH) level between those on a low-protein diet with ad-hoc phosphate binder use and those on a moderate-protein diet with ad-hoc phosphate binder use at 18 months (mean serum PTH level 3.4 pmol/l lower in the low-protein diet group [95% CI -7.3 to 0.5]).*

A low-protein diet (+ ad-hoc binders) compared with an ad libitum diet (moderate-protein intake prescribed as minimum) (+ ad-hoc binders)

Critical outcomes

2.1.3.7 *Very-low-quality evidence from 1 RCT of 64 patients showed a low-protein diet with ad-hoc phosphate binder use to be associated with a mean serum phosphate level 0.05 mmol/l lower (95% CI -0.28 to 0.18) than an ad libitum diet with ad-hoc phosphate binder use at 18 months, although the effect was not statistically significant.*

Important outcomes

2.1.3.8 *Very-low-quality evidence from the RCT of 64 patients showed a low-protein diet with ad-hoc phosphate binder use to be associated with a mean serum PTH level 5.9 pmol/l lower (95% CI -10.9 to -0.9, i.e. statistically significant) than an ad libitum diet with ad-hoc phosphate binder use at 18 months.*

A supplemented very-low-protein diet compared with a low-protein diet

Important outcomes

2.1.3.9 Very-low-quality evidence from 1 RCT of 202 patients showed that, as a percentage of the prescribed protein intake, those on a very-low-protein diet supplemented with a mixture of keto acids and amino acids exceeded the relevant prescription to a greater extent than those on a low-protein diet (difference in medians 23.4% more).

A supplemented very-low-protein diet (+ Ca supplementation) compared with a low-protein diet (+ Ca supplementation)

Critical outcomes

2.1.3.10 Very-low-quality evidence from 1 RCT of 58 patients showed that, as a percentage of the prescribed protein intake, those on a very-low-protein diet supplemented with a mixture of keto acids and amino acids exceeded the relevant prescription to a greater extent than those on a low-protein diet when estimated by urinary urea nitrogen (MD 64.1% more [95% CI 47.2 to 81.0, i.e. statistically significant])[3].

2.1.3.11 Very-low-quality evidence from the same RCT of 58 patients showed that, as a percentage of the prescribed protein intake, those on a very-low-protein diet supplemented with a mixture of keto acids and amino acids exceeded the relevant prescription to a greater extent than those on a low-protein diet when estimated by 3-day diet diary (MD 29.9% more)[3].

2.1.3.12 Very-low-quality evidence from the RCT of 58 patients comparing a very-low-protein diet supplemented with a mixture of keto acids and amino acids and calcium and a low-protein diet supplemented with calcium, showed little difference in the deviation of mean

[3] Note: actual intake in the intervention group fell into the 'low-protein' rather than the 'very-low-protein' range (the difference in actual intake between the groups was, however, statistically significant).

phosphate intake from that prescribed, with both groups demonstrating good mean adherence[4].

A supplemented very-low-protein diet (+ vitamin D) compared with a low-protein diet (+ Ca-based binders/supplements + vitamin D)

Critical outcomes

2.1.3.13 *Very-low-quality evidence from 1 RCT of 40 patients showed a very-low-protein diet supplemented with a mixture of keto acids and amino acids and vitamin D to be associated with a mean serum phosphate level 0.04 mmol/l lower (95% CI -0.25 to 0.17) than a low-protein diet supplemented with vitamin D at 12 months, although the effect was not statistically significant.*

Important outcomes

2.1.3.14 *Very-low-quality evidence from the same RCT of 40 patients showed a very-low-protein diet supplemented with a mixture of keto acids and amino acids and vitamin D to be associated with a mean serum PTH level 9.8 pmol/l lower (95% CI -15.8 to -3.8, i.e. statistically significant) than a low-protein diet supplemented with vitamin D at 12 months.*

A supplemented very-low-protein diet (+ ad-hoc binders) compared with a low-protein diet (+ ad-hoc binders)

Critical outcomes

2.1.3.15 *Very-low-quality evidence from 3 RCTs analysing a total of 87 patients showed a very-low-protein diet supplemented with a mixture of keto acids and amino acids and ad-hoc phosphate binders to be associated with a mean serum phosphate level 0.30 mmol/l lower (95% CI -0.43 to -0.18, i.e. statistically*

[4] Note: actual intake in the intervention group fell into the 'low-protein' rather than the 'very-low-protein' range (the difference in actual intake between the groups was, however, statistically significant).

significant) than a low-protein diet with ad-hoc phosphate binder use (mean follow-up ~48.5 weeks)[5].

2.1.3.16 *Very-low-quality evidence from 1 RCT of 23 patients showed that, as a percentage of the prescribed protein intake, those on a very-low-protein diet supplemented with a mixture of keto acids and amino acids and ad-hoc phosphate binders exceeded the relevant prescription to a greater extent than those on a low-protein diet with ad-hoc phosphate binder use when estimated at 4 months by urinary urea nitrogen (MD 80.0% more [95% CI 56.1 to 103.9, i.e. statistically significant])[5].*

2.1.3.17 *Very-low-quality evidence from the same RCT, in this case analysing 22 patients, showed that, as a percentage of the prescribed protein intake, those on a very-low-protein diet supplemented with a mixture of keto acids and amino acids and ad-hoc phosphate binders exceeded the relevant prescription to a greater extent than those on a low-protein diet with ad-hoc phosphate binder use when estimated at 4 months by 3-day diet diary, although this was not statistically significant (MD 28.3% more [95% CI -1.7 to 58.3])[6].*

2.1.3.18 *Very-low-quality evidence from 1 RCT of 45 patients showed that, as a percentage of the prescribed protein intake, the extent to which mean protein intake at 48 weeks exceeded the relevant prescription was not statistically significantly different in those on a very-low-protein diet supplemented with a mixture of keto acids and amino acids and ad-hoc phosphate binders compared to those on a*

[5] Note: actual intake in the intervention group fell into the 'low-protein' rather than the 'very-low-protein' range, and fell into the 'moderate-protein' rather than the 'low-protein' range in the control group when measured by urinary urea nitrogen (the difference in actual intake between the groups was, however, statistically significant).

[6] Note: actual intake in the intervention group fell into the 'low-protein' rather than the 'very-low-protein' range when estimated at 4 months by 3-day diet diary (the difference in actual intake between the groups was, however, statistically significant).

low-protein diet with ad-hoc phosphate binder use (deviation of 8.4% more [95% CI -2.4 to 19.2]).

2.1.3.19 *Very-low-quality evidence from 1 RCT of 44 patients showed that, as a percentage of the prescribed protein intake, those on a very-low-protein diet supplemented with a mixture of keto acids and amino acids and ad-hoc phosphate binders exceeded the relevant prescription to a greater extent than those on a low-protein diet with ad-hoc phosphate binder use at 36 months (difference in medians 27.7% more)[7].*

2.1.3.20 *Very-low-quality evidence from 1 RCT of 45 patients showed that, as a percentage of the prescribed energy intake, those on a very-low-protein diet supplemented with a mixture of keto acids and amino acids and ad-hoc phosphate binders fell below the relevant prescription to a greater extent than in those on a low-protein diet with ad-hoc phosphate binder use at 4 months (MD 3.7% more).*

2.1.3.21 *Very-low-quality evidence from an RCT of 24 patients showed that, as a percentage of the prescribed energy intake, those on a very-low-protein diet supplemented with a mixture of keto acids and amino acids and ad-hoc phosphate binders fell below the relevant prescription to a lesser extent than in those on a low-protein diet with ad-hoc phosphate binder use at 48 weeks, although this effect was not statistically significant (MD 2.7% less [95% CI -1.2 to 6.6]).*

2.1.3.22 *Very-low-quality evidence from 1 RCT of 45 patients showed that a very-low-protein diet supplemented with a mixture of keto acids and amino acids and ad-hoc phosphate binders was associated with a larger proportion of patients defined as malnourished than among those on a low-protein diet with ad-hoc phosphate binder use (OR 1.34 [95% CI 0.56 to 3.23]), although the difference was not*

[7] Note: actual intake in the intervention group fell into the 'low-protein' rather than the 'very-low-protein' range (the difference in actual intake between the groups was, however, statistically significant).

statistically significant and the proportions were the same as those observed at baseline.

2.1.3.23 *Very-low-quality evidence from 1 RCT of 255 patients showed that a very-low-protein diet supplemented with a mixture of keto acids and amino acids and ad-hoc phosphate binders was associated with a smaller proportion of patients undergoing first hospitalisation than among those on a low-protein diet with ad-hoc phosphate binder use (OR 0.87 [95% CI 0.49 to 1.55]), although the difference was not statistically significant.*

Important outcomes

2.1.3.24 *Very-low-quality evidence from 2 RCTs of 77 patients in total showed that a very-low-protein diet supplemented with a mixture of keto acids and amino acids and ad-hoc phosphate binders was associated with a smaller proportion of patients requiring the prescription of phosphate binders than among those on a low-protein diet with ad-hoc phosphate binder use (OR 0.07 [95% CI 0.01 to 0.59, i.e. statistically significant])[8].*

2.1.3.25 *Very-low-quality evidence from 2 RCTs analysing a total of 41 patients showed a very-low-protein diet supplemented with a mixture of keto acids and amino acids and ad-hoc phosphate binders to be associated with a mean serum PTH level 9.88 pmol/l lower (95% CI -12.73 to -7.03, i.e. statistically significant) than a low-protein diet with ad-hoc phosphate binder use (mean follow-up 11 months)[8] .*

A supplemented very-low-protein diet (+ ad-hoc binders + vitamin D) compared with a low-protein diet (+ ad-hoc binders + vitamin D)

Critical outcomes

[8] Note: actual intake in the intervention group fell into the 'low-protein' rather than the 'very-low-protein' range, and fell into the 'moderate-protein' rather than the 'low-protein' range in the control group when measured by urinary urea nitrogen (the difference in actual intake between the groups was, however, statistically significant).

2.1.3.26 Very-low-quality evidence from 2 RCTs analysing a total of 57 patients showed a very-low-protein diet supplemented with a mixture of keto acids and amino acids, vitamin D and ad-hoc phosphate binders to be associated with a mean serum phosphate level 0.30 mmol/l lower (95% CI -0.58 to -0.01, i.e. statistically significant) than a low-protein diet with vitamin D and ad-hoc phosphate binder use[9].

2.1.3.27 Very-low-quality evidence from 1 RCT of 15 patients showed that, as a percentage of the prescribed protein intake, those on a very-low-protein diet supplemented with a mixture of keto acids and amino acids, vitamin D and ad-hoc phosphate binders exceeded the relevant prescription to a greater extent than those on a low-protein diet with vitamin D and ad-hoc phosphate binder use, although the difference was not statistically significant (MD 45.0% more [95% CI -25.9 to 115.9])[9].

2.1.3.28 Very-low-quality evidence from 1 RCT of 19 patients found that fewer patients on a very-low-protein diet supplemented with a mixture of keto acids and amino acids, vitamin D and ad-hoc phosphate binders required/were prescribed calcium supplementation than those on a low-protein diet with vitamin D and ad-hoc phosphate binders (0/10 versus 3/9 respectively)[9].

Important outcomes

2.1.3.29 Very-low-quality evidence from 1 RCT of 19 patients found that fewer patients on a very-low-protein diet supplemented with a mixture of keto acids and amino acids and vitamin D required/were prescribed phosphate binders than those on a low-protein diet with vitamin D (0/10 versus 3/9 respectively)[9].

[9] Note: actual intake fell into the 'low-protein' rather than the 'very-low-protein' range; actual protein intake in the intervention group was 0.66 g/kg/day and 0.72 g/kg/day in the control group (MD 0.06 lower [95% CI -0.43 to 0.31, that is, not statistically significant]).

2.1.3.30 Very-low-quality evidence from 1 RCT of 42 patients showed that a very-low-protein diet supplemented with a mixture of keto acids and amino acids, vitamin D and ad-hoc phosphate binders to be associated with a mean serum PTH level 33.9 pmol/l lower (95% CI -43.5 to -24.3, i.e. statistically significant) than a low-protein diet with vitamin D and ad-hoc phosphate binder use.

2.1.4 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that serum phosphate, adherence with dietary prescription, and adverse events such as malnutrition were critical for decision-making. The need for additional phosphate management was considered important for decision-making, but not critical. Following the review of the evidence, malnutrition and adherence with treatment featured prominently in the GDG's discussions. In addition to being a surrogate outcome, the GDG noted that there is a lot of variability in PTH measurements, in both the level of PTH in the serum and the ability of laboratory techniques to detect these levels. Therefore, PTH was not deemed to be a sufficiently reliable basis from which to formulate recommendations.
Trade-off between benefits and harms	A very-low-protein diet supplemented with keto and amino acids was associated with the use of fewer concurrent phosphate binders and appeared to be effective in reducing serum phosphate. However, the GDG had concerns over the quality and applicability of the evidence. Many studies were powered for other outcomes, such as the preservation of renal function or patient responsiveness to erythropoietin, and most of the diets examined were accompanied by concurrent treatments, including phosphate binders and vitamin D, which could confound the observed effects. The GDG was unsure whether the beneficial effect observed was because of the diet or the calcium-based keto acids in the supplement, which may have phosphate-binding properties. Consequently, the supplement may overestimate the phosphate-lowering effect of the very-low-protein diet. As a result, the GDG did not have confidence in the findings of the studies in the context of managing hyperphosphataemia. Despite significant protein restriction, malnutrition did not appear to be a significant problem with any of the diets reviewed. However, the GDG had concerns about the possible lack of sensitivity of the non-standardised definitions used in 1 of the papers (Cianciaruso et al, 2009), which may underestimate the actual incidence of malnutrition. In addition, the GDG noted that adherence with the higher energy prescriptions used in the evidence seemed good, and because of this the long-term impact of protein restriction on nutritional status may be masked, requiring much longer follow-up periods to observe adverse effects relating to malnutrition. The GDG was also concerned that the studies may have had insufficient sample sizes, further reducing their sensitivity to detect malnutrition. The small number of events recorded support this suggestion.

	Concerns relating to restricted diets also included ‘sub-clinical’ malnutrition that may easily be missed in patients on low- or very-low-protein diets. It was noted that in current practice clinicians aim to maintain patients' dietary protein intake at or above the recommended minimum for CKD patients, rather than restrict nutritional intake in patients with advanced CKD. It was noted that in the case of supplemented protein restricted diets the keto and amino acids may simply alleviate the harmful effects of very-low-protein diets, leading to the reduced rates of malnutrition and hospitalisation rates observed. There are a number of possible explanations for this association, such as a beneficial effect on nutritional status through substitution for the restricted protein or a positive impact relating to the alleged phosphate-binding properties of these supplements, although there is currently insufficient evidence available. If patients are prescribed a very-low-protein diet supplemented with keto and amino acids, the GDG was concerned that non-adherence to the supplements might still lead to malnutrition; the additional pill burden of the supplements was a significant concern. However, no evidence on patient adherence with keto/amino acid supplements was found. Adherence with protein restrictions was poor in all of the diets reviewed. There was no evidence on patients’ views (for example, quality of life), although the GDG felt the observed low adherence with protein restrictions to be indicative. It was felt that expecting patients to comply with protein restrictions, particularly given the unpalatability of such diets, is potentially unrealistic. The GDG considered that the risks and disadvantages of a protein-restricted diet, with or without keto and amino acid supplementation, were greater than the benefit of the observed phosphate reduction and therefore did not feel it appropriate to recommend this kind of diet for the management of hyperphosphataemia in adults with advanced CKD. For the reasons outlined above, the GDG did not feel that the evidence was sufficient to recommend restricting protein intake below minimum recommended nutrient intake levels, the accepted standards used for protein intake in adults. According to the current Renal Association guidelines, recommended protein intake levels for adults with CKD stage 4 or 5 who are not on dialysis is a minimum of 0.75 g/kg of ideal body weight/day. Furthermore, given that very-low-protein diets supplemented with keto and amino acids also have a large pill burden, the GDG felt that phosphate binders would be more clinically appropriate than supplementation with keto and amino acids. Although there was no evidence on the effectiveness of a low-phosphate diet without protein restriction (for example exchanging foods with a high phosphate to protein ratio for foods with a low phosphate to protein ratio), there was consensus among the GDG that this has been effective in their own clinical experience. The GDG considered that advising patients to reduce their intake of phosphate-rich foods is good clinical practice. The GDG also felt that the same principle could be extended to the nutritional supplements/substitutes currently used in CKD management to maintain protein intake, giving low-phosphate options where possible.

