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Dietary interventions for mineral and bone disorder in people with chronic kidney disease (Review)

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[Intervention Review]

Dietary interventions for mineral and bone disorder in people with chronic kidney disease

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ABSTRACT

Background

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a systemic dysfunction of mineral and bone metabolism in people with CKD. Recent research shows that phosphate retention plays a significant role in the development of CKD-MBD. Compared with drug therapies, dietary interventions may be simple, inexpensive and feasible for phosphate retention. However, there is little evidence to support these interventions.

Objectives

Our objective was to assess the benefits and harms of any dietary intervention for preventing and treating CKD-MBD.

Search methods

We searched Cochrane Kidney and Transplant's Specialised Register to 27 August 2015 through contact with the Trials' Search Co-ordinator using search terms relevant to this review. We also searched the Chinese Biomedicine Database (CBM) (1976 to August 2015), China Knowledge Resource Integrated Database (CNKI) (1979 to August 2015), and VIP (1989 to August 2015).

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs looking at dietary interventions for prevention or treatment of CKD-MBD were eligible for inclusion.

Data collection and analysis

Two authors independently assessed the eligibility, methodological quality, and extracted data. Continuous outcomes (serum calcium level, serum phosphorus level, calcium × phosphate product, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF-23) and alkaline phosphatase) were expressed as mean difference (MD) with 95% confidence interval (CI). Dichotomous outcomes (mortality) were expressed as risk ratio (RR) with 95% CI. We used a random-effects model to meta-analyse studies.

Main results

Nine studies were included in this review which analysed 634 participants. Study duration ranged from 4 to 24 weeks. The interventions included calcium-enriched bread, low phosphorus intake, low protein intake, very low protein intake, post haemodialysis supplements and hypolipaemic diet. Only one study reported death; none of the included studies reported cardiovascular events or fractures. There was insufficient reporting of design and methodological aspects among the included studies to enable robust assessment of risk of bias.

There was limited and low-quality evidence to indicate that calcium-enriched bread increased serum calcium (1 study, 53 participants: MD -0.16 mmol/L, 95% CI -0.51 to -0.31), decreased serum phosphorus (53 participants: MD -0.41 mmol/L, 95% CI -0.51 to -0.31) and decreased the calcium × phosphate product (53 participants: MD -0.62 $mmol^2/L^2$, 95% CI -0.77 to -0.47).

Very low protein intake was not superior to conventional low protein intake in terms of effect on serum phosphorus (2 studies, 41 participants: MD -0.12 mmol/L, 95% CI -0.50 to 0.25), serum calcium (MD 0.00 mmol/L, 95% CI -0.17 to 0.17), or alkaline phosphatase (MD -22.00 U/L, 95% CI -78.25 to 34.25). PTH was significantly lower in the very low protein intake group (2 studies, 41 participants: MD -69.64 pmol/L, 95% CI -139.83 to 0.54).

One study reported no significant difference in the number of deaths between low phosphorus intake and normal diet (279 participants: RR 0.18, 95% CI 0.01 to 3.82). Low phosphorus intake decreased serum phosphorus (2 studies, 359 participants: MD -0.18 mmol/L, 95% CI -0.29 to -0.07; $I^2 = 0\%$).

One study reported post-haemodialysis supplements did not increase serum phosphorus compared to normal diet (40 participants: MD 0.12 mmol/L, 95% CI -0.24 to 0.49).

One study reported low phosphorus intake plus lanthanum carbonate significantly decreased FGF-23 (19 participants: MD -333.80 RU/mL, 95% CI -526.60 to -141.00), but did not decrease serum phosphorus (19 participants: MD -0.10 mg/dL, 95% CI -0.38 to 0.58) or PTH (19 participants: MD 31.60 pg/mL, 95% CI -29.82 to 93.02).

Authors' conclusions

There was limited low quality evidence to indicate that dietary interventions (calcium-enriched bread or low phosphorus/protein intake) may positively affect CKD-MBD by increasing serum calcium, decreasing serum phosphorus, the calcium × phosphate product and FGF-23. Large and well-designed RCTs are needed to evaluate the effects of various interventions for people with CKD-MBD.

PLAIN LANGUAGE SUMMARY

Are changes to diet effective to manage mineral and bone abnormalities in people with chronic kidney disease?

Problems with mineral and bone metabolism are very common in people with chronic kidney disease (CKD) which can lead to broken bones (fracture), heart and blood circulation (cardiovascular) problems, and sometimes death. Many pharmaceutical treatments used to treat mineral-bone disease can have side effects and cause problems for patients. We wanted to find out if specific diets (such as low protein or phosphorus intake) were better or worse than normal diets or pharmaceutical treatments.

We searched the literature to August 2015 and included nine studies that analysed 634 participants; durations of studies ranged from 4 and 24 weeks. The interventions included calcium-enriched bread, low phosphorus intake, low protein intake, very low protein intake, post-haemodialysis supplements and low lipid diet. Only one study reported death; none of the included studies reported cardiovascular events or fractures. One study reported adverse events. There was insufficient reporting of design and methodological aspects among the included studies to enable robust assessment of risk of bias.

We found scant evidence to suggest that restricting protein or phosphorus in the diet may have positive effects for people with CKD. Evidence from one small, low quality study suggested that calcium-enriched bread may help to increase calcium and decrease phosphorus and the calcium × phosphate product.

Evidence was assessed as low quality, and was insufficient to inform clinical decision-making about the value of dietary modification for people with CKD-MBD. None of the included studies reported our primary outcomes of cardiovascular events or fracture; only one study reported adverse events.

Summary of findings for the main comparison. Calcium-enriched bread versus calcium acetate for people with CKD-MBD

Calcium-enriched bread versus calcium acetate for people with CKD-MBD						
Patient or population: people with CKD-MBD **Settings:** outpatient dialysis unit **Intervention:** calcium-enriched bread **Comparison:** calcium acetate						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Calcium acetate	**Calcium-enriched bread**				
Serum phosphorus Follow-up: mean 14 weeks	Mean serum phosphorus (control) **2.08 mmol/L**	Mean serum phosphorus (intervention) **0.41 mmol/L lower** (0.51 to 0.31 lower)		53 (1)	⊕⊖⊖⊖ **very low** [1,2]	
Serum calcium Follow-up: mean 14 weeks	Mean serum calcium (control) **2.11 mmol/L**	Mean serum calcium (intervention) **0.16 mmol/L higher** (0.09 to 0.23 higher)		53 (1)	⊕⊖⊖⊖ **very low** [1,2]	
Calcium × phosphate product Follow-up: mean 14 weeks	Mean calcium × phosphate product (control) **4.42 mmol^2/L^2**	Mean calcium × phosphate product (intervention) **0.62 mmol^2/L^2 lower** (0.77 to 0.47 lower)		53 (1)	⊕⊖⊖⊖ **very low** [1,2]	
Alkaline phosphatase activity Follow-up: mean 14 weeks	Mean alkaline phosphatase activity (control) **95 IU/L**	Mean alkaline phosphatase activity (intervention) **10 IU/L higher** (2.7 lower to 22.7 higher)		53 (1)	⊕⊖⊖⊖ **very low** [1,2]	
Mortality	Not reported	Not reported	Not estimable	-	Not estimable	
Cardiovascular events	Not reported	Not reported	Not estimable	-	Not estimable	
Fracture	Not reported	Not reported	Not estimable	-	Not estimable	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The study reported using randomised controlled methods, but details of random sequence generation, allocation concealment and blinding were not reported
[2] Only one published study was included.

Summary of findings 2. Very low versus low protein diet for people with CKD-MBD

Very low versus low protein diet for people with CKD-MBD

Patient or population: people with CKD-MBD
Settings: outpatient clinic
Intervention: very low protein intake
Comparison: low protein intake

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Very low protein diet	Low protein diet				
Serum phosphorus Follow-up: 9 to 18 months	Mean serum phosphorus (control) **1.2 to 1.32 mmol/L**	Mean serum phosphorus (intervention) **0.12 mmol/L lower** (0.5 lower to 0.25 higher)		41 (2)	⊕⊖⊖⊖ **very low** [1,2,3]	
PTH Follow-up: 9 to 18 months	Mean PTH (control) **23.11 to 139 pmol/L**	Mean PTH (intervention) **9.98 pmol/L lower** (12.85 to 7.1 lower)		41 (2)	⊕⊖⊖⊖ **very low** [1,2,3]	
Serum calcium Follow-up: mean 9 months	Mean serum calcium (control) **2.3 mmol/L**	Mean serum calcium (intervention) **No higher** (0.17 lower to 0.17 higher)		22 (1)	⊕⊖⊖⊖ **very low** [1,4]	
Alkaline phosphatase	Mean alkaline phosphatase (control)	Mean alkaline phosphatase (intervention)		22 (1)	⊕⊖⊖⊖ **very low** [1,4]	