	In children, the GDG felt that malnutrition is of much greater concern than hyperphosphataemia. Progressive CKD is often associated with decreased spontaneous dietary protein intake, which is a priority for treatment given the need to maintain growth and adequate nutritional status. For these reasons, as well as the lack of paediatric evidence available, the GDG could not recommend a diet based on protein restriction for children. Recommended intakes are instead age-specific according to reference nutrient intakes.
Economic considerations	This question was not prioritised for health economic analysis because the majority of resource inputs are outside the NHS and personal social services perspective.
Quality of evidence	No evidence was found for children. For adults, little significant evidence was found to suggest that low-protein prescriptions are effective in managing serum phosphate, although it was felt that this could be a consequence of the poor quality of the evidence. No evidence was found regarding the use of phosphate restriction alone demonstrating, for example, the effectiveness of a low-phosphate diet achieved without protein restriction or through the restriction of food and drink containing phosphate additives. No evidence was found that compared a moderate protein restriction to high protein or ad libitum protein intake. The GDG questioned the generalisability of the evidence to a UK setting – particularly in terms of dietary differences – because none of the studies are UK-based. Additionally, many of the studies were performed in outpatient renal clinics in hospitals, and therefore do not capture the care of these patients in primary care settings or when hospitalised. The GDG also felt that the age of the studies may further reduce the generalisability of the evidence because of changes in practice over time. Furthermore, many of the studies excluded patients with diabetes and patients who have had transplants, and included only those anticipated to have good adherence to the prescribed diets and with a good nutritional status at baseline. For these reasons, the population in the evidence base may not be generalisable to the whole population of patients with CKD stages 4 or 5 in England and Wales. The GDG was concerned about the reliability of the non-standardised definition of malnutrition used by 1 of the studies in place of widely recognised and accepted standards such as the Subjective Global Assessment of Nutrition (SGA) and Mini Nutritional Assessment (MNA). Adherence with dietary prescriptions was not regularly reported; instead, papers reported mean actual intakes for each group, which the reviewer then compared to prescriptions, producing a surrogate measure of adherence. The GDG also had concerns regarding the known variability of PTH measurements between laboratories; this variation is particularly concerning in the multicentre trials included, especially if those studies used multiple laboratories to analyse their biochemical outcomes. It was noted that studies were often designed for purposes other than the management of hyperphosphataemia, such as slowing renal decline. For this reason, outcomes of interest were often secondary and concurrent treatments (such as phosphate binders or calcium/vitamin D supplementation) were often used, and at least

	1 paper excluded those with metabolic imbalances such as hyperphosphataemia. Moreover, the ad-hoc phosphate binder use and vitamin D supplementation observed may be driving some of the results, particularly those for serum phosphate and PTH. Reporting in many of the studies was poor. For example, details of study designs were often unclear and results were not always cited in the text of the papers, requiring the reviewer to read the data off available graphs. Additionally, it was not always clear what dietary advice was provided, in what manner it was provided, or who provided it. Unit-of-analysis errors were also common, with analyses not following the intent-to-treat principle.
Other considerations	Keto and amino acid supplementation is not currently used in regular practice in the UK; the GDG felt that making recommendations about their use without further evidence on their safety and effectiveness would be premature. According to the consensus of the GDG, based upon their clinical knowledge and experience, usual practice is to advise a reduction in certain types of food: generally those with a high phosphate to protein ratio, such as some dairy products and nuts, or food and drinks with high levels of phosphate additives, such as cola drinks or processed foods. The emphasis is more on the phosphate content of food and drinks rather than focusing on the restriction of protein. The definition of 'moderate-protein diet' used in the analysis (0.75–1.2 g/kg/day) corresponds to the approximately normal level of protein intake for adults in the UK (although the top end of this range would be considered relatively high for CKD patients who are not on dialysis). A distinction needs to be noted between a 'moderate-protein diet' and a 'moderate-protein restriction' because these are not the same intervention. There is limited guidance regarding recommended nutrient intakes for phosphate in adults with CKD. There is some guidance available for children, but the evidence informing this guidance is limited. The GDG noted relevant recommendations in 'Chronic kidney disease' (NICE clinical guideline 73).

2.1.5 Recommendations and research recommendations for dietary management for people with stage 4 or 5 CKD who are not on dialysis

Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203.

2.2 Dietary management for people with stage 5 CKD who are on dialysis

2.2.1 Review question

For people with stage 5 CKD who are on dialysis, is the dietary management of phosphate effective in managing serum phosphate and its associated outcomes compared to placebo or other treatments? Which dietary methods are most effective?

2.2.2 Evidence review

This review question focused on the use of dietary interventions in the prevention and treatment of hyperphosphataemia in patients with stage 5 CKD who are on dialysis. These interventions are based on varying degrees of restriction in the intake of phosphate and/or protein, with or without supplementation with keto and amino acids, or on the exchange of a proportion of dietary protein with a low-phosphate protein substitute.

For this review question, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials and the Centre for Reviews and Dissemination) using a broad search strategy, pulling in all papers relating to the dietary management of hyperphosphataemia in CKD. Only RCTs that compared a dietary intervention with either a placebo or another comparator in patients with stage 5 CKD who are on dialysis were considered for inclusion.

Trials were excluded if:

- the population included people with CKD stages 1 to 4 **or**
- the population included people with a diagnosis of CKD stage 5 who are not on dialysis.

From a database of 3026 abstracts, 244 full-text articles were ordered (including 107 identified through review of relevant bibliographies) and 3 papers describing 3 primary studies were selected (Guida et al., 2011; Jiang

et al., 2009; Li et al., 2011). No paediatric studies meeting the inclusion criteria were found. Table 2 lists the details of the included studies.

In order to define the interventions covered and aid an overarching analysis of the dietary management of hyperphosphataemia, protein levels in interventions that included protein restriction were categorised (through review of the available literature and discussion with the GDG) as follows:

- less than or equal to 0.8 g of protein per kilogram of bodyweight per day: very-low-protein diet
- more than 0.8 g to less than or equal to 1.0 g of protein per kilogram of bodyweight per day: low-protein diet
- more than 1.0 g to less than or equal to 1.2 g of protein per kilogram of bodyweight per day: moderate-protein diet
- more than 1.2 g of protein per kilogram of bodyweight per day: high-protein diet.

These definitions are different to those used in the analysis of dietary interventions in patients with stage 4 or 5 CKD who are not on dialysis because of the different protein requirements of this population. A certain amount of protein tends to be lost from the body through dialysis; therefore, a high level of protein restriction poses a greater concern over malnutrition. For this reason, the lowest thresholds for protein intake are set at a higher level in patients with stage 5 CKD who are on dialysis.

None of the papers reported adherence, an outcome considered critical to decision-making by the GDG, in a binary manner. Rather than defining a patient as ‘adherent’ or ‘non-adherent’ to the dietary prescriptions, authors provided mean levels of actual protein intake. In order to use these continuous measures as indicators of adherence that could be compared across studies and interventions, the reviewer converted these mean actual intake levels into a percentage of the prescribed level. For example:

Prescribed protein intake	Reported mean actual protein intake	Actual protein intake expressed as a percentage of the prescribed level
0.6 g/kg of body weight/day	0.72 g/kg of body weight/day	120% of prescription that is, actual intake exceeded prescription by 20%

Mean differences (MDs) were calculated for continuous outcomes and odds ratios (ORs) for binary outcomes, as well as the corresponding 95% confidence intervals (CIs) where sufficient data were available. There was no pooling of studies because of the lack of similarity in the interventions used.

Table 2 Summary of included studies for dietary management for adults with stage 5 CKD who are on dialysis

Study	Population	Intervention	Control	Follow-up
Low-phosphorus protein supplement (+ binders) compared with usual diet (+ binders)				
Guida et al, 2011 RCT Italy	n = 27 Haemodialysis treatment for at least 6 months No allergy to cow's milk protein Hyperphosphataemia (serum phosphate ≥ 6.5 mg/dl (i.e. ≥ 2.1 mmol/l)) Stable dialysis dose and modality, dietary intakes, body weight and biochemical markers for at least 3 months All patients were on thrice weekly 4-hour standard bicarbonate haemodialysis Baseline serum phosphate (mean±SD): Intervention = 2.7±0.4 mmol/l Control = 2.6±0.2 mmol/l	Patients not asked to change their eating habits or their total protein/energy intakes Partially replace dietary protein intake with a low-phosphorus, low-potassium whey protein concentrate (PROther), instructed to consume 30–40 g dissolved in liquid in place of usual daily portion sizes of protein-rich foods (including milk consumed at breakfast and meat, fish, eggs or dairy and poultry products consumed at lunch time) Most patients received both phosphate binders (sevelamer hydrochloride, lanthanum carbonate, calcium carbonate, and aluminium hydroxide) and vitamin D analogues – continued pre-study regimen	Usual diet maintained Most patients received both phosphate binders (sevelamer hydrochloride, lanthanum carbonate, calcium carbonate, and aluminium hydroxide) and vitamin D analogues – continued pre-study regimen	3 months Blood samples taken before each dialysis session
Very-low-protein diet compared with moderate-protein diet				
Jiang et al, 2009 RCT Shanghai, China	n = 30 (29 analysed at month 12) note: as trial had 3 arms, the moderate-protein diet group was split in 2 to give 2 pair-wise comparisons Stable peritoneal dialysis for at least 1 month Urine output of ≥ 800 ml or eGFR of ≥ 2 ml/min/1.73 m^2 (calculated as an average of the creatinine and urea clearances by 24 hour urine) (that is, residual renal function) Age 18–80 years Baseline serum phosphate (mean±SD): Intervention = 1.46±0.35 mmol/l Control = 1.28±0.32 mmol/l See evidence tables in appendix E for full inclusion/exclusion criteria	0.6–0.8 g protein/kg ideal body weight/day	1.0–1.2 g protein/kg ideal body weight/day	12 months Patients were assessed 'serially' for 12 months (data given for baseline, 1 month, 2 months, and then every 2 months)
Supplemented very-low-protein diet compared with moderate-protein diet				

Jiang et al, 2009 RCT Shanghai, China	n = 30 (28 analysed at month 12) note: as trial had 3 arms, the MPD group has been split in 2 to give 2 pair-wise comparisons Stable peritoneal dialysis for at least 1 month Urine output of ≥ 800 ml or eGFR of ≥ 2 ml/min/1.73 m^2 (calculated as an average of the creatinine and urea clearances by 24 hour urine) (that is, residual renal function) Age 18–80 years Baseline serum phosphate (mean±SD): Intervention = 1.48±0.36 mmol/l Control = 1.28±0.32 mmol/l See evidence tables in appendix E for full inclusion/exclusion criteria	0.6–0.8 g protein/kg ideal body weight/day 0.12 g KA (Ketosteril)/kg ideal body weight/day	1.0–1.2 g protein/kg ideal body weight/day	12 months Patients were assessed 'serially' for 12 months (data given for baseline, 1 month, 2 months, and then every 2 months)
Supplemented very-low-protein diet + phosphate restriction compared with moderate-protein diet				
Li et al, 2011 RCT Shanghai, China	n = 40 Patients on maintenance haemodialysis 3 times/week for more than 3 months with Kt/V above 1.2 and no residual renal function Patients who also had uncontrolled hyperphosphataemia – serum phosphate > 5.5 mg/dl (i.e. > 1.8mmol/l) – after 3 months of conventional calcium carbonate treatment and low-calcium dialysate (1.25 mEq/l) therapy to maintain normal serum calcium levels Baseline serum phosphate (mean±SD): Intervention = 2.34±0.46 mmol/l Control = 2.30±0.5 mmol/l See evidence tables in appendix E for full inclusion/exclusion criteria	0.8 g of protein/kg ideal body weight/day 500 mg phosphate/day 12 pills of KA (Ketosteril)/day 30–35 kcal/kg/day	1.0–1.2 g protein/kg ideal body weight/day according to the patient's normal diet	8 weeks Monitored at baseline, 1 week, 2 weeks, 4 weeks and 8 weeks[1]

[1] Full study lasted 16 weeks: after 8 weeks on the intervention diet, the intervention group switched to the control diet and were observed for 8 weeks; the control group were on the control diet for the duration of the 16-week study period. Data is only extracted from the initial 8-week RCT period, and not for the 8-week observation period following.

Abbreviations: BMI, body mass index; Ca x P product, calcium-phosphorus product; eGFR, estimated glomerular filtration rate; KA, keto acids; Kt/V, quantification of dialysis treatment adequacy; MPD, moderate-protein diet; RCT, randomised controlled trial; SD, standard deviation.

Summary GRADE profile 8 Low-phosphorus protein supplement compared with no intervention in adults with stage 5 CKD who are on dialysis

Outcome	Number of Studies	Number of patients		Effect	Quality
		Low-phosphorus protein supplement	No intervention		
Serum phosphate 3-month follow-up	1 RCT Guida et al, 2011	15	12	*Absolute effect* MD = 0.7 mmol/l lower (95% CI:1.0 to 0.4 lower)	Low
Serum iPTH (immunoradiometric assay) 3-month follow-up	1 RCT Guida et al, 2011	15	12	*Absolute effect* MD = 28.9 pmol/l lower (95% CI:36.5 to 21.3 lower)	Very low
Abbreviations: CI, confidence interval; iPTH, intact parathyroid hormone; MD, mean difference; RCT, randomised controlled trial.					

Summary GRADE profile 9 Very-low-protein diet compared with moderate-protein diet in adults with stage 5 CKD who are on dialysis

Outcome	Number of Studies	Number of patients		Effect	Quality
		Very-low-protein diet	Moderate-protein diet		
Serum phosphate 12-month follow-up	1 RCT Jiang et al, 2009	18	9[1]	*Absolute effect* MD = 0.17 mmol/l lower (95% CI: 0.52 lower to 0.18 higher)	Very low
Adherence to protein prescription (% of prescription, calculated from 3-day diet diary) 12-month follow-up	1 RCT Jiang et al, 2009	18	9[1]	*Absolute effect* MD = 15.5% higher	Very low
Adverse events – malnutrition (% of patients malnourished, as defined by SGA) 12-month follow-up	1 RCT Jiang et al, 2009	18	9[1]	*Relative effect* OR = 0.54 (95% CI: 0.25 to 1.17)	Very low
Adverse events – hospitalisation (% of patients hospitalised) 12-month follow-up	1 RCT Jiang et al, 2009	20	10[1]	*Relative effect* OR = 0.46 (95% CI: 0.08 to 2.54)	Very low
Serum iPTH 12-month follow-up	1 RCT Jiang et al, 2009	18	9[1]	*Absolute effect* Difference in medians = 1.8 pmol/l higher	Very low

Study is a 3-arm trial (LPD versus sLPD versus MPD); the reviewer has therefore broken down the data into 2 pair-wise comparisons, with the population of the common comparator (the MPD group) divided in 2 for the analysis: for LPD versus MPD, n (MPD) = 9; for sLPD versus MPD (see GRADE profile below), n (MPD) = 8 (except for 'adverse events [hospitalisation]': for LPD versus MPD, n [MPD] = 10; for sLPD versus MPD, n [MPD] = 10)

Abbreviations: CI, confidence interval; iPTH, intact parathyroid hormone; LPD, low-protein diet; MD, mean difference; moderate-protein diet; OR, odds ratio; RCT, randomised controlled trial; SGA, subjective global assessment of nutrition; sLPD, supplemented low-protein diet.

Summary GRADE profile 10 Supplemented very-low-protein diet compared with moderate-protein diet in adults with stage 5 CKD who are on dialysis

Outcome	Number of Studies	Number of patients		Effect	Quality
		Supplemented very-low-protein diet	Moderate-protein diet		
Serum phosphate 12-month follow-up	1 RCT Jiang et al, 2009	18	8[1]	*Absolute effect* MD = 0.22 mmol/l lower (95% CI: 0.58 lower to 0.14 higher)	Very low
Adherence to protein prescription (% of prescription, calculated from 3-day diet diary) 12-month follow-up	1 RCT Jiang et al, 2009	18	8[1]	*Absolute effect* MD = 3% higher	Very low
Adverse events – malnutrition (% of patients malnourished, as defined by SGA) 12-month follow-up	1 RCT Jiang et al, 2009	0%	20%[1]	*Absolute effect* 20 fewer per 100	Very low
Adverse events – hospitalisation (% of patients hospitalised) 12-month follow-up	1 RCT Jiang et al, 2009	5/20	7/10[1]	*Relative effect* OR = 0.62 (95% CI: 0.12 to 3.21) *Absolute effect* 11 fewer per 100 (48 fewer to 18 more)	Very low
Serum iPTH 12-month follow-up	1 RCT Jiang et al, 2009	18	8[1]	*Absolute effect* Difference in medians = 16.0 pmol/l lower	Very low

Study is a 3-arm trial (LPD versus sLPD versus MPD); the reviewer has therefore broken down the data into 2 pair-wise comparisons, with the population of the common comparator (the MPD group) divided in 2 for the analysis: for sLPD versus MPD, n (MPD) = 8; for LPD versus MPD (see GRADE profile above), n (MPD) = 9 (except for 'adverse events [hospitalisation]': for LPD versus MPD, n [MPD] = 10; for sLPD versus MPD, n [MPD] = 10)

Abbreviations: CI, confidence interval; iPTH, intact parathyroid hormone; LPD, low-protein diet; MD, mean difference; moderate-protein diet; OR, odds ratio; RCT, randomised controlled trial; SGA, subjective global assessment of nutrition; sLPD, supplemented low-protein diet.

Summary GRADE profile 11 Supplemented very-low-protein diet + phosphate restriction compared with moderate-protein diet in adults with stage 5 CKD who are on dialysis

Outcome	Number of Studies	Number of patients		Effect	Quality
		Supplemented very-low-protein diet + phosphate restriction	Moderate-protein diet		
Serum phosphate 8-week follow-up	1 RCT Li et al, 2011	20	20	*Absolute effect* MD = 0.5 mmol/l lower (95% CI: 0.7 to 0.3 lower)	Very low
Adherence to protein prescription (% of prescription, calculated from 3-day diet diary) 8-week follow-up	1 RCT Li et al, 2011	20	20	*Absolute effect* MD = 7.5% higher	Very low
Adherence to protein prescription (% of prescription, calculated from nPCR) 8-week follow-up	1 RCT Li et al, 2011	20	20	*Absolute effect* MD = 9.6% higher	Very low
Adverse events – malnutrition (% of patients malnourished, as defined by MNA of < 17) 8-week follow-up	1 RCT Li et al, 2011	0/20	0/20	*Absolute effect* 0 fewer per 100	Very low
Abbreviations: CI, confidence interval; MD, mean difference; MNA, mini-nutritional assessment; nPCR, normalised protein catabolic rate; RCT, randomised controlled trial.					

See appendix E for the evidence tables and GRADE profiles in full.

2.2.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual'.

Dietary management for people with stage 5 CKD who are on dialysis

A low-phosphorus protein substitute compared with no intervention

Critical outcomes

2.2.3.1 Low-quality evidence from 1 RCT of 27 patients showed a diet in which normal dietary protein is partially exchanged for a low-phosphorus protein substitute to be associated with a mean serum phosphate level 0.7 mmol/l lower (95% CI -1.0 to -0.4, i.e. statistically significant) than in patients receiving no intervention (that is, usual diet) at 3 months.

Important outcomes

2.2.3.2 Very-low-quality evidence from the RCT of 27 patients showed a diet in which normal dietary protein is partially exchanged for a low-phosphorus protein substitute to be associated with a mean serum PTH level 28.9 pmol/l lower (95% CI -36.5 to -21.3, i.e. statistically significant) than in patients receiving no intervention (that is, usual diet) at 3 months.

A very-low-protein diet compared with a moderate-protein diet

Critical outcomes

2.2.3.3 Very-low-quality evidence from 1 RCT of 27 patients showed a very-low-protein diet to be associated with a mean serum phosphate level 0.17 mmol/l lower (95% CI -0.52 to 0.18) than in patients on a moderate-protein diet at 12 months, although the difference was not statistically significant[10].

[10] Note: actual intake fell into the 'low-protein' rather than the 'very-low-protein' range; actual protein intake in the very-low-protein diet group was 0.90 g/kg/day and 0.97 g/kg/day in the moderate-protein diet group (MD 0.07 lower [95% CI -0.19 to 0.05]).

2.2.3.4 *Very-low-quality evidence from the RCT of 27 patients showed that, as a percentage of the prescribed protein intake, those on a very-low-protein diet exceeded the relevant prescription to a greater extent than those on a moderate-protein diet at 12 months (MD 15.5% more)[11].*

2.2.3.5 *Very-low-quality evidence from the RCT of 27 patients found that 8.2% fewer patients were defined as malnourished on a very-low-protein diet compared to a moderate-protein diet (OR 0.54 [95% CI 0.25 to 1.17]), although the difference was not statistically significant[11].*

2.2.3.6 *Very-low-quality evidence from the RCT of 30 patients found that 15% fewer patients were hospitalised on a very-low-protein diet compared to a moderate-protein diet (OR 0.46 [95% CI 0.08 to 2.54]), although the difference was not statistically significant[11].*

Important outcomes

2.2.3.7 *Very-low-quality evidence from the RCT of 27 patients showed a very-low-protein diet to be associated with a median serum PTH level 1.8 pmol/l higher than in patients on a moderate-protein diet at 12 months[11].*

A very-low-protein diet supplemented with keto acids compared with a moderate-protein diet

Critical outcomes

2.2.3.8 *Very-low-quality evidence from 1 RCT of 26 patients showed a very-low-protein diet supplemented with a mixture of keto acids and amino acids to be associated with a mean serum phosphate level 0.22 mmol/l lower (95% CI -0.58 to 0.14) than in patients on a moderate-protein diet at 12 months.*

[11] Note: actual intake fell into the 'low-protein' rather than the 'very-low-protein' range; actual protein intake in the very-low-protein diet group was 0.90 g/kg/day and 0.97 g/kg/day in the moderate-protein diet group (MD 0.07 lower [95% CI -0.19 to 0.05]).

2.2.3.9 Very-low-quality evidence from the RCT of 26 patients showed that, as a percentage of the prescribed protein intake, those on a very-low-protein diet supplemented with a mixture of keto acids and amino acids exceeded the relevant prescription to a greater extent than those on a moderate-protein diet when estimated by 3-day diet diary at 12 months (MD 3% more).

2.2.3.10 Very-low-quality evidence from the RCT of 26 patients found that 20% fewer patients were defined as malnourished on a very-low-protein diet supplemented with a mixture of keto acids and amino acids compared to a moderate-protein diet (no patients in the supplemented very-low-protein diet group were defined as malnourished).

2.2.3.11 Very-low-quality evidence from 1 RCT of 30 patients found that 10% fewer patients were hospitalised among those on a very-low-protein diet supplemented with a mixture of keto acids and amino acids compared to those on a moderate-protein diet (OR 0.62 [95% CI 0.12 to 3.21]), although the difference was not statistically significant.

Important outcomes

2.2.3.12 Very-low-quality evidence from 1 RCT of 26 patients showed a very-low-protein diet supplemented with a mixture of keto acids and amino acids to be associated with a median serum PTH level 16.0 pmol/l lower than in patients on a moderate-protein diet at 12 months.

A very-low-protein diet supplemented with keto acids + phosphate restriction compared with a moderate-protein diet

Critical outcomes

2.2.3.13 Very-low-quality evidence from 1 RCT of 40 patients showed a very-low-protein and low-phosphate diet supplemented with a mixture of keto acids and amino acids to be associated with a

mean serum phosphate level 0.5 mmol/l lower (95% CI -0.7 to -0.3, i.e. statistically significant) than in patients on a moderate-protein diet at 12 months[12,13].

2.2.3.14 *Very-low-quality evidence from 1 RCT of 40 patients showed that, as a percentage of the prescribed protein intake, those on a very-low-protein and low-phosphate diet supplemented with a mixture of keto acids and amino acids exceeded the relevant prescription to a greater extent than those on a moderate-protein diet when estimated by normalised protein catabolic rate at 8 weeks (MD 9.6% more)[12].*

2.2.3.15 *Very-low-quality evidence from the same RCT showed that, as a percentage of the prescribed protein intake, those on a very-low-protein and low-phosphate diet supplemented with a mixture of keto acids and amino acids exceeded the relevant prescription to a greater extent than those on a moderate-protein diet when estimated by 3-day diet diary at 8 weeks (MD 7.5% more)[14].*

2.2.3.16 *Very-low-quality evidence from 1 RCT of 40 patients found no difference in the number of patients defined as malnourished on a very-low-protein and low phosphate diet supplemented with a mixture of keto acids and amino acids compared to a moderate-protein diet (0 in both groups)[12].*

[12] Note: actual intake in the intervention group fell into the 'low-protein' rather than the 'very-low-protein' range, and into the 'high-protein' rather than the 'moderate-protein' range in the control group when estimated by the normalised protein catabolic rate (the difference in actual intake between the groups was, however, statistically significant).
[13] Phosphate intake was considerably reduced in the intervention group compared to the control (mean difference [95% CI] at 8 weeks = -305 mg/day [-376 to -234]).
[14] Note: actual intake in the intervention group fell into the 'low-protein' rather than the 'very-low-protein' range when estimated by 3-day diet diary (the difference in actual intake between the groups was, however, statistically significant).

2.2.4 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that those considered critical or important for decision-making were the same as those in the review of dietary management in patients with CKD stage 4 or 5 who are not on dialysis.
Trade-off between benefits and harms	Protein restriction (without supplementation with keto and amino acids) had only a marginal positive impact on serum phosphate and PTH; both increased during the study, only to a lesser extent than among those with a 'normal' protein intake. The effect of protein restriction without supplementation on the incidence of malnutrition and hospitalisation was not significantly different from that of people with a 'normal' protein intake. The GDG noted that adherence with the prescribed protein restriction was very poor, with no significant difference in the actual intake between the 2 groups. This was the likely cause of the similarity in the results of the 2 groups. The GDG was concerned that the risk of malnutrition on a protein restricted diet without supplementation could not be determined. The GDG was also concerned that the study may have been underpowered in terms of sample size, further reducing the sensitivity to detect malnutrition. The small number of events recorded support the suggestion that this study was underpowered. The addition of keto and amino acid supplements to protein restricted diets did not have a significantly different effect on serum phosphate levels compared to those with a 'normal' protein intake, although it did significantly improve adherence, as well as the incidence of malnutrition and hospitalisation. However, the GDG was again concerned that the study may have been underpowered in terms of sample size, reducing their sensitivity to detect malnutrition. Concerns relating to restricted diets also included 'sub-clinical' malnutrition that may easily be missed in those on low- or very-low-protein diets. It was noted that in current practice, clinicians aim to increase protein, or at least maintain patients' dietary intakes at reference nutrient intake levels, rather than restrict nutritional intake in patients on dialysis. The GDG noted that supplementation with keto and amino acids may alleviate the harmful effects of very-low-protein diets, leading to the reduced rates of malnutrition and hospitalisation rates observed. There are a number of possible explanations for this association, such as a beneficial effect on nutritional status through substitution for the restricted protein or a positive impact relating to the alleged phosphate-binding properties of calcium-based keto acids, although there is currently insufficient evidence available. If patients are prescribed a very-low-protein diet supplemented with keto and amino acids, the GDG was concerned that non-adherence with the supplements might still lead to malnutrition; the additional pill burden of these supplements was considered a significant concern in this area. However, no data were found on patient adherence with keto and/or amino acid supplements. The GDG did not feel that the evidence for benefits outweighed the possible risks and disadvantages of significant protein restriction in these patients (whether supplemented by keto and amino acids or not), particularly given the lack of effect on serum phosphate.

	Therefore, the GDG did not feel it appropriate to recommend diets based on protein restriction for the management of hyperphosphataemia in adults on dialysis. According to the current guidance from the British Dietetic Association's Renal Nutrition Group, the recommended nutrient intake for protein in adults on haemodialysis is a minimum of 1.1 g/kg of ideal body weight/day; the recommended nutrient intake for protein in adults on peritoneal dialysis is a minimum of 1.1 to 1.2 g/kg of ideal body weight/day. For the reasons outlined above, the GDG did not feel that the evidence was sufficient to recommend restricting protein intake below these levels. Furthermore, given that very-low-protein diets supplemented with keto and amino acids also have a large pill burden, the GDG felt that phosphate binders would be more clinically appropriate than supplementation with keto and amino acids. In children, the GDG felt that malnutrition is a greater concern than hyperphosphataemia. Progressive CKD is often associated with decreases in spontaneous dietary protein intake and dialysis with a loss of protein from the body; effects that clinicians feel are a priority for treatment given the particular need to maintain growth and adequate nutritional status. For these reasons, accompanied by the lack of paediatric evidence available, the GDG could not recommend a diet based on protein restriction for children. In addition, as the GDG felt that, for a variety of reasons, it would never be part of standard practice in the management of hyperphosphataemia to limit a child's protein intake, it would be inappropriate to make such a recommendation. Recommended protein intakes are instead age-specific according to reference nutrient intakes, plus additional protein to attempt to compensate for the potential of dialytic and other protein losses. Although observed within a short follow-up period, the GDG felt that, in the only study to examine it, limiting phosphate intake had a large impact in reducing serum phosphate, particularly when compared to the effectiveness of a similar intervention differing only in its lack of prescribed phosphate restriction. This result reflected the observations of the GDG in their own clinical and personal experience. The group considered advising patients to reduce their intake of phosphate-rich foods to reflect good clinical practice. Exchanging a proportion of dietary protein with a low-phosphate protein substitute seems to be an effective intervention, with significant effects on serum phosphate and PTH. The GDG was, however, concerned that the follow-up was relatively short, the sample size was small, and the study was not UK-based (Italy). These observations lead to reduced confidence in the results observed and uncertainty over the intervention's long-term effects (for example, on nutritional status). There was also uncertainty as to the sustainability of the low-phosphate protein supplement as a long-term intervention, particularly as there are no data available on adherence or patients' views on the intervention (such as quality-of-life data) and the GDG was unsure of its palatability. Additionally, it was felt that this could constitute further and unwelcome 'medicalisation' of the life of patients with advanced CKD. The group felt that more evidence is required before a recommendation can be made for the use of such low-phosphate protein supplements as an intervention for the management of

	hyperphosphataemia. However, extending the principle that dietary restriction of food and drink rich in phosphate is desirable, the GDG felt that low-phosphate options should be considered in instances where children or young people require nutritional supplements and/or substitutes to maintain protein intake.
Economic considerations	This question was not prioritised for health economic analysis as the majority of resource inputs are outside of NHS personal social services perspective.
Quality of evidence	There was considerable variation across the 3 included papers in terms of design and the interventions used, and no evidence was found for children. The GDG noted that the limited evidence provided little for consideration. In particular, little significant or reliable evidence was found to suggest that low-protein prescriptions are effective in managing serum phosphate, although it was felt that this could be a consequence of the poor quality of the evidence and the general failure to meet the high requirements of protein restriction. The GDG also questioned the generalisability of the evidence to a UK setting – particularly in terms of dietary differences in the 2 studies based in China – because none of the studies are UK-based. It was felt that generalisability was further limited by the short follow-up periods in 2 of the papers and the relatively small sample sizes across all 3 papers. Additionally, 1 of the studies excluded patients who have had transplants, and all 3 included only patients with a good nutritional status at baseline. For these reasons, the population in the evidence base may not be generalisable to the whole population of dialysis patients in England and Wales. The GDG raised concerns relating to the measures used for 2 of the outcomes. The incidence of adherence with dietary prescription was not regularly reported; instead, papers reported mean actual intakes for each group, which the reviewer then compared to prescriptions, producing a surrogate measure of adherence. The GDG also had reservations regarding the known variability of PTH measurements. It was noted that 1 study was powered for purposes other than the management of serum phosphate, focusing instead on the preservation of residual renal function. Outcomes of interest in this study were therefore secondary. In another study, the patients' pre-study regimens of phosphate binders were continued. Although use was well-balanced at baseline, these concurrent treatments may have influenced the good results observed for serum phosphate and PTH in those on the low-phosphate protein substitute. Reporting across the studies was poor. For example, details of study designs were often unclear and results were not always cited in the text of the papers, requiring the reviewer to read the data off available graphs. Additionally, it was not always clear what dietary advice was provided, in what manner it was provided, or who provided it. Unit-of-analysis errors were also common, with analyses not following the intent-to-treat principle.
Other considerations	Keto and amino acids supplementation is not currently used in practice in the UK; therefore, it was felt that making recommendations about their use without further evidence on their safety and effectiveness would be premature.

	Usual practice is to advise a reduction in certain types of food: generally those with a high phosphate to protein ratio, such as some dairy products and nuts, or food and drinks with high levels of phosphate additives, such as cola drinks or processed foods. The emphasis is more on the phosphate content of food and drinks rather than focusing on the restriction of protein. There is limited guidance available regarding recommended nutrient intakes for phosphate in adults with CKD. There is some guidance available for children, but the evidence informing this guidance is limited. The GDG noted relevant recommendations in 'Chronic kidney disease' (NICE clinical guideline 73).

2.2.5 Recommendations and research recommendations for dietary management for people with stage 5 CKD who are on dialysis

Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203.

2.3 Patient information strategies

2.3.1 Review question

For people with stage 4 or 5 CKD, both those on dialysis and those who are not, are patient information strategies effective at promoting adherence to phosphate-lowering dietary interventions, or in the management of serum phosphate and its associated outcomes? Which patient information strategies are most effective?

2.3.2 Evidence review

This review question focused on the use of patient information and education interventions to promote adherence to phosphate-lowering dietary interventions, in the context of both the prevention and treatment of hyperphosphataemia, in patients with stage 4, 5 or 5D CKD. These interventions ranged from the provision of written educational material, to educational videos, to counselling sessions of varying frequency, delivered one-on-one or to groups of patients. Other interventions consisted of

behavioural feedback and patient contracts or combinations of multiple concurrent approaches, including 2 or more of the following: written educational material, educational videos, counselling sessions, self-management tools (such as medication charts, individualised menus and food exchange lists) or competitions.

For this review question, papers were identified from a number of different databases (Medline, Medline in Process, Embase, the Cochrane Database of Systematic Reviews, the Centre for Reviews and Dissemination's DARE and HTA databases, and PsycINFO) using a broad search strategy, pulling in all papers relating to the use of patient information and education interventions to promote adherence to phosphate-lowering dietary interventions in patients with CKD. RCTs, non-randomised controlled trials (non-RCTs) and controlled before-and-after studies comparing a patient education intervention with either no intervention or another comparator were considered for inclusion.

Trials were excluded if:

- the population included people with CKD stages 1 to 3 **or**
- the trial examined only the information to be covered by education, rather than the strategy by which it should be delivered.

From a database of 1143 abstracts, 112 full-text articles were ordered (including 9 identified through review of relevant bibliographies) and 9 papers (7 RCTs, 1 cluster RCT and 1 non-RCT) describing 9 primary studies were selected (Ashurst and Dobbie, 2003; Baraz et al., 2010; Campbell et al., 2008; Chen et al., 2006; Ford et al., 2004; Morey et al., 2008; Shaw-Stuart and Stuart, 2000; Sullivan et al., 2009; Tanner et al., 1998). No paediatric studies meeting the inclusion criteria were found. Table 3 lists the details of the included studies.

The reviewer analysed studies together where possible, producing a number of pooled comparisons. These were structured as follows:

- *Patient education versus no intervention (beyond usual care).*

Three papers were included in this pooled comparison (2 RCTs and 1 cluster RCT). Data from the 2 RCTs could be meta-analysed for knowledge scores and serum phosphate. The cluster RCT data for these outcomes could not be included in the meta-analysis because of the unit-of-analysis error found within the paper (data were analysed at the participant-level rather than cluster-level, and insufficient information was available for the reviewer to correct this). Therefore, this cluster RCT data, along with the other non-meta-analysed data from each paper, were recorded individually.

- *Interventions including counselling-based education versus written material alone.*

Two papers were included in this pooled comparison (both RCTs). Because of the absence of common outcomes between the papers, no meta-analysis was performed; data for each outcome from each paper were recorded individually.

- *Multiple component interventions versus single component interventions.*

Four papers were included in this pooled comparison (all RCTs). Data from all 4 papers could be meta-analysed for serum phosphate. The other, non-meta-analysed data from each paper were recorded individually.

- *Multiple component interventions versus specific single component interventions.*

These comparisons were designed to further differentiate the more general comparison above into the specific single component comparators of the 5 included papers: individual patient counselling alone (2 papers), written material alone (1 paper) and video education alone (1 paper). Data from the 2 papers comparing multiple component interventions against individual patient counselling alone could be meta-analysed for serum phosphate. The other, non-meta-analysed data from each paper were recorded individually.

Significant heterogeneity was observed across all of the included studies, particularly in relation to the structure and content of the interventions studied. There was also considerable variation in the locations of many of these studies, with few conducted in the UK.