Follow-up: mean 9 months	**123 U/L**	**22 U/L lower** (78.25 lower to 34.25 higher)			
Mortality	Not reported	Not reported	Not estimable	-	Not estimable
Cardiovascular events	Not reported	Not reported	Not estimable	-	Not estimable
Fracture	Not reported	Not reported	Not estimable	-	Not estimable

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The study reported using randomised controlled methods, but details of random sequence generation, allocation concealment and blinding were not reported
[2] Very low protein intake (0.3 g/kg/d) showed a positive effect; low protein diet (0.4 g/kg/d) showed a negative effect.
[3] Only published, small studies were included. Some negative results were reported.
[4] Only one published study was included.

Summary of findings 3. Low phosphorus versus normal diet for people with CKD-MBD

Low phosphorus versus normal diet for people with CKD-MBD

Patient or population: people with CKD-MBD
Settings: multicentre
Intervention: low phosphorus diet
Comparison: normal diet

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Normal diet	**Low phosphorus diet**				
Serum phosphorus	Mean serum phosphorus (control) **2 mmol/L**	Mean serum phosphorus (intervention) **0.22 mmol/L lower**		80 (1)	⊕⊖⊖⊖ **very low** [1,2]	

Follow-up: mean 6 months		(0.41 to 0.03 lower)			
Mortality	Not reported	Not reported	Not estimable	-	Not estimable
Cardiovascular events	Not reported	Not reported	Not estimable	-	Not estimable
Fracture	Not reported	Not reported	Not estimable	-	Not estimable

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The study reported using randomised controlled methods, but details of random sequence generation, allocation concealment and blinding were not reported
[2] Only one published study was included.

Summary of findings 4. Post-haemodialysis dietary supplement versus normal diet for people with CKD-MBD

Post-haemodialysis dietary supplement versus normal diet for people with CKD-MBD

Patient or population: people with CKD-MBD undergoing haemodialysis
Settings: HD unit
Intervention: post-haemodialysis dietary supplement
Comparison: normal diet

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Normal diet	Post-haemodialysis dietary supplement				
Serum phosphorus Follow-up: mean 1 month	Mean serum phosphorus (control) **2.1 mmol/L**	Mean serum phosphorus (intervention) **0.12 mmol/L higher** (0.24 lower to 0.49 higher)		54 (2)	⊕⊖⊖⊖ **Very low** [1,2]	

Serum phosphorus - home-prepared dietary supplement versus normal diet Follow-up: mean 1 month	Mean serum phosphorus (control) **2.1 mmol/L**	Mean serum phosphorus (intervention) **0.06 mmol/L higher** (0.45 lower to 0.57 higher)		30 (1)	⊕⊖⊖⊖ **very low** [1,3]
Serum phosphorus - commercial dietary supplement versus normal diet Follow-up: mean 1 month	Mean serum phosphorus (control) **2.1 mmol/L**	Mean serum phosphorus (intervention) **0.19 mmol/L higher** (0.34 lower to 0.72 higher)		24 (1)	⊕⊖⊖⊖ **very low** [1,3]
Mortality	Not reported	Not reported	Not estimable	-	Not estimable
Cardiovascular events	Not reported	Not reported	Not estimable	-	Not estimable
Fracture	Not reported	Not reported	Not estimable	-	Not estimable

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1 Studies reported using randomised controlled methods, but did not report details of random sequence generation, allocation concealment, or blinding
2 Only published, small studies were included. Some negative results were reported.
3 Only one published study was included.