Many of the papers did not report adherence, an outcome considered critical to decision-making by the GDG, in a binary manner. Rather than defining a patient as 'adherent' or 'non-adherent' with the dietary prescriptions, authors often provided mean levels of actual protein intake. In order to use these continuous measures as indicators of adherence that could be compared across studies and interventions, the reviewer converted these mean actual intake levels into a percentage of the prescribed level. For example:

Prescribed protein intake	**Reported mean actual protein intake**	**Actual protein intake expressed as a percentage of the prescribed level**
0.6 g/kg of body weight/day	0.72 g/kg of body weight/day	120% of prescription that is, actual intake exceeded prescription by 20%

Additionally, for the purpose of this review, the summary term 'self-management tool' has been used to collectively describe the aids used to help patients in managing their dietary intake or serum phosphate levels in response to the education provided. These tools range from a fridge magnet detailing high-phosphate foods, to an individualised tracking chart that used visual goals to engage patients in achieving phosphate control.

Mean differences (MDs) were calculated for continuous outcomes and odds ratios (ORs) for binary outcomes, as well as the corresponding 95% confidence intervals (CIs) where sufficient data were available. Where meta-analysis was possible, a forest plot is also presented.

Table 3 Summary of included studies on patient information strategies for adults

Study	Population	Intervention	Control	Follow-up
Regular individual oral counselling + written educational material + self-management tool (serum phosphate control) compared with no intervention (beyond usual care)				
Ford et al, 2004 RCT Louisiana, US	n = 70 (63 completed the study) Haemodialysis patients Mean serum phosphate of > 6.0 mg/dl (i.e. > 1.9 mmol/l) for 3 months prior to the study Baseline serum phosphate (mean±SD): Intervention = 2.2±0.2 mmol/l Control = 2.3±0.4 mmol/l See evidence tables in appendix E for full inclusion/exclusion criteria	In addition to routine care, 20–30 mins/month of diet education focusing on improving serum phosphate control Education sessions: Dietitian stressed the importance of all aspects of phosphate control: prevention of renal bone disease; foods high in phosphate; medications; importance of diet, dialysis and drug therapy Educational tools (bright and attention-grabbing, and including analogies to which patients could relate) included: posters/flipcharts; picture handouts; puzzles; individualised phosphate tracking tool (self-monitoring phosphate levels using visual goals)	Routine care (no education): Review of monthly laboratory report by the dietitian during monthly nutrition rounds Although the dietitian did discuss abnormal phosphate levels with these patients, additional patient education materials were not provided	6 months Monitored monthly
One-off individual oral counselling + written educational material + self-management tool (serum phosphate control) compared with no intervention (beyond usual care)				
Sullivan et al, 2009 Cluster RCT Ohio, US	n = 279 Long-term haemodialysis for at least 6 months Most recent serum phosphate level and mean level for the previous 3 months both above 5.5 mg/dl (i.e. above 1.8 mmol/l) 18 years or older Baseline serum phosphate (mean±SD): Intervention = 2.3±0.4 mmol/l Control = 2.3±0.3 mmol/l See evidence tables in appendix E for full inclusion/exclusion criteria	Face-to-face education: Coordinator met in person with each intervention patient during a dialysis treatment in the first month of the study Provided approximately 30 minutes of education regarding phosphorus-containing additives and their effect on the phosphate content of foods Educational device: A small magnifier in a plastic case, on which common phosphorus-containing additives were printed Patients were instructed to use the magnifier and list of additives when purchasing food to avoid any items whose ingredient lists include phosphorus-containing additives	Continued to receive pre-study nutritional care from their facility's registered dietitian, which included nutritional status assessment, monthly laboratory test result review (including serum phosphorus levels), and education regarding the renal diet (including the deleterious effects of hyperphosphataemia, dietary sources of phosphorus and ways to limit phosphorus intake) A study coordinator telephoned control patients during the second month of the study and asked questions about how often they read nutrition facts labels and ingredient lists, ate meals from fast-food restaurants, and received phosphorus-related recommendations from their facility dietitian	3 months Monitoring unclear – at baseline and at 3 months?

		Written material: Each patient also received a handout for each fast-food restaurant the patient reported eating at more than once a month, tailored to the menus of common fast-food chains in the area. Each handout listed specific menu items to be avoided because they contained phosphorus additives, as well as better choices that were free of phosphorus additives and were compatible with other renal dietary requirements. Study coordinator telephoned patients during the second month to reinforce the instructions and answer any questions	Did not receive any education or feedback from study coordinators	
One-off individual oral counselling + written educational material + self-management tool (serum phosphate control) compared with written material alone				
Ashurst & Dobbie, 2003 RCT London, UK	n = 58 (56 analysed) Dialysis patients with serum phosphate of at least one value above 1.7 mmol/l during 3-month monitoring Over 18 years Clinically stable Baseline serum phosphate (mean): Intervention = 1.96 mmol/l Control = 1.98 mmol/l See evidence tables in appendix E for full inclusion/exclusion criteria	Teaching session (approximately 40 minutes in length), administered by a single, trained dietitian on an individual basis Used an education tool to improve the patients' knowledge of phosphate balance in dialysis patients and to assist patients in controlling their own phosphate level. The education package, 'A Patient's Guide to Keeping Healthy: Managing Your Phosphate' comprised: A teaching booklet which included: a cartoon and written description of phosphate and calcium functions, absorption and excretion; information on PTH and vitamin D function, their interaction, ways to control their balance, and the consequences of increased levels in the body; therapeutic approaches to phosphate management and the patient's role, including diet, dialysis and phosphate binders; emphasized the importance of adherence with treatment and medications Medication record chart - a sheet given to each subject in both groups - one side had the patient's personal details and phosphate binder prescription, as well as a table to be filled in with the medication dose taken at each meal, the other side had blood results for	Written material delivered on the dialysis unit by the renal haemodialysis dietitian, who was not the research dietitian Renal staff nurses or physicians refer those patients with persistent hyperphosphataemia for dietary advice. The dietetic consultation involves a diet history to assess the patient's intake, followed by phosphate restriction advice based on an A4 double-sided diet sheet. This diet sheet briefly explains about hyperphosphataemia and its association with bone disease; there is also a list of high-phosphate foods to be avoided and suitable low-phosphate alternatives. Patients were given the same medication record chart as the intervention group Patients in the control group were only told their biochemistry results if they asked or if they were above the recommended levels; they did not receive the education session nor the education booklet	3 months Monitored monthly

		phosphate, calcium and Ca x P product and the normal range for each Refrigerator magnet Patients were asked to complete the medication chart for 2 consecutive weeks Gave appropriate individual advice about diet, medication adherence and lifestyle		
One-off individual oral counselling + written educational material + self-management tool (dietary management) compared with individual oral counselling				
Chen at al, 2006 RCT Peking, China	n = 70 Patients on peritoneal dialysis for 3 months Clinically stable Baseline serum phosphate (mean±SD): Intervention = 1.67±0.23 mmol/l Control = 1.67±0.25 mmol/l See evidence tables in appendix E for full inclusion/exclusion criteria	All patients received intensive training ('traditional' method) within 2 weeks of catheter implementation (patients enrolled 3 months after dialysis) Detailed information about food contents and appropriate weight were taught by an experienced dietitian Portion-sized food aids were used Patients educated to maintain a daily protein intake level of 0.8–1.2 g/kg/day Patients taught to correctly record their 3-day dietary intakes In addition, intervention group patients received: Education utilising: individualised menu from the dietitian based on food preferences; an exchange list as a reference – every food in 1 list contains an equivalent amount of protein; patients were taught how to correctly use their menu by referring to the exchange list; portion-sized food aids	All patients received intensive training ('traditional' method) within 2 weeks of catheter implementation (patients enrolled 3 months after dialysis) Detailed information about food contents and appropriate weight were taught by an experienced dietitian Portion-sized food aids were used Patients educated to maintain a daily protein intake level of 0.8 to 1.2 g/kg/day Patients taught to correctly record their 3-day dietary intakes	1 month Pre-and post-intervention (at 1 month)
Regular individual oral counselling (dietary management) compared with written material alone				
Campbell et al, 2008 RCT Brisbane, Australia	n = 62 (50 analysed) Adults (older than 18 years) CKD with eGFR < 30 ml/min/1.73 m^2 Not previously seen by a dietitian for stage 4 CKD	Administered by a single dietitian Individualised dietary prescription, including 125–146 kj/kg/day (i.e. 30–35 kcal/kg/day) and 0.75–1.0 g protein/kg/day The patients were provided with an initial individual consultation at baseline of up to 60 minutes duration followed by a telephone consultation, commonly of 15–	Patients received generic nutrition information for patients with CKD, as provided in regular practice	12 weeks Monitoring unclear – pre- and post-intervention?

	Absence of malnutrition from a cause other than CKD Not expected to require RRT within 6 months Baseline serum phosphate (mean±SD): Intervention = no data available Control = no data available See evidence tables in appendix E for full inclusion/exclusion criteria	30 minutes duration, bi-weekly for the first month, then monthly Structure: 1. Clinical Data Initial: medical history; dialysis treatment plan; anthropometry; biochemistry Follow-up: changes in medical treatment, medications etc; changes in biochemistry 2. Interview Initial: nutrition assessment and appetite; evaluate food record; functional ability; psychosocial issues; readiness to change Follow-up: 24-hour dietary recall; recall of changes made 3. Determine the treatment plan: discussion on the role and effect of diet on renal disease; nutrition prescription; development of goals and target strategies 4. Self-management training: goal setting; menu planning; education on identifying protein, energy and other nutrients; recipe modification; label reading 5. Expected outcomes: meeting set goals; making appropriate food choice; maintains body weight, muscle and fat stores; biochemistry within range		
Regular individual oral counselling + written material (serum phosphate control) compared with one-off individual oral counselling				
Morey et al, 2008 RCT London, UK	n = 67 (60 completed the study) On maintenance haemodialysis for > 6 months Mean serum phosphate level persistently above of < 1.8 mmol/l over the 3-month review period Age older than 18 years	Individual review by a specialist renal research dietitian – assessed/advised monthly from baseline until the end of the study period Dietitian assessed subjects' diets using diet histories, and made an approximation of dietary phosphate content and nutritional adequacy, as well as phosphate binder adherence by self-report against prescription Subjects were advised and educated about dietary phosphate restriction and adherence with phosphate binder prescription while maintaining nutritional	Individual review by a specialist renal research dietitian - assessed/advised infrequently, that is, at baseline and at the end of the study period Dietitian assessed subjects' diets using diet histories, and made an approximation of dietary phosphate content and nutritional adequacy, as well as phosphate binder adherence by self-report against prescription Subjects were advised and educated about dietary phosphate restriction and adherence with	6 months Monitored monthly

	Baseline serum phosphate (mean±SD): Intervention = 2.05±0.5 mmol/l Control = 2.24±0.5 mmol/l See evidence tables in appendix E for full inclusion/exclusion criteria	adequacy, and a variety of strategies were employed to encourage dietary modification, including: motivational counselling; negotiation; behaviour modification therapy; reminders; reinforcement; supportive care; both written and verbal The research dietitian individualised strategies to each subject Patients were educated on how to match phosphate binders to the phosphate content of a meal; the dietitian also liaised with the medical team to adjust phosphate binder prescriptions to better match the needs of the individual patient	phosphate binder prescription while maintaining nutritional adequacy	
Regular individual behavioural feedback and contracting (serum phosphate control) compared with no intervention (beyond usual care)				
Tanner et al, 1998 RCT Alabama, US	n = 40 (38 completed the study) On haemodialysis for at least 2 months Age range 26-78 years A history of non-adherence for at least 1 month (non-adherence was defined as: interdialytic weight gain of 3 kg or greater on weekdays and 4 kg or greater on weekends for 6 of the 12 dialysis sessions and/or monthly serum phosphate levels of > 5.9 mg/dl (i.e. > 1.9 mmol/l)) Baseline serum phosphate (mean±SD): Intervention = no data available Control = no data available See evidence tables in appendix E for full inclusion/exclusion criteria	Monthly progress reports and behavioural contracts were reviewed each month with subjects by the investigator; copies were given to the subjects Monthly feedback included: Posting of subject's phosphorus level and number of acceptable IDWG on the monthly progress report – 'smiley' face stickers were used to represent acceptable values and 'frown' stickers for unacceptable values The reports were used to educate subjects on acceptable and unacceptable phosphate values and IDWG Provision of rewards, if indicated – subjects were provided with 'smiley' face stickers to wear for each criteria met, and an additional reward (stickers/candy) if both criteria were met Instruction on recommended dietary behaviours Setting of 1 or 2 monthly goals (increasing in complexity over time) to improve subjects' phosphate and fluid control, which were written on a new contract; this contract was dated and signed by the investigator and subject	No intervention (usual care)	6 months Serum phosphate data monitored (and provided for) each month; other outcomes were only monitored pre- and post-intervention

		Review of previous month's contract goals and progress – together, the subject and investigator identified reasons for non-adherence and/or improvement from the previous month		
Video + oral counselling + competitive competition (serum phosphate control) compared with regular individual oral counselling + written material				
Shaw-Stuart & Stuart, 2000 Non-RCT North Carolina, US	n = 81 Adult patients with end-stage renal failure Currently receiving haemodialysis Patients were not at risk for malnutrition Baseline serum phosphate (mean±SD): Intervention = 2.03±0.09 mmol/l Control = 2.01±0.11 mmol/l See evidence tables in appendix E for full inclusion/exclusion criteria	Educational program: 'A Taste for Life': An educational, informational, motivational patient adherence program directed at dietary and medical regimens Included: flip chart overviewing the basics of bone disease; 'bone disease demonstrator', which dramatised the progression of renal osteodystrophy without intervention; interactive educational modules; educational booklets; motivational posters; creative games and puzzles; videos In-house educational materials depicting alternatives to high phosphate foods In-centre achievement contest: 'Bone Voyage': Group divided into teams: assembled to include a balanced sample of high and low adherence patients Objective was to foster a competitive spirit and raise awareness of adherence in an effort to facilitate patient self-management Pitted teams racing against each other in sailboats from a start to finish line on a game poster that hung in the centre Movement of a team from start to finish depended on respective teams achieving goals set for the contest Points were added up for each team, and at the end of the third month, the team with the most points won. Prizes were awarded to winning teams and most improved patients each month and at the end of the 3 months	Patients were followed-up regularly by a staff dietitian and were counselled monthly concerning phosphate levels during the entire 9-month study period Therapy was on an individual basis and involved: Nutrition counselling consistent with the American Dietetic Association's National Renal Diet Instruction regarding the use of phosphate binders In-house printed information supplemented verbal instruction	12 months Monitored monthly
Oral interactive group counselling sessions + written material (general CKD + diet) compared with educational video viewed alone				

Baraz et al, 2010 RCT Tehran, Iran	n = 63 Aged older than 18 years Receiving haemodialysis routinely 3 times a week Receiving haemodialysis for at least 6 months Living in a home setting Not received any educational intervention in the past Baseline serum phosphate (mean±SD): Intervention = 1.99±0.49 mmol/l Control = 2.02±0.47 mmol/l	Patients invited to attend a class on the days after their haemodialysis sessions Two educational sessions of up to 30 minutes The principal investigator (a renal nurse expert) performed the teaching intervention The education was didactic and interactive: Patients could ask questions at the time of the class An explicitly interactive portion of the program was held at the end of the class - in this part of the session, patients were encouraged to offer support to each other At the end of group sessions, each patient received a teaching booklet ('A Patient Guide to Controlling Dietary Regimen') to take home The 2 interventions had similar content, covering: General knowledge about ESRD and dietary management for haemodialysis Identification of restricted/non-restricted food Fluid restrictions Possible reasons for adherence and non-adherence	Individually approached during 2 consecutive dialysis sessions in a week A 30-minute educational film was shown to each patient while they were having haemodialysis – each patient was started on haemodialysis, and then 1-2 hours after initiation of haemodialysis and ensuring that the patient was stable and ready, they were invited to watch the film The 2 interventions had similar content, covering: General knowledge about ESRD and dietary management for haemodialysis Identification of restricted/non-restricted food Fluid restrictions Reasons for adherence and possible reasons for non-adherence	2 months Monitored bi-monthly
Abbreviations: BMI, body mass index; Ca x P product, calcium-phosphorus product; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IDWG, inter-dialytic weight gain; PTH, parathyroid hormone; RCT, randomised controlled trial; RRT, renal replacement therapy; SD, standard deviation.				

Summary GRADE profile 12 Patient education compared with no intervention (beyond usual care) for adults

Outcome	Number of Studies	Number of patients		Effect	Quality
		Patient education	No intervention (beyond usual care)		
Changes in adherence-promoting behaviours - frequency of reading ingredients lists (measured on scale from 0–100; 0 = lowest reading behaviour score; 100 = highest possible reading behaviour score) 3-month follow-up	1 cluster RCT Sullivan et al, 2009	145	134	*Absolute effect* MD = 22 higher (95% CI:15 to 30 higher)	Very low
Changes in adherence-promoting behaviours - frequency of reading nutritional fact labels (measured on scale from 0–100; 0 = lowest reading behaviour score; 100 = highest possible reading behaviour score) 3-month follow-up	1 cluster RCT Sullivan et al, 2009	145	134	*Absolute effect* MD = 9% higher (95% CI:1 to 17 higher)	Very low
Knowledge scores (pooled) 6-month follow-up	2 RCTs Tanner et al, 1998 Ford et al, 2004	60	41	*Absolute effect* MD = 8.50% (95% CI:5.88 lower to 22.88 higher)	Very low
Change in knowledge scores[1] 3-month follow-up	1 cluster RCT Sullivan et al, 2009	145	134	*Absolute effect* MD = 3% higher (95% CI: 1 lower to 7 higher)	Very low
Change in knowledge scores[1] 6-month follow-up	1 RCT Tanner et al, 1998	32	31	*Absolute effect* MD = 6.97% higher	Very low
Change in knowledge scores[1] 6-month follow-up	1 RCT Ford et al, 2004	28	10	*Absolute effect* MD = 7.6% higher	Very low
Serum phosphate (pooled)[2]	2 RCTs	60	40	*Absolute effect*	Very low

6-month follow-up	Tanner et al, 1998 Ford et al, 2004			MD = 0.19 mmol/l lower (95% CI: 0.87 lower to 0.49 higher)	
Serum phosphate[2] 3-month follow-up	1 cluster RCT Sullivan et al, 2009	145	134	*Absolute effect* MD = 0.2 mmol/l lower (95% CI:0.3 lower to 0 higher)	Very low
Changes in beliefs and attitudes towards health - perceptions of self-efficacy for self-monitoring (Self-Efficacy Survey scores: 13–14 points = high; 15–26 points = moderate; 27–29 points = low) 6-month follow-up	1 RCT Tanner et al, 1998	28	10	*Absolute effect* MD = 1.01 points higher[3]	Very low
Changes in beliefs and attitudes towards health – health beliefs (Health Beliefs Survey scores: 9–10 points = high; 11–19 points = moderate; 20–27 points = low) 6-month follow-up	1 RCT Tanner et al, 1998	28	10	*Absolute effect* MD = 1.00 points higher[4]	Very low

[1] Data available for outcome inappropriate for meta-analysis across studies

[2] Data extracted from the cluster RCT suffered from a unit-of-analysis error (analysed at the level of the individual patient, not at the level of the cluster); there was insufficient data available for the reviewer to reduce the size of the trial to its effective sample size, and therefore the data will not be pooled with the other serum phosphate data

[3] Scores in both groups, at both baseline and at 6 months, were interpreted as 'moderate'

[4] Scores in both groups, at both baseline and at 6 months, were interpreted as 'high'

Abbreviations: CI, confidence interval; MD, mean difference; RCT, randomised controlled trial.

Summary GRADE profile 13 Interventions including counselling compared with written material alone for adults

Outcome	Number of Studies	Number of patients		Effect	Quality
		Interventions including counselling	Written material alone		
Adherence to protein prescription (% of prescription, calculated from 3-day diet diary) 12-week follow-up	1 RCT Campbell et al, 2008	24	26	*Absolute effect* MD = 0%	Very low
Adherence to energy prescription (% of prescription, calculated from 3-day diet diary) 12-week follow-up	1 RCT Campbell et al, 2008	24	26	*Absolute effect* MD = 9.4% higher	Very low
Serum phosphate 3-month follow-up	1 RCT Ashurst & Dobbie, 2003	29	27	*Absolute effect* MD = 0.34 mmol/l lower (95% CI: 0.58 to 0.10 lower)	Very low
Abbreviations: CI, confidence interval; MD, mean difference; RCT, randomised controlled trial.					

Summary GRADE profile 14 Multiple component education/information interventions compared with single component education/information interventions for adults

Outcome	Number of Studies	Number of patients		Effect	Quality
		Multiple component education/information interventions	Single component education/information interventions		
Adherence to protein prescription (number of patients that reached prescribed targets were considered adherent - dietary protein intake greater than 0.8 g/kg/day and less than 1.2 g/kg/day) 1-month follow-up	1 RCT Chen et al, 2006	20/35 (57.1%)	8/35 (22.9%)	*Relative effect* OR = 4.5 (95% CI 1.6 to 12.66): *Absolute effect* 34 more per 100 (9 more to 56 more)	Very low
Adherence to protein prescription (% of prescription, calculated from 3-day diet diary) 1-month follow-up	1 RCT Chen et al, 2006	35	35	*Absolute effect* MD = 0%	Very low
Phosphate binder requirement (number of patients in whom phosphate binders could be withdrawn) 6-month follow-up	1 RCT Morey et al, 2008	1/34 (2.9%)	1/33 (3.0%)	*Relative effect* OR = 0.97 (95% CI: 0.06 to 16.17) *Absolute effect* 0 fewer per 100 (from 3 fewer to 31 more)	Very low
Serum phosphate (pooled) 3-month follow-up (mean)	4 RCTs Chen et al, 2006 Morey et al, 2008 Ashurst & Dobbie, 2003 Baraz et al, 2010	130	126	*Absolute effect* MD = 0.09 mmol/l (95% CI: 0.23 lower to 0.04 higher)	Very low

Serum phosphate (number of patients with serum phosphate within acceptable limits) 2-month follow-up	1 RCT Baraz et al, 2010	18/32	18/31	*Relative effect* OR = 0.93 (95% CI: 0.34 to 2.52) *Absolute effect* 2 fewer per 100 (from 26 fewer to 20 more)	Very low
Abbreviations: CI, confidence interval; MD, mean difference; OR, odds ratio; RCT, randomised controlled trial.					

Summary GRADE profile 15 Multiple component education/information interventions compared with individual patient counselling alone for adults

Outcome	Number of Studies	Number of patients		Effect	Quality
		Multiple component education/information interventions	Individual patient counselling alone		
Adherence to protein prescription (number of patients that reached prescribed targets were considered adherent - dietary protein intake greater than 0.8 g/kg/day and less than 1.2 g/kg/day) 1-month follow-up	1 RCT Chen et al, 2006	20/35 (57.1%)	8/35 (22.9%)	*Relative effect* OR = 4.5 (95% CI 1.6 to 12.66): *Absolute effect* 34 more per 100 (9 more to 56 more)	Very low
Adherence to protein prescription (% of prescription, calculated from 3-day diet diary) 1-month follow-up	1 RCT Chen et al, 2006	35	35	*Absolute effect* MD = 0%	Very low
Phosphate binder requirement (number of patients in whom phosphate binders could be withdrawn) 6-month follow-up	1 RCT Morey et al, 2008	1/34 (2.9%)	1/33 (3.0%)	*Relative effect* OR = 0.97 (95% CI: 0.06 to 16.17) *Absolute effect* 0 fewer per 100 (from 3 fewer to 31 more)	Very low
Serum phosphate (pooled) 3-month follow-up (mean)	1 RCT Chen et al, 2006 Morey et al, 2008	69	68	*Absolute effect* MD = 0.01 mmol/l (95% CI: 0.1 lower to 0.08 higher)	Very low
Abbreviations: CI, confidence interval; MD, mean difference; OR, odds ratio; RCT, randomised controlled trial.					

Summary GRADE profile 16 Multiple component education/information interventions compared with written material alone for adults

Outcome	Number of Studies	Number of patients		Effect	Quality
		Multiple component education/information interventions	Written material alone		
Serum phosphate 3-month follow-up	1 RCT Ashurst & Dobbie, 2003	29	27	*Absolute effect* MD = 0.34 mmol/l lower (95% CI: 0.58 to 0.10 lower)	Very low
Abbreviations: CI, confidence interval; MD, mean difference; RCT, randomised controlled trial.					

Summary GRADE profile 17 Multiple component education/information interventions compared with video education alone for adults

Outcome	Number of Studies	Number of patients		Effect	Quality
		Multiple component education/information interventions	Video education alone		
Serum phosphate 2-month follow-up	1 RCT Baraz et al, 2010	32	31	*Absolute effect* MD = 0.05 mmol/l lower (95% CI: 0.22 lower to 0.13 higher)	Very low
Serum phosphate (number of patients with serum phosphate within acceptable limits) 2-month follow-up	1 RCT Baraz et al, 2010	18/32	18/31	*Relative effect* OR = 0.93 (95% CI: 0.34 to 2.52) *Absolute effect* 2 fewer per 100 (from 26 fewer to 20 more)	Very low
Abbreviations: CI, confidence interval; MD, mean difference; OR, odds ratio; RCT, randomised controlled trial.					

Summary GRADE profile 18 Oral counselling + video + competitive competition compared with regular individual oral counselling + written material for adults

Outcome	Number of Studies	Number of patients		Effect	Quality
		Oral counselling + video + competitive competition	Regular individual oral counselling + written material		
Serum phosphate 12-month follow-up	1 observational study Shaw-Stuart & Stuart, 2000	50	31	*Absolute effect* MD = 0.19 mmol/l lower (95% CI: 0.24 to 0.14 lower)	Very low
Abbreviations: CI, confidence interval; MD, mean difference.					

See appendix E for the evidence tables and GRADE profiles in full.

2.3.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual'.

Patient information strategies

Patient education compared with no intervention (beyond usual care)

Critical outcomes

2.3.3.1 Very-low-quality evidence from 1 cluster RCT of 279 patients showed a greater increase in adherence-promoting behaviours in those who had received a patient education intervention compared to those who had not at 3 months. The frequency of reading ingredients lists increased by 22% (95% CI 15 to 30, i.e. statistically significant) and the frequency of reading nutritional fact labels increased by 9% (95% CI 1 to 17, i.e. statistically significant) in the patient education group compared to those who received usual care only.

Important outcomes

2.3.3.2 Very-low-quality evidence from 2 RCTs analysing a total of 101 patients showed that at 6 months, mean knowledge scores were 8.50% higher (95% CI 5.88 to 22.88, i.e. statistically significant) in those who received a patient education intervention compared to those who did not. Knowledge scores in the patient education groups improved by 6.97% and 7.6% than in the 2 groups receiving usual care only.

2.3.3.3 Very-low-quality evidence from the cluster RCT of 279 patients found that at 3 months, knowledge scores in the patient education group improved by 3% (95% CI -1 to 7) than in those who received usual care only, although the difference was not statistically significant.

2.3.3.4 Very-low-quality evidence from the 2 RCTs of 100 patients showed patient education to be associated with a mean serum phosphate

level 0.19 mmol/l lower (95% CI -0.87 to 0.49) at 6 months than in patients who received usual care only, although the difference was not statistically significant.

2.3.3.5 *Very-low-quality evidence from the cluster RCT of 279 patients found patient education to be associated with a mean serum phosphate level 0.2 mmol/l lower (95% CI -0.3 to no difference, i.e. statistically significant) at 3 months than in patients who received usual care only.*

2.3.3.6 *Very-low-quality evidence from 1 RCT of 38 patients showed no difference in the changes observed in patients' beliefs and attitudes towards health, as measured by a 'self-efficacy survey' and a 'health beliefs survey', whether patients had received a patient education intervention or usual care only.*

Interventions including counselling compared with written material alone

Critical outcomes

2.3.3.7 *Very-low-quality evidence from 1 RCT of 50 patients showed that at 12 weeks there was no difference in the amount of deviation of the mean protein intake (estimated by 3-day diet diary) from the prescribed level of protein intake between those who received counselling-based interventions and those who received the renal units' standard written educational material following a diet history, with both means falling within the prescribed limits.*

2.3.3.8 *Very-low-quality evidence from the RCT of 50 patients showed that, as a percentage of the prescribed energy intake, those who received counselling-based interventions fell below the relevant prescription to a greater extent than those who received the renal units' standard written educational material following a diet history, when estimated by 3-day diet diary at 12 weeks (MD 9.4% less).*

Important outcomes

2.3.3.9 Very low-quality evidence from an RCT of 56 patients showed counselling-based interventions to be associated with a mean serum phosphate level 0.34 mmol/l lower (95% CI -0.58 to -0.10, i.e. statistically significant) at 3 months than in patients who received the renal units' standard written educational material following a diet history.

Multiple component interventions compared with single component interventions

Critical outcomes

2.3.3.10 Very-low-quality evidence from 1 RCT of 70 patients showed that after 1 month, significantly more patients who received multicomponent educational interventions were considered to be adherent with dietary protein prescriptions than those who received single-component educational interventions (OR 4.5 [95% CI 1.60 to 12.66, i.e. statistically significant]).

2.3.3.11 Very-low-quality evidence from the RCT of 70 patients showed that at 1 month, there was no difference in the amount of deviation of the mean protein intake (estimated by 3-day diet diary) from the prescribed level of protein intake between those who received multicomponent educational interventions and those who received single-component educational interventions.

2.3.3.12 Very-low-quality evidence from 1 RCT of 67 patients showed that after 6 months, there was no statistically significant difference in the number of patients who could have phosphate binders withdrawn from their regimen between those who received multicomponent educational interventions and those who received single-component educational interventions (OR 0.97 [95% CI 0.06 to 16.17]).

Important outcomes

2.3.3.13 *Very-low-quality evidence from 4 RCTs of 256 patients in total showed no statistically significant difference in mean serum phosphate levels between those who received multicomponent educational interventions and those who received single-component educational interventions (mean serum phosphate level 0.09 mmol/l lower [95% CI -0.23 to 0.04; mean follow-up of 3 months]).*

2.3.3.14 *Very-low-quality evidence from 1 RCT of 63 patients showed that after 2 months there was no statistically significant difference in the number of patients considered to have serum phosphate within acceptable limits between those who received multicomponent educational interventions and those who received single-component educational interventions (OR 0.93 [95% CI 0.34 to 2.52]).*

Multiple component interventions (one-off individual oral counselling + written educational material + self-management tool; regular individual oral counselling + written educational material) compared with individual patient counselling alone

Critical outcomes

2.3.3.15 *Very-low-quality evidence from 1 RCT of 70 patients showed that after 1 month, significantly more patients who received multicomponent educational interventions were adherent with dietary protein prescriptions than those who received individual patient counselling alone (OR 4.5 [95% CI 1.60 to 12.66, i.e. statistically significant]).*

2.3.3.16 *Very-low-quality evidence from the RCT of 70 patients showed that at 1 month, there was no difference in the amount of deviation of the mean protein intake (estimated by 3-day diet diary) from the prescribed level of protein intake between those who received*

multicomponent educational interventions and those who received individual patient counselling alone.

2.3.3.17 *Very-low-quality evidence from 1 RCT of 67 patients showed that after 6 months, there was no statistically significant difference in the number of patients who could have phosphate binders withdrawn from their regimen between those who received multicomponent educational interventions and those who received individual patient counselling alone (OR 0.97 [95% CI 0.06 to 16.17]).*

Important outcomes

2.3.3.18 *Very-low-quality evidence from 2 RCTs of 137 patients in total showed multicomponent educational interventions to be associated with a mean serum phosphate level 0.01 mmol/l lower (95% CI -0.10 to 0.08) than patients who received individual patient counselling alone (mean follow-up of 3 months), although the difference was not statistically significant.*

Multiple component interventions (one-off individual oral counselling + written educational material + self-management tool) compared with written material alone

Important outcomes

2.3.3.19 *Very-low-quality evidence from 1 RCT of 56 patients showed multicomponent educational interventions to be associated with a mean serum phosphate level 0.34 mmol/l lower (95% CI -0.58 to -0.10, i.e. statistically significant) at 3 months than patients who received written educational material alone.*

Multiple component interventions (interactive group counselling + written educational material) compared with video education alone

Important outcomes

2.3.3.20 *Very-low-quality evidence from 1 RCT of 63 patients showed that after 2 months, there was no statistically significant difference in the*

number of patients considered to have serum phosphate within acceptable limits between those who received multicomponent educational interventions and those who received video education alone (OR 0.93 [95% CI 0.34 to 2.52]).

2.3.3.21 *Very-low-quality evidence from the RCT of 63 patients showed multicomponent educational interventions to be associated with a mean serum phosphate level 0.05 mmol/l lower (95% CI -0.22 to 0.13) than in patients who received individual patient counselling alone at 2 months, although the difference was not statistically significant.*

Oral counselling + video + competition compared with regular individual oral counselling + written material

Important outcomes

2.3.3.22 *Very-low-quality evidence from 1 non-RCT of 81 patients showed the intervention (oral counselling and a video relating to serum phosphate control, plus a competition) to be associated with a mean serum phosphate level 0.19 mmol/l lower (95% CI -0.24 to -0.14, i.e. statistically significant) at 12 months than that in patients who received the control (oral counselling and written material relating to dietary management and phosphate binder use for serum phosphate control).*

2.3.4 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the possible outcomes and agreed that serum phosphate, changes in adherence-promoting behaviours, and adherence with dietary prescription were critical to their decision-making. Phosphate binder requirement, changes in knowledge and changes in beliefs and attitudes towards health were considered important, though not critical. The lack of evidence led to limited differentiation in the relative value of these outcomes, although following review of the evidence serum phosphate featured prominently in the GDG's discussions. Although important to decision-making, it was felt that adherence-promoting behaviours, knowledge and beliefs and attitudes towards health were only meaningful in the management of hyperphosphataemia in the context of an associated change in serum phosphate levels, rather than as endpoints themselves. In isolation, these outcomes do not necessarily translate directly into a meaningful effect in the management of serum phosphate. Therefore, when interpreting data relating to these 3 outcomes the GDG looked for both a change in the outcomes and a concurrent significant difference in serum phosphate between trial arms. Knowledge about phosphate-lowering dietary interventions was felt to be particularly far removed, or 'indirect', in its impact on serum phosphate control and was therefore downgraded in quality as a surrogate outcome. The GDG felt that improving a person's knowledge of a subject does not always bring about changes in that person's behaviour. In this way, improved knowledge relating to the dietary management of hyperphosphataemia alone does not directly necessitate better adherence with dietary prescriptions or improvements in serum phosphate control. However, it was noted that this may be different in the case of parents and carers of children with CKD, who may be more protective towards the children in their care and likely to place greater importance on advice given.
Trade-off between benefits and harms	Patient education interventions that exceed 'usual care' had a positive effect on adherence, although the evidence was limited and of low quality. Greater improvements in knowledge and beliefs and attitudes towards health following these interventions appeared to be limited when compared to usual care, and serum phosphate levels were not significantly different between the 2 groups; again, the evidence was limited and of low (or very low) quality. The GDG felt that, despite its limitations, the evidence supported the view that usual care is sufficient in improving a patient's serum phosphate control, and that interventions over and above this may not be necessary in routine practice. In defining what constitutes good 'usual' practice, the GDG noted that counselling-based interventions were more effective than written material alone, although the evidence was of very low quality and there was some uncertainty over the statistical methods employed. The GDG felt that, in their experience and in conjunction with this evidence, advisory counselling sessions with patients represent good clinical practice. It was felt that counselling-based educational sessions represent an effective opportunity to explore different dietary management options with patients, as well as to monitor their

	suitability and progress. The GDG considered individualised approaches to be particularly important as different patients will have different diets, needs and preferences. These should be evaluated through dietary assessment, from which a treatment regimen can be developed. Additionally, people learn and respond to interventions in different ways and different approaches to dietary education and management may therefore need to be explored over the course of a patient's treatment. However, it was felt that such exploration would not routinely require the use of an educational programme using multiple delivery methods (for example, including counselling sessions and comprehensive written material and videos/DVDs and self-management tools). Such interventions were not found to deliver a significant additional benefit over the effect seen following simpler, single-approach interventions, although again the quality of evidence was low or very low. Given the broad, in-depth knowledge required in formulating effective, individualised therapeutic options, the GDG felt that a specialist renal dietitian would be the most appropriate person to conduct a patient's dietary assessment and offer them individualised advice. It was also felt that early contact with a dietitian is important as a means of preventing patient misinformation, for example what constitutes phosphate-rich food and drink. The risks of misinformation can also be reduced by appropriately trained, multidisciplinary healthcare professionals/teams, who also play an important role in a patient's ongoing dietary education, reinforcing nutritional advice and providing support on a more day-to-day basis. It is important for patients, especially those in the early stages of CKD, to understand the need to manage their health and minimise the risks they face. Education empowers many patients to take steps to limit such risks and, in this instance, to minimise the impact of high phosphate levels on their bones and vasculature. The GDG noted, however, that in practice some settings do not always have adequate access to a specialist renal dietitian. In these circumstances, the use of referrals and/or forward-planning before a patient reaches stage 4 CKD would be necessary to achieve the best level of care. The GDG highlighted that, although no evidence was found for this population; children need to be considered separately because parents and/or carers provide food and drink, and because their dietary needs change as they get older. Therefore, parents and/or carers should also be educated, and the monitoring and revision of advice will need to be more frequent depending on the age of the child and their nutritional and clinical status. Because of the specific nature of children's dietary needs and habits, the GDG felt that a specialist renal dietitian, specifically a paediatric specialist renal dietitian, would be the most appropriate person to conduct a child's dietary assessment and offer the individualised advice. The multidisciplinary health professionals and teams that support a child's ongoing dietary management should be similarly aware of the specific requirements of children with CKD, and the ways in which these change over time. The GDG also felt that it is important to include information relating to phosphate binder use, giving the specific example of the need to take binders with high-phosphate snacks and not simply with meals, as

	well as the need to match binder dose with the phosphate load in the snack or meal.
Economic considerations	Early contact with a dietitian will require adequate availability. It is not just dietitians who play a role in patient education; nurses, doctors and psychologists also play an important role, and these healthcare professionals should be appropriately trained. Dietitians will have a role in educating and supporting them. The GDG noted that substantial resources and costs would be incurred in the development of complex, non-individualised programmes of multiple, concurrent educational approaches, with little evidence for additional benefit.
Quality of evidence	No studies compared the intervention of interest against a true 'no intervention' comparator, only usual care. Limited evidence was found for those not on dialysis (only 1 study), and no evidence on education interventions in children was found. Definitions of usual care varied across the studies, and were not always clear or explicit. A significant amount of heterogeneity/diversity was observed across the interventions examined; it was difficult to pool studies to produce overarching interpretations of effectiveness. Content, in addition to the structure of the interventions, varied widely across the studies; for example, some interventions focused on serum phosphate control through diet, some on serum phosphate control more generally (for example, the use of binders), and some on more general dietary management in CKD (for example, information on fluid intake). There were differences between the papers in the populations studied. Most notably, some studies included only those expected to be adherent, some only those expected to be non-adherent. The GDG questioned how applicable the evidence is to a UK setting, particularly as many of the studies were not conducted in the UK: 1 in Iran, 1 in China, 1 in Australia and a number in the US. Also, many of the studies were performed in outpatient renal clinics in hospitals, and therefore do not capture the care of patients in primary care settings or when hospitalised. Additionally, a number of the studies included only patients who were not anticipated to have good adherence to the prescribed diets and who had not previously received any dietary education. Furthermore, only 1 of the 9 included studies, which was small in size (n=62) and duration (12 weeks), examined the effectiveness of patient education strategies in patients not on dialysis. For these reasons, the population in the evidence base may not be generalisable to the whole population of patients with CKD stages 4, 5 or 5D in England and Wales. Adherence with dietary prescription was not regularly reported; instead, papers reported mean actual intakes for each group, which the reviewer then compared to prescriptions, producing a surrogate measure of adherence. Reporting in many of the studies was poor: details of study designs were often unclear, results were not always cited in the text of the papers, requiring the reviewer to read the data off available graphs, and 1 paper did not contain a statistics section leaving uncertainty as to the measure of variance used. Unit-of-analysis errors were also common, with analyses not following the intent-to-treat principle, and

	2 studies had follow-up periods that the GDG considered too short (less than 3 months).
Other considerations	In the context of the evidence reviewed, the 'standard care' provided seems to be sufficient for educating patients, although what constitutes 'standard care' is likely to vary across the UK. Concerns were raised that some patients receive a level of care that is below the standard of the studies reviewed, particularly in the long periods of time they wait to receive dietary advice. Nurses play a significant role in the education process. They may have the most contact and often the greatest rapport with patients, and are important members of the multidisciplinary teams in reinforcing and supporting implementation of the nutritional advice developed by the dietitian. The GDG noted relevant recommendations in 'Chronic kidney disease' (NICE clinical guideline 73).

2.3.5 Recommendations and research recommendations for patient information strategies

Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203.

2.4 Use of phosphate binders in people with stage 4 or 5 CKD who are not on dialysis

This section was updated and replaced in 2018. See www.nice.org.uk/guidance/ng203/evidence for the 2018 evidence reviews.

2.5 Use of phosphate binders in people with stage 5 CKD who are on dialysis

This section was updated and replaced in 2018. See www.nice.org.uk/guidance/ng203/evidence for the 2018 evidence reviews.

2.6 Use of supplements in people with stage 4 or 5 CKD who are not on dialysis

2.6.1 Review question

For people with stage 4 or 5 CKD who are not on dialysis, are prescribed supplements, alone or in conjunction with other interventions, effective compared to placebo or other treatments in managing serum phosphate and its associated outcomes? Which are the most effective supplements?

2.6.2 Evidence review

This review question focused on the use of supplements in the prevention and treatment of hyperphosphataemia in patients with stage 4 or 5 CKD who are not on dialysis. These supplements could consist of a variety of vitamins and minerals.

For this review question, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews and the Centre for Reviews and Dissemination) using a broad search strategy, pulling in all papers relating to the management of hyperphosphataemia in CKD using supplements. Only RCTs that compared a supplementation intervention with either a placebo or another comparator in patients with stage 4 or 5 CKD who are not on dialysis were considered for inclusion.

Trials were excluded if:

- the population included people with CKD stages 1 to 3 **or**
- the population included people on dialysis **or**
- supplementation was intended for any reason other than for the management of hyperphosphataemia.

From a database of 2020 abstracts, 20 full-text articles were ordered, though no papers were found to be suitable for inclusion in the analysis.

Supplementation using vitamin D and its metabolites was also not considered for this review and was excluded at the scoping stage. It was felt that their effectiveness is not disputed and they are already an accepted and cost-effective part of standard clinical practice.

2.6.3 Evidence statements

2.6.3.1 No evidence on the clinical effectiveness of supplements in the management of hyperphosphataemia in people with CKD stages 4 or 5 who are not on dialysis was identified.

2.6.4 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that those considered critical or important for decision-making were the same as those in the reviews of phosphate binder effectiveness.
Trade-off between benefits and harms	No evidence was found to examine the benefits and harms of using supplements in the management of hyperphosphataemia in people with stage 4 or 5 CKD who are not on dialysis. However, the GDG felt that the evidence found in patients with CKD stage 5 who are on dialysis could be extrapolated to this population because it is likely that the efficacy of the intervention would be similar, regardless of whether the person was on dialysis or not. See '3.7 Use of supplements in people with stage 5 CKD who are on dialysis' for the review of this evidence.
Economic considerations	Because the GDG did not feel that the available evidence supported the use of supplements, it was not necessary to conduct a cost-effectiveness analysis for this question.
Quality of evidence	No evidence was identified for the use of supplements in the management of hyperphosphataemia in people with stage 4 or 5 CKD who are not on dialysis.
Other considerations	No other considerations were identified.

2.7 Use of supplements in people with stage 5 CKD who are on dialysis

2.7.1 Review question

For people with stage 5 CKD who are on dialysis, are prescribed supplements, alone or in conjunction with other interventions, effective compared to placebo or other treatments in managing serum phosphate and its associated outcomes? Which is the most effective prescribed supplement?

2.7.2 Evidence review

This review question focused on the use of supplements in the prevention and treatment of hyperphosphataemia in patients with stage 5 CKD who are on dialysis. These supplements could consist of a variety of vitamins and minerals, though in the evidence located included: niacinamide, calcium and L-carnitine supplementation.

For this review question, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews and the Centre for Reviews and Dissemination) using a broad search strategy, pulling in all papers relating to the management of hyperphosphataemia in CKD using supplements. Only RCTs that compared a supplement with either a placebo or another comparator in patients with stage 5 CKD who are on dialysis were considered for inclusion.

Trials were excluded if:

- the population included people with CKD stages 1 to 4 **or**
- the population included people with CKD stage 5 who were not on dialysis **or**
- supplementation was intended for any reason other than for the management of hyperphosphataemia.

From a database of 2020 abstracts, 20 full-text articles were ordered and 5 papers describing 5 primary studies were selected (Young et al., 2009; Shahbazian et al., 2011; Rudnicki et al., 1993; Chertow et al., 1999; Cibulka et

al., 2007). No paediatric studies meeting the inclusion criteria were found. Table 9 lists the details of the included studies.

Supplementation using vitamin D and its metabolites was also not considered for this review and was excluded at the scoping stage. It was felt that their effectiveness is not disputed and they are already an accepted and cost-effective part of standard clinical practice.

There was pooling of the 2 studies comparing niacinamide supplementation against placebo, although there was some heterogeneity present. This heterogeneity resulted from the use of different concurrent interventions that are known to impact the outcomes of interest, but also the different types of dialysis used.

Where meta-analysis was possible, a forest plot is also presented. Mean differences (MDs) were calculated for continuous outcomes and odds ratios (ORs) for binary outcomes, as well as the corresponding 95% confidence intervals (CIs) where sufficient data were available.

Table 9 Summary of included studies for the use of supplements in adults with stage 5 CKD who are on dialysis

Study	Population	Intervention	Control	Follow-up
Nicotinamide compared with placebo				
Young et al, 2009 RCT Missouri, US	Randomised = 17 (intervention = 8; control = 9) Analysed = 14 (intervention = 7; control = 7) Age > 18 years On peritoneal dialysis for > 3 months Dose of phosphate binder(s) stable over the previous 2 weeks Plasma phosphate > 4.9 mg/dl (i.e. 1.6 mmol/l) based on the most recent laboratory data within 1 month of enrolment (note: this threshold is within recommended phosphate levels, though at the upper end) Patients with phosphate values > 3.9 mg/dl meeting all other inclusion criteria were eligible, if consenting, for a reduction in the current phosphate binder dose followed by repeat screening within 2–4 weeks; they were then eligible for continued participation if the repeat phosphate value exceeded 4.9 mg/dl Baseline serum phosphate (mean±SD): Intervention = 1.65±0.32 mmol/l Control = 1.74±0.23 mmol/l See evidence tables in appendix E for full inclusion/exclusion criteria	Nicotinamide (250 mg per capsule) and placebo were packaged as identically appearing capsules Dosing increased throughout study period: study medication or placebo was started at 250 mg twice daily, increased to 500 mg twice daily after 2 weeks and to 75 0 mg twice daily after 4 weeks Changes in phosphate binder dose were not allowed except if phosphate values exceeded 6.5 mg/dl (i.e. 2.1 mmol/l) or fell below 3 mg/dl (i.e. 1.0 mmol/l) Active vitamin D and cinacalcet doses were required to remain stable - i.e. followed pre-study protocol	Placebo packaged as identically appearing capsules Dosing increased throughout study period: study medication or placebo was started at 250 mg twice daily, increased to 500 mg twice daily after 2 weeks and to 750 mg twice daily after 4 weeks Changes in phosphate binder dose were not allowed except if phosphate values exceeded 6.5 mg/dl (i.e. 2.1 mmol/l) or fell below 3 mg/dl (i.e. 1.0 mmol/l) Active vitamin D and cinacalcet doses were required to remain stable - i.e. followed pre-study protocol	8 weeks Serum phosphate and corrected calcium measured every 2 weeks Incidence of adverse events (diarrhoea) recorded for the 8-week study period
Shahbazian et al, 2011 RCT Ahvaz, Iran	Randomised = 48 (intervention = 24; control = 24) Analysed = 48 Age ≥ 18 years Fasting serum phosphate ≥ 5 mg/dl (i.e. ≥ 1.6 mmol/l) (note: this threshold is within recommended phosphate levels, though at the very upper end) Maintaining on haemodialysis for more than 2 months	Immediate release nicotinamide tablets (500 mg) During the first 4 weeks, nicotinamide was administered 500 mg/day, and then it was administered 1,000 mg/day in weeks 5 to 8. In case of adverse effects, phosphate level ≤ 3.5 (i.e. 1.1 mmol/l) or > 8 mg/dl (i.e. 2.6 mmol/l),	Placebo tablets Usual doses of calcium carbonate - i.e. followed pre-study protocol (note: unclear if calcium carbonate taken as a supplement or a phosphate binder)	8 weeks Serum phosphate and corrected calcium measured every 4 weeks

	Constant dosage of phosphate binders during past 2 weeks Patients had residual renal function of < 10 ml/min Dialysate concentration of calcium was similar for all patients (in these centres, only 1 kind of dialysate is used) Baseline serum phosphate (mean±SD): Intervention = 1.91±0.19 mmol/l Control = 1.88±0.11 mmol/l See evidence tables in appendix E for full inclusion/exclusion criteria	thrombocytopenia (platelet counts less than 150,000/mm^3), or clinical findings of low platelet count, the research committee decided on adjusting the dose or other necessary measures Usual doses of calcium carbonate - i.e. followed pre-study protocol (note: unclear if calcium carbonate taken as a supplement or a phosphate binder)		Incidence of adverse events (diarrhoea) recorded for the 8-week study period
Sevelamer hydrochloride + calcium supplementation compared with sevelamer hydrochloride alone				
Chertow et al, 1999 RCT US	Randomised = 71 (intervention = 36; control = 35) Analysed = 71 Age ≥ 18 years Thrice weekly haemodialysis for at least 3 months Regular calcium- and/or aluminium-based phosphate binders, with or without vitamin D metabolite replacement therapy at stable doses for at least 1 month before screening; all pre-study phosphate binders discontinued 2 weeks before treatment phase Participants whose serum phosphate concentration rose to 6.0 mg/dl (i.e. 1.9 mmol/l) or above after 2-week phosphate binder washout period were entered into treatment phase; participants whose serum phosphate rose to above 12 mg/dl (i.e. 3.9 mmol/l) were entered immediately into the treatment phase without necessarily completing the 2-week washout Baseline serum phosphate (mean±SD): Intervention = 2.51±0.10 mmol/l Control = 2.75±0.13 mmol/l See evidence tables in appendix E for full inclusion/exclusion criteria	900 mg of elemental calcium taken in the form of calcium carbonate once nightly on a on an empty stomach Initial dose of sevelamer hydrochloride (RenaGel) was determined by the highest level of serum phosphate during the 2-week phosphate binder washout period: 2 x 465 mg capsules 3 times daily with meals for serum phosphate concentrations > 6.0 mg/dl (i.e. 1.9 mmol/l) and < 7.5 mg/dl (i.e. 2.4 mmol/l); 3 x 465 mg capsules 3 times daily with meals for serum phosphate concentrations > 7.5 mg/dl (i.e. 2.4 mmol/l) and < 9.0 mg/dl (i.e. 2.9 mmol/l); 4 x 465 mg capsules 3 times daily with meals for serum phosphate concentrations > 9.0 mg/dl (i.e. 2.9 mmol/l) Sevelamer hydrochloride doses were titrated up and down by 3 capsules per day every 3 weeks (at 3, 6 and 9 weeks after treatment commencement), with the goal of achieving serum phosphate	Initial dose of sevelamer hydrochloride (RenaGel) was determined by the highest level of serum phosphate during the 2-week phosphate binder washout period: 2 x 465 mg capsules 3 times daily with meals for serum phosphate concentrations > 6.0 mg/dl (i.e. 1.9 mmol/l) and < 7.5 mg/dl (i.e. 2.4 mmol/l); 3 x 465 mg capsules 3 times daily with meals for serum phosphate concentrations > 7.5 mg/dl (i.e. 2.4 mmol/l) and < 9.0 mg/dl (i.e. 2.9 mmol/l); 4 x 465 mg capsules 3 times daily with meals for serum phosphate concentrations > 9.0 mg/dl (i.e. 2.9 mmol/l) Sevelamer hydrochloride doses were titrated up and down by 3 capsules per day every 3 weeks (at 3, 6 and 9 weeks after treatment commencement), with the goal of achieving serum phosphate concentrations between 2.5 (i.e. 0.6 mmol/l) and 5.5 mg/dl (i.e. 1.8 mmol/l)	12 weeks Incidence of mortality and adverse events (vomiting, nausea, constipation, and diarrhoea) recorded for the 12-week study period Serum phosphate and calcium measured weekly

		concentrations between 2.5 (i.e. 0.6 mmol/l) and 5.5 mg/dl (i.e. 1.8 mmol/l) Participants were asked to maintain their usual eating habits without any intentional changes in dietary restrictions Participants were not permitted to take any aluminium-based products, or any additional calcium-based products Vitamin D metabolite doses were maintained at baseline levels except in the event of significant hypo- or hypercalcaemia	Participants were asked to maintain their usual eating habits without any intentional changes in dietary restrictions Participants were not permitted to take any calcium- or aluminium-based products Vitamin D metabolite doses were maintained at baseline levels except in the event of significant hypo- or hypercalcaemia	
L-carnitine supplementation compared with placebo				
Cibulka et al, 2007 RCT Czech Republic	Randomised = 112 Analysed = 83 (intervention = 44; control = 39) Criteria for randomisation: Regular haemodialysis – 4 hours 3 times weekly All patients had a GFR < 0.2 ml/sec (i.e. < 12 ml/min) Baseline serum phosphate (median (range)): Intervention = 1.74 mmol/l (0.71 – 3.71) Control = 1.71 mmol/l (1.02 – 3.50)Exclusion criteria (for those who were randomised but who were not included in the analysis): kidney transplant; non-adherence; change of residence; restitution of kidney function; change in vitamin D dose during trial	15 mg of L-carnitine/kg of body weight in a short intravenous infusion after each haemodialysis session (i.e. 3 times weekly) All patients received calcium carbonate phosphate binder therapy Patients continued pre-study vitamin D treatment	Isotonic solution of sodium chloride in a short intravenous infusion after each haemodialysis session (i.e. 3 times weekly) All patients received calcium carbonate phosphate binder therapy Patients continued pre-study vitamin D treatment	6 months Incidence of mortality recorded for the 6-month study period Serum phosphate and calcium measured every 3 months
Abbreviations: Ca, calcium ions; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; RCT, randomised controlled trial; SD, standard deviation.				

Summary GRADE profile 51 Nicotinamide compared with placebo in adults with stage 5 CKD who are on dialysis

Outcome	Number of Studies	Number of patients		Effect	Quality
		Nicotinamide[1]	Placebo[1]		
Serum phosphate (pooled) 8-week follow-up	2 RCTs Shahbazian et al, 2011 Young et al, 2009	31	31	*Absolute effect* MD = 0.30 mmol/l lower (95% CI:0.42 to 0.17 lower)	Very low
Change in serum phosphate 8-week follow-up	1 RCT Young et al, 2009	7	7	*Absolute effect* MD = 0.36 mmol/l lower (95% CI: 0.64 to 0.07 lower)	Very low
Serum phosphate (number of patients to experience an increase in serum phosphate from baseline to the end of the study period) 8-week follow-up	1 RCT Young et al, 2009	1/7 (14.3%)	5/7 (71.4%)	*Relative effect* OR = 0.07 (95% CI: 0.01 to 0.97) *Absolute effect* 57 fewer per 100 (1 fewer to 69 fewer)	Very low
Adverse events – diarrhoea (number of patients to experience diarrhoea) 8-week follow-up	2 RCTs Shahbazian et al, 2011 Young et al, 2009	5/32 (15.6%)	0/33 (0%)	*Relative effect* OR = 6.78 (95% CI: 0.73 to 62.69)	Very low
Serum calcium 8-week follow-up	1 RCT Young et al, 2009	7	7	*Absolute effect* MD = 0.05 mmol/l lower (95% CI: 0.21 lower to 0.11 higher)	Very low

[1] The 2 studies had different co-treatments, received by both the intervention and control groups:

Shahbazian et al, 2011: pre-study calcium carbonate regimen (note: unclear if calcium carbonate was used as a binder or as a supplement)

Young et al, 2009: pre-study phosphate binder, active vitamin D and cinacalcet regimens

Abbreviations: CI, confidence interval; MD, mean difference; OR, odds ratio; RCT, randomised controlled trial.

Summary GRADE profile 52 Sevelamer hydrochloride + calcium supplementation (+ pre-study vitamin D regimen) compared with sevelamer hydrochloride (+ pre-study vitamin D regimen) in adults with stage 5 CKD who are on dialysis

Outcome	Number of Studies	Number of patients		Effect	Quality
		Sevelamer hydrochloride + calcium supplementation (+ pre-study vitamin D regimen)	Sevelamer hydrochloride (+ pre-study vitamin D regimen)		
Mortality (number of deaths among patients hospitalised during study) 12-week follow-up	1 RCT Chertow et al, 1999	2/36 (5.6%)	0/35 (0%)	*Relative effect* OR = 0.21 (95% CI: 0.01 to 4.44)	Very low
Serum phosphate 12-week follow-up	1 RCT Chertow et al, 1999	36	35	*Absolute effect* MD = 0.31 mmol/l lower (95% CI: 0.59 to 0.04 lower)	Very low
Change in serum phosphate 12-week follow-up	1 RCT Chertow et al, 1999	36	35	*Absolute effect* MD = 0.03 mmol/l lower (95% CI: 1.83 lower to 1.77 higher)	Very low
Serum phosphate (number of patients to achieve a therapeutic response - serum phosphate at or below washout level or <1.78mmol/l) 12-week follow-up	1 RCT Chertow et al, 1999	35/36 (97.2%)	33/35 (94.3%)	*Relative effect* OR = 1.03 (95% CI: 0.14 to 7.75) *Absolute effect* 0 more per 100 (from 24 fewer to 5 more)	Very low
Change in serum calcium 12-week follow-up	1 RCT Chertow et al, 1999	36	35	*Absolute effect* MD = 0.08 mmol/l higher (95% CI:0.01 lower to 0.16 higher)	Very low
Serum calcium (% of patients to experience hypercalcaemia) 12-week follow-up	1 RCT Chertow et al, 1999	21.1%	2.4%	*Relative effect* OR = 10.88 (95% CI: 2.77 to 42.70) *Absolute effect*	Very low

				19 more per 100 (4 to 49 more)	
Note: the 2 groups were not comparable in terms of their serum phosphate at the start of the treatment period (the mean difference was statistically significant at -0.24 mmol/l (95% CI -0.29 to -0.19)), nor their serum calcium x phosphorus product (both were higher in the control group). It also appears that there was a greater prevalence of hypercalcaemia in the intervention group at the start of treatment. Additionally, vitamin D use different at baseline, but the difference was not statistically significant (intervention group = 60% use vitamin D versus 42% in control group [p = 0.16]) Abbreviations: CI, confidence interval; MD, mean difference; OR, odds ratio; RCT, randomised controlled trial.					

Summary GRADE profile 53 L-carnitine supplementation (+ calcium carbonate + pre-study vitamin D regimen) compared with placebo (+ calcium carbonate + pre-study vitamin D regimen) in adults with stage 5 CKD who are on dialysis

Outcome	Number of Studies	Number of patients		Effect	Quality
		L-carnitine supplementation (+ calcium carbonate + pre-study vitamin D regimen)	Placebo (+ calcium carbonate + pre-study vitamin D regimen)		
Mortality (number of deaths among patients) 6-month follow-up	1 RCT Cibulka et al, 2007	7/44	9/39	*Relative effect* OR = 0.63 (95% CI: 0.21 to 1.89) *Absolute effect* 7 fewer per 100 (17 fewer to 13 more)	Very low
Serum phosphate 6-month follow-up	1 RCT Cibulka et al, 2007	44	39	*Absolute effect* Difference in medians = 0.08 mmol/l lower	Very low
Serum calcium 6-month follow-up	1 RCT Cibulka et al, 2007	44	39	*Absolute effect* Difference in medians = 0.04 mmol/l lower	Very low
Abbreviations: CI, confidence interval; OR, odds ratio; RCT, randomised controlled trial.					

See appendix E for the evidence tables and GRADE profiles in full.

2.7.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual'.

Use of supplements in people with stage 5 CKD who are on dialysis

Nicotinamide compared with placebo

Critical outcomes

2.7.3.1 Very-low-quality evidence from 2 RCTs of 62 participants in total showed nicotinamide supplementation to be associated with a mean serum phosphate level 0.30 mmol/l lower (95% CI -0.42 to -0.17, i.e. statistically significant) than that associated with placebo at 8 weeks.

2.7.3.2 Very-low-quality evidence from 1 RCT of 14 participants showed that at 8 weeks, nicotinamide supplementation was associated with a mean decrease in serum phosphate levels of 0.23 mmol/l (SD 0.29) and placebo with a mean increase in serum phosphate levels of 0.13 mmol/l (SD 0.26) (MD 0.36 mmol/l lower [95% CI -0.64 to -0.07, i.e. statistically significant]).

2.7.3.3 Very-low-quality evidence from 1 RCT of 14 participants showed that a smaller proportion of participants that received nicotinamide supplementation experienced an increase in serum phosphate from baseline to the end of the 8-week study period than among those that received placebo (OR 0.07 [95% CI 0.01 to 0.97, i.e. statistically significant]).

Important outcomes

2.7.3.4 Very-low-quality evidence from 2 RCTs of 65 participants showed no statistically significant difference in the proportion of participants that experienced diarrhoea during the 8-week study period, between those that received nicotinamide supplementation and those that received placebo (OR 6.78 [95% CI 0.73 to 62.69]).

2.7.3.5 Very-low-quality evidence from 1 RCT of 14 participants showed no statistically significant difference in mean serum corrected calcium level between those that received nicotinamide supplementation and those that received placebo at 8 weeks (MD 0.05 mmol/l lower [95% CI -0.21 to 0.11]).

Sevelamer hydrochloride + calcium supplementation compared with sevelamer hydrochloride

Critical outcomes

2.7.3.6 Very-low-quality evidence from 1 RCT of 71 participants showed no statistically significant difference in the number of deaths during the 12-week study period between those that received sevelamer hydrochloride and calcium supplementation and those that received sevelamer hydrochloride alone (OR 0.21 [95% CI 0.01 to 4.44]).

2.7.3.7 Very-low-quality evidence from 1 RCT of 71 participants showed sevelamer hydrochloride and calcium supplementation to be associated with a mean serum phosphate level 0.31 mmol/l lower (95% CI -0.59 to -0.04, i.e. statistically significant) than that associated with sevelamer hydrochloride alone at 6 months[15].

2.7.3.8 Very-low-quality evidence from 1 RCT of 71 participants showed no statistically significant difference in the mean change in serum phosphate levels during the 6-month study period between those that received sevelamer hydrochloride and calcium supplementation and those that received sevelamer hydrochloride alone (MD 0.03 mmol/l lower [95% CI -1.83 to 1.77]).

2.7.3.9 Very-low-quality evidence from 1 RCT of 71 participants showed no statistically significant difference in the number of patients to achieve a therapeutic response (defined as serum phosphate at or

[15] Note: the difference in mean serum phosphate at treatment initiation was statistically significant between the 2 groups, with a mean in the group taking sevelamer hydrochloride with supplemental calcium of 2.51 mmol/l and of 2.75 mmol/l in the group taking sevelamer hydrochloride alone (MD 0.24 mmol/l (95% CI -0.29 to -0.19)).

below the participant's pre-binder washout level or < 1.78 mmol/l) during the 12-week study period between those that received sevelamer hydrochloride and calcium supplementation and those that received sevelamer hydrochloride alone (OR 1.03 [95% CI 0.14 to 7.75]).

Important outcomes

2.7.3.10 *Very-low-quality evidence from 1 RCT of 71 participants showed no statistically significant difference in the mean change in serum calcium levels during the 6-month study period between those that received sevelamer hydrochloride and calcium supplementation and those that received sevelamer hydrochloride alone (MD 0.08 mmol/l higher [95% CI -0.01 to 0.16]).*

2.7.3.11 *Very-low-quality evidence from 1 RCT of 71 participants showed that a greater proportion of participants that received sevelamer hydrochloride and calcium supplementation experienced hypercalcaemia during the 12-week study period than among those that received sevelamer hydrochloride alone (OR 10.88 [95% CI 2.77 to 42.70, i.e. statistically significant]).*

L-carnitine supplementation compared with placebo

Critical outcomes

2.7.3.12 *Very-low-quality evidence from 1 RCT of 83 participants showed no statistically significant difference in the number of deaths during the 6-month study period between those that received L-carnitine supplementation and those that received placebo (OR 0.63 [95% CI 0.21 to 1.89]).*

2.7.3.13 *Very-low-quality evidence from 1 RCT of 83 participants showed L-carnitine supplementation to be associated with a median serum phosphate level 0.08 mmol/l lower than that associated with placebo.*

Important outcomes

2.7.3.14 Very-low-quality evidence from 1 RCT of 83 participants showed L-carnitine supplementation to be associated with a median serum calcium level 0.04 mmol/l lower than that associated with placebo.

2.7.4 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that those considered critical or important for decision-making were the same as those in the reviews of phosphate binder effectiveness.
Trade-off between benefits and harms	From the 2 studies identified, the GDG noted that nicotinamide appears to be effective in lowering serum phosphate levels. Fewer patients experienced an increase in these levels when taking nicotinamide, instead achieving a greater mean decrease in serum phosphate over the study period and lower mean levels at the endpoint. It also appeared that the incidence of diarrhoea was not significantly different between those taking the supplement and those taking placebo. However, the GDG felt that the study periods involved (both studies lasted for 8 weeks) and the sizes of the samples used (14 and 48 patients) were not sufficient to detect a significant difference in the risk of experiencing side effects. The GDG was concerned that the side effects of nicotinamide could be comparable to those associated with nicotinic acid, including: nausea, vomiting, abdominal pain and dyspepsia; flushing; pruritus and rash. No evidence was found on these adverse effects. Additionally, no data were found concerning the mortality, adherence or quality of life associated with this supplement. One study was found to examine the effectiveness of calcium supplementation in controlling serum phosphate. The comparison was made between sevelamer hydrochloride supplemented with calcium carbonate and sevelamer hydrochloride alone. The GDG distinguished calcium carbonate's use as a supplement from its use as a binder by the timing of its consumption; calcium carbonate supplementation is taken on an empty stomach and calcium carbonate binders are taken with meals. The addition of supplemental calcium to sevelamer hydrochloride was associated with a significantly lower mean serum phosphate level at the study's end compared to sevelamer hydrochloride alone. However, the GDG concluded that this was not due to the intervention's greater effectiveness in controlling serum phosphate because the intervention group had a significantly lower mean serum phosphate level at the start of treatment. This view was further supported by the finding that there was not a significant difference between the mean changes in serum phosphate of the 2 groups over the course of the study. The GDG noted that the use of additional calcium supplementation did, however, result in an increase in hypercalcaemic events and an almost statistically significant increase in mean serum calcium. The GDG felt that there were considerable concerns over when calcium

	carbonate should and should not be given, and how this might link to the binders that an individual may or may not be given. The available evidence only supports the use of calcium carbonate as a phosphate binder (reviewed in section 3.5), taken with food not on an empty stomach. The GDG noted that the need to take any phosphate binder with a meal, as opposed to as a supplement on an empty stomach, was an important step in ensuring therapeutic success. On reviewing all available evidence, the GDG did not feel that the use of any of the above supplements for the sole purpose of actively controlling serum phosphate could be recommended, particularly as the use of supplements could add further to the treatment burden already experienced by patients on a demanding regimen. The GDG felt that the evidence outlined above could be extrapolated to those with CKD stages 4 and 5 who are not on dialysis and to children.
Economic considerations	Because the GDG did not feel that the available evidence supported the use of supplements, it was not necessary to conduct a cost-effectiveness analysis for this question.
Quality of evidence	No data were available for age groups other than adults. No evidence was found relating to cardiovascular calcification scores, adherence and quality of life, and the GDG also noted the short length of follow-up in the trials that studied mortality. A range of co-treatments were used across the studies, and concerns were noted over their potential influence as confounders. In particular, heterogeneity was noted for the 2 studies pooled in order to assess the effectiveness of nicotinamide. The co-treatments in 1 paper consisted of the patients' pre-study phosphate binder, vitamin D and cinacalcet regimens, and the patients' pre-study calcium carbonate regimen in the other. Additionally, the types of dialysis used were different in the 2 papers: peritoneal dialysis and maintenance haemodialysis respectively. Reporting in many of the studies was poor. For example, details of study designs were often unclear and results were not always cited in the text of the papers, requiring the reviewer to read the data off available graphs. Unit-of-analysis errors were also common, with analyses not following the intent-to-treat principle.
Other considerations	The use of supplementation in the management of hyperphosphataemia could add further to the treatment burden already experienced by patients on a demanding regimen.

2.7.5 Recommendations and research recommendations for use of supplements in people with stage 5 CKD who are on dialysis

Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203.

2.8 Sequencing of treatments

2.8.1 Review question

In the management of hyperphosphataemia in people with stage 4 or 5 CKD, in what order should available treatments be considered? What are the clinical indications for commencing each?

2.8.2 Evidence review

This review question focused on the sequencing of interventions in the prevention and treatment of hyperphosphataemia in patients with stage 4 or 5 CKD, including those on dialysis. These interventions could include dietary interventions, phosphate binders, supplements including vitamin D, and dialysis.

For this review question, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Health Technology Assessment Database [HTA] and the Database of Abstracts of Reviews of Effects [DARE]). A broad search strategy was used, pulling in all papers relating to the sequencing of interventions in the management of hyperphosphataemia in patients with CKD. RCTs, quasi-RCTs, systematic reviews, non-randomised controlled trials, cohort studies, cross-sectional studies and case-control studies were eligible for inclusion.

Trials were excluded if:

- the population included people with stages 1 to 3 CKD **or**

- they did not compare a sequence of interventions with another sequence of interventions.

From a database of 1868 abstracts, 16 full-text articles were ordered, although no papers were found to be suitable for inclusion in the analysis.

2.8.3 Evidence statements

2.8.3.1 No evidence was identified on the sequencing of interventions in order to maximise the management of hyperphosphataemia in people with stage 4 or 5 CKD, nor in people with stage 5 CKD who are on dialysis.

2.8.4 Health economic modelling

Health economic analysis within this guideline focused on evaluation of phosphate binders for people with stage 5 CKD who are on dialysis. These results assisted the GDG in making recommendations regarding the sequencing of phosphate binders. See section 3.5.4 and appendix F for full details on the health economic analysis and modelling carried out for the guideline.

2.8.5 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that those considered critical or important for decision-making were the same as those in the reviews of phosphate binder effectiveness.
Trade-off between benefits and harms	Although no evidence was found concerning the relative effectiveness of different treatment sequences, the GDG reached a consensus regarding best practice, using their clinical knowledge and experience. The GDG felt strongly that the 2 key interventions for the management of hyperphosphataemia in people with advanced CKD are, as first-line, dietary management and, as second-line, phosphate binders. They also emphasised the cyclical nature of this sequence, stressing that clinicians should continue to periodically review the dietary and binder regimens throughout the treatment pathway. The sequencing of these 2 interventions in this manner was determined through consensus among the GDG. The GDG noted that dialysis efficacy and vitamin D and its analogues are known to influence serum phosphate control. However, it was felt that these are not part of the primary treatment sequence of hyperphosphataemia, rather they fall in parallel. By this, the GDG meant that, while they impact serum phosphate, these interventions would be brought in to the treatment pathway for reasons other than

	hyperphosphataemia: for example, vitamin D for management of serum calcium, serum PTH and/or hyperparathyroidism, and dialysis for severe decline in renal function. For this reason, the GDG did not feel it appropriate to specify the clinical conditions in which vitamin D or dialysis should be initiated within the treatment of hyperphosphataemia. However, acknowledging their impact on serum phosphate (and other relevant biochemical parameters, such as serum calcium), they noted that diet and binder prescriptions should be reviewed when vitamin D or dialysis regimens are initiated or adjusted. GDG discussions regarding the sequencing of phosphate binders were included in earlier reviews (see sections 3.4 and 3.5).
Economic considerations	No health economic evidence was available to inform the GDG's consideration of the optimal sequence of different modes of treatment. However, the de novo health economic model developed to examine the cost–utility of phosphate binders provided evidence on the cost-effectiveness of different sequences of binders (see section 3.5.4). It should be noted that, in the GDG's experience, different phosphate binders may be used in combination, rather than wholesale switching from one to another. The model was not able to explore the cost-effectiveness of different combinations of phosphate binders due to a complete absence of evidence on the effectiveness of such combinations.
Quality of evidence	No evidence was found to examine the effectiveness of different treatment sequences for the management of hyperphosphataemia in people with stage 4 or 5 CKD, including those on dialysis.
Other considerations	The GDG felt it important to note the necessity of continuous, regular monitoring of the treatment regimen used to manage a patient's serum phosphate, as well as the importance of adjusting the regimen when a patient's phosphate control is not at the desired level. In addition to taking into account the impact of dialysis and vitamin D on the effectiveness of the regimen, it was felt that adherence should also be taken into consideration at each review.

2.8.6 Recommendations and research recommendations for sequencing of treatments

Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203.

Research recommendations

See appendix B for full details of research recommendations.

Research recommendation B5

For adults with stage 4 or 5 CKD, including those on dialysis, what is the most effective sequence or combination of phosphate binders to control serum phosphate?

3 References

Dietary management for people with stage 4 or 5 CKD who are not on dialysis

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Dietary management for people with stage 5 CKD who are on dialysis

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Use of phosphate binders in children with stage 5 CKD who are on dialysis

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No studies found

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Sequencing of treatments

No studies found

4 Glossary and abbreviations

Glossary

Calcium

Calcium is a mineral in the blood, but can also be found throughout the body. Its primary function is to work in conjunction with phosphate to form teeth and bones. However, it also plays a number of other roles in the body, including in the clotting of blood, the transmission of nerve impulses, and the appropriate support of connective tissue.

It enters the blood through the digestion and absorption of food and drink in the intestine. The kidneys control the amount of phosphate in the blood, removing excess and passing it out of the body in the urine. Calcium is also removed from the blood through its incorporation in new bone.

Serum calcium can be measured in a number of different forms.

- 'Ionised', or 'free', serum calcium is the biologically active proportion of the calcium in the blood. In other words, it is freely flowing in the blood and not attached to proteins.
- 'Total' serum calcium is the ionised calcium plus any calcium in the blood that is bound to proteins. The main purpose of this binding is the transport of calcium around the body, and the main protein with which this occurs is albumin.

'Corrected' serum calcium is an estimate of the total serum calcium. The calculation attempts to account for the amount of albumin-bound calcium in the blood, and gives an estimate of what the total serum calcium would be if serum albumin levels were within normal ranges. A typical correction is that for every 1 g/l that the albumin concentration is below this mean, the calcium concentration is 0.02 mmol/l below what it would be if the albumin concentration was normal.

Ionised serum calcium does not vary with the albumin level. It is therefore useful to measure ionised serum calcium when the serum albumin is not

within normal ranges, or when a calcium disorder is suspected despite a normal total calcium level.

Chronic kidney disease (CKD)

The term ‘chronic kidney disease’ describes abnormal kidney function and/or structure. It is defined as ‘chronic’ as the condition is long-lasting and often progresses over time.

The US ‘National Kidney Foundation kidney disease outcomes quality initiative’ (NKF-KDOQI) classification divides CKD into 5 stages according to the extent of a person’s loss of renal function. Stages 4 and 5, the stages covered in this guideline, are the most advanced stages of the condition. Stage 4 is defined by a glomerular filtration rate (GFR) of 15–29 ml/min/1.73 m^2, and stage 5 by a GFR of less than 15 ml/min/1.73 m^2. A GFR of over 90 ml/min/1.73 m^2 is considered normal unless there is other evidence of kidney disease.

A decline in, or absence of, kidney function leads to a range of adverse effects, including: fluid retention, anaemia, abnormal levels of lipids in the blood, protein–energy malnutrition and disturbances in bone and mineral metabolism. Additionally, CKD often exists together with other conditions, such as cardiovascular disease and diabetes.

Dietary management

Dietary management is, in general, a non-pharmacological approach to managing hyperphosphataemia involving the adjustment of a patient’s diet to reduce the amount of phosphate they consume. This can be achieved, for example, by reducing the intake of food and drinks with a high phosphate to protein ratio, such as some dairy products and nuts, or a high level of phosphate additives, such as cola drinks or processed foods. However, it is also important that a patient’s nutritional status is maintained at a healthy level.

Dialysis

Dialysis is an artificial process for filtering waste and excess water from the blood. It is a form of renal replacement therapy and is often initiated when

chronic kidney disease advances to end-stage renal disease, in which there is a complete or almost complete loss of renal function.

Extended dominance

In health economic modelling, each intervention is compared to the next most effective alternative by calculating the incremental cost-effectiveness ratio (ICER). Extended dominance occurs when the ICER for a given treatment alternative is higher than that of the next, more effective, alternative. A treatment option that is extendedly dominated, that is, has a higher ICER and lower effectiveness, will almost always be rejected in favour of a treatment option with a lower ICER and greater effectiveness.

Hypercalcaemia

Hypercalcaemia is the abnormal elevation of calcium in the blood. The condition arises because of insufficient filtering of calcium from the blood by poorly functioning kidneys. This, in turn, means that a certain amount of the calcium does not leave the body in the urine, instead remaining in the blood.

Other causes of hypercalcaemia include a high intake of calcium, for example through the diet or medications, and high levels of vitamin D or parathyroid hormone, which increase the absorption of calcium in the intestine and its release from bone. Calcium is also obtained from dialysate in haemodialysis.

High serum calcium levels can lead to increases in morbidity and mortality through, for example, abnormalities of bone and joint morphology, increased vascular and soft tissue calcification, and cardiovascular disease.

Hyperphosphataemia

Hyperphosphataemia is an abnormal elevation of phosphate in the blood. The condition arises because of insufficient filtering of phosphate from the blood by poorly functioning kidneys. This, in turn, means that a certain amount of the phosphate does not leave the body in the urine, instead remaining in the blood.

Dietary phosphate intake can further contribute to hyperphosphataemia; food and drink with a large phosphate to protein ratio, such as dairy products, or a

large amount of phosphate additives are of particular concern in patients with chronic kidney disease.

High serum phosphate levels can directly and indirectly increase parathyroid hormone secretion, leading to the development of secondary hyperparathyroidism and increases in morbidity and mortality. Hyperphosphataemia can contribute to an increased incidence of fracture, abnormalities of bone and joint morphology, vascular and soft tissue calcification, and cardiovascular disease.

Multiple treatment comparison

Well-conducted randomised controlled trials are the 'gold standard' for directly comparing the effectiveness of different treatments. However, for some conditions there are many different treatments available, many of which have not been directly compared in head-to-head trials.

If there is a lack of evidence from direct comparison trials, or the available evidence is limited, results from different trials can be used to indirectly estimate the effects of a treatment relative to each of the other treatments. In this way, a multiple treatment comparison uses a network of the available direct and indirect comparisons to provide an overall picture of the available treatments. Indirect comparisons can also be used to strengthen the estimates of effect gained from direct comparisons.

Phosphate

Phosphate is a mineral in the blood, and can be found in all cells in the body. Its primary function is to work in conjunction with calcium to form teeth and bones. However, it also plays a number of other roles in the body, including in the metabolism of fats and carbohydrates, the repair and maintenance of cells and tissues, the transmission of nerve impulses and the functioning of the kidneys.

It enters the blood through the digestion and absorption of food and drink in the small intestine. The kidneys control the amount of phosphate in the blood, removing excess and passing it out of the body in the urine.

Phosphate binders

Phosphate binders are pharmacological interventions that bind to dietary phosphate while it is in the stomach, preventing its absorption into the blood. Instead, the bound phosphate is passed out of the body in the faeces.

A range of phosphate binders are licensed in the UK, though they can broadly be defined as calcium-based and non-calcium-based. They are available as pills, chewable tablets, capsules and powders.

Because the phosphate-binding action occurs in the stomach, it is important that these medications are taken with food and not on an empty stomach.

Self-management tool

For the purpose of this guideline, the summary term 'self-management tool' was used to collectively describe the aids used to help patients to manage their dietary intake or serum phosphate levels alongside education or counselling.

These tools ranged from a fridge magnet detailing high-phosphate foods, to an individualised tracking chart that uses visual goals to engage patients in achieving phosphate control.

Supplements

Supplements are a potentially wide range of substances, including vitamins, minerals and macronutrients (protein, carbohydrate and fat). A supplement is often defined as a preparation intended to provide nutrients that may be missing from a person’s diet or may not be consumed in sufficient quantities. However, in this guideline, supplements were defined as vitamins, minerals and other substances that control serum phosphate through effects other than phosphate-binding.

In sections 3.6 and 3.7 of this guideline, in which the use of supplements for the explicit purpose of managing hyperphosphataemia was reviewed, the classification of calcium as a phosphate binder was distinguished from that as a supplement through the timing of its administration. As defined in this guideline, calcium-based phosphate binders are taken with food while calcium

supplements are taken on an empty stomach when the phosphate-binding effect will be limited.

Please see the NICE glossary for an explanation of terms not described above.

Abbreviations

Abbreviation	Term
AA	Amino acid
ACR	Albumin to creatinine ratio
Any-B	Any binder
C-based	Calcium-based binder
CA	Calcium acetate
CAMG	Calcium acetate with magnesium carbonate
CC	Calcium carbonate
CCr	Creatinine clearance
CHF	Chronic heart failure
CI	Confidence interval / credibility interval
CKD	Chronic kidney disease
CV	Cardiovascular
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
GDG	Guideline Development Group
GFR	Glomerular filtration rate
GI	Gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
IDWG	Interdialytic weight gain
KA	Keto acid
LC	Lanthanum carbonate
LPD	Low-protein diet
MD	Mean difference
MG	Magnesium carbonate
MNA	Multi-nutritional assessment
MPD	Moderate-protein diet
MTC	Multiple treatment comparison
nPCR	Normalised protein catabolic rate
OR	Odds ratio

P	Placebo
PTH	Parathyroid hormone
PTx	Parathyroidectomy
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RR	Relative risk
RRT	Renal replacement therapy
SC	Sevelamer carbonate
SCr	Serum creatinine
SD	Standard deviation
SGA	Subjective Global Assessment of nutrition
SH	Sevelamer hydrochloride
sLPD	Supplemented low-protein diet
sVLPD	Supplemented very-low-protein diet
Tx	Kidney transplant
VLPD	Very-low-protein diet

5 Other information

5.1 Scope

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover. The scope of this guideline is given in appendix C.

5.2 Implementation

NICE has developed tools to help organisations implement this guidance.

5.3 Other versions of this guideline

5.3.1 NICE guideline

The NICE guideline contains all the recommendations, without the information on methods and evidence.

5.3.2 NICE pathway

The recommendations from this guideline have been incorporated into a NICE pathway.

5.3.3 Information for the public

A summary of the recommendations is available for the public ('Information for the public').

We encourage NHS and third sector, including voluntary, organisations to use this text in their own information about hyperphosphataemia.

5.4 Related NICE guidance

Details are correct at the time of publication (Mar 2013). Further information is available on the NICE website.

Published

General

- Patient experience in adult NHS services. NICE clinical guidance 138 (2012).
- Medicines adherence. NICE clinical guidance 136 (2011).

Condition-specific

- Peritoneal dialysis. NICE clinical guideline 125 (2011).
- Anaemia management in people with chronic kidney disease. NICE clinical guideline 114 (2011).
- Chronic kidney disease. NICE clinical guideline 73 (2008).
- Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy. NICE technology appraisal guidance 117 (2007).

Under development

NICE is developing the following guidance (details available from the NICE website):

- Acute kidney injury. NICE clinical guideline. Publication expected August 2013.
- Chronic kidney disease (update). NICE clinical guideline. Publication expected July 2014.

Appendix A Contributors and declarations of interests

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Declarations of interests

GDG Member	Interest Declared	Type of Interest	Decisions Taken
Gary McVeigh	None		
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Appendix B List of all research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

B1 Phosphate binders in adults with CKD stage 4 or 5

Which binders are most effective in controlling serum phosphate in adults with stage 4 or 5 CKD who are not on dialysis?

Why this is important

Limited evidence was found on the use of phosphate binders in adults with stage 4 or 5 CKD. While it is possible in some instances to extrapolate from the evidence on people with stage 5 CKD who are on dialysis, it is not ideal. Therefore, a series of RCTs should be conducted to examine the comparative effectiveness of various phosphate binders against each other for the management of serum phosphate in adults with stage 4 or 5 CKD. These trials should examine the long-term (ideally 12-month) effects of the various binders on outcomes such as serum phosphate, serum calcium, adverse events and the ability of the binders to control serum phosphate and calcium within the given ranges.

B2 Effectiveness and safety of aluminium hydroxide in adults

In adults with stage 4 or 5 CKD, including those on dialysis, what is the long-term effectiveness and safety of aluminium hydroxide in controlling serum phosphate?

Why this is important

Limited evidence was found on the efficacy of aluminium hydroxide in adults and no evidence was found on the long-term efficacy and safety of aluminium

hydroxide. A series of RCTs should be conducted separately in adults with stages 4 or 5 CKD who are not on dialysis and those with stage 5 who are on dialysis. These trials should be run for a minimum of 12 months and should examine the effect of aluminium hydroxide on outcomes such as serum phosphate, serum calcium, adverse events and the ability of the binders to control serum phosphate and calcium within the given ranges. In addition, specific data should be collected on aspects relating to aluminium toxicity.

B3 Effectiveness and safety of magnesium carbonate in adults

In adults with stage 4 or 5 CKD, including those on dialysis, what is the long-term effectiveness and safety of magnesium carbonate in controlling serum phosphate?

Why this is important

Limited evidence was found on the use of magnesium carbonate to control serum phosphate. However, the evidence that was assessed suggested that magnesium carbonate could be very effective in controlling serum phosphate. A series of RCTs should be conducted separately in adults with stages 4 or 5 CKD who are not on dialysis and those with stage 5 who are on dialysis. These trials should be run for a minimum of 12 months and should examine the effect of magnesium carbonate on outcomes such as serum phosphate, serum calcium, adverse events and the ability of the binders to control serum phosphate and calcium within the given ranges. In addition, specific data should be collected on aspects relating to magnesium toxicity.

B4 Phosphate binders in children

Which binders are most effective in controlling serum phosphate in children with stage 4 or 5 CKD, including those who are on dialysis?

Why this is important

Limited evidence was found on the use of phosphate binders in children with stage 5 CKD who are on dialysis, and none was found for those with stage 4 or 5 CKD who are not on dialysis. Therefore, a series of RCTs should be

conducted that examine the comparative effectiveness of various phosphate binders against each other for the management of serum phosphate. These RCTs should be conducted separately in those with stages 4 or 5 CKD who are not on dialysis and those with stage 5 who are on dialysis. These trials should examine the long-term (ideally 12-month) effects of the various binders on outcomes such as serum phosphate, serum calcium, adverse events and the ability of the binders to control serum phosphate and calcium within the given ranges, as well as the most appropriate sequencing of binders.

B5 Sequencing and combining of phosphate binders in adults

For adults with stage 4 or 5 CKD, including those on dialysis, what is the most effective sequence or combination of phosphate binders to control serum phosphate?

Why this is important

It is thought that the longer people remain on calcium-based binders, the greater their risk of developing hypercalcaemia. However, no evidence was found on the most appropriate sequence or combination of phosphate binders a person should receive to control serum phosphate and serum calcium. A series of RCTs should be conducted separately in adults with stages 4 or 5 CKD who are not on dialysis and those with stage 5 who are on dialysis. These trials should be run for a minimum of 12 months and should examine comparative effectiveness of various sequences and combinations of available phosphate binders on outcomes such as serum phosphate, serum calcium, adverse events and the ability of the binders to control serum phosphate and calcium within the given ranges.

Appendix C Guideline scope

See separate file.

Appendix D How this guideline was developed

See separate file.

Appendix E Evidence tables

See separate file.

Appendix F Full health economic report

See separate file.

Appendix G Clinical guideline technical assessment unit analysis (phosphate binders)

See separate file.