Summary of findings 5. Low phosphorus intake (avoiding food additives) versus normal diet for people with CKD-MBD

low phosphorus intake (avoiding food additives) versus normal diet for people with CKD-MBD

Patient or population: patients with CKD-MBD
Settings: multicentre
Intervention: low phosphorus intake (avoiding food additives)
Comparison: normal diet

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments

	Assumed risk	Corresponding risk			
	Normal diet	**Low phosphorus intake (avoiding food additives)**			
Serum phosphorus Follow-up: mean 3 months	Mean serum phosphorus (control) **20.7 mmol/L**	Mean serum phosphorus (intervention) **1.7 mmol/L lower** (3.01 to 0.39 lower)		279 (1)	⊕⊝⊝⊝ **very low** [1,2]
Mortality Follow-up: mean 3 months	**Study population**		**RR 0.18** (0.01 to 3.82)	279 (1)	⊕⊕⊕⊝ **moderate** [2]
	15 per 1000	**3 per 1000** (0 to 55)			
	Medium risk population				
	15 per 1000	**3 per 1000** (0 to 55)			
Cardiovascular events	Not reported	Not reported	Not estimable	-	Not estimable
Fracture	Not reported	Not reported	Not estimable	-	Not estimable

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** relative risk

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] It was assessed as unclear risk of selection bias, performance bias and detection bias.
[2] Only one published study was included.

Summary of findings 6. Low phosphorus intake plus placebo versus ad libitum diet plus placebo for people with CKD-MBD

Low phosphorus intake plus placebo versus ad libitum diet plus placebo for people with CKD-MBD

Patient or population: patients with CKD-MBD
Settings: clinical research centre
Intervention: low phosphorus intake plus placebo
Comparison: ad libitum diet plus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	ad libitum diet plus placebo	Low phosphorus intake plus placebo				
Serum phosphorus Follow-up: mean 3 months	Mean serum phosphorus (control) **3.5 mg/dL**	Mean serum phosphorus (intervention) **0.1 mg/dL higher** (0.48 lower to 0.68 higher)		20 (1)	⊕⊝⊝⊝ **very low** [1]	
FGF-23 Follow-up: mean 3 months	MeanFGF-23 (control) **-5.6 RU/mL**	Mean FGF-23 (intervention) **2.3 RU/mL higher** (13.18 lower to 17.78 higher)		20 (1)	⊕⊝⊝⊝ **very low** [1,2]	
PTH Follow-up: mean 3 months	Mean PTH (control) **49.8 pg/mL**	Mean PTH (intervention) **25.6 pg/mL higher** (5.13 to 46.07 higher)		20 (1)	⊕⊝⊝⊝ **very low** [1,2]	
Mortality	Not reported	Not reported	Not estimable	-	Not estimable	
Cardiovascular events	Not reported	Not reported	Not estimable	-	Not estimable	
Fracture	Not reported	Not reported	Not estimable	-	Not estimable	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Only one published study was included. However, the result was negative.
[2] The study declared to have using randomised controlled methods, but no details of random sequence generation or allocation concealment. Performance bias, attrition bias and reporting bias were assessed as high risk.

Summary of findings 7. Low phosphorus intake plus lanthanum carbonate versus ad libitum diet plus lanthanum carbonate for people with CKD-MBD

Low phosphorus intake plus lanthanum carbonate versus ad libitum diet plus lanthanum carbonate for people with CKD-MBD

Patient or population: patients with CKD-MBD
Settings: clinical research centre
Intervention: Low phosphorus intake plus lanthanum carbonate
Comparison: ad libitum diet plus lanthanum carbonate

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	ad libitum diet plus lanthanum carbonate	Low phosphorus intake plus lanthanum carbonate				
Serum phosphorus Follow-up: mean 3 months	Mean serum phosphorus (control) **3.3 mg/dL**	Mean serum phosphorus (intervention) **0.1 mg/dL higher** (0.38 lower to 0.58 higher)		19 (1)	⊕⊖⊖⊖ **very low** [1,2]	
FGF-23 Follow-up: mean 3 months	Mean FGF-23 (control) **24.3 RU/mL**	Mean FGF-23 (intervention) **333.80 RU/mL lower** (141.00 lower to 526.6 higher)		19 (1)	⊕⊖⊖⊖ **very low** [1,3]	
PTH Follow-up: mean 3 months	Mean PTH (control) **68.9 pg/mL**	Mean PTH (intervention) **31.6 pg/mL higher** (29.82 lower to 93.02 higher)		19 (1)	⊕⊖⊖⊖ **very low** [1,2]	
Mortality	Not reported	Not reported	Not estimable	-	Not estimable	
Cardiovascular events	Not reported	Not reported	Not estimable	-	Not estimable	
Fracture	Not reported	Not reported	Not estimable	-	Not estimable	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The study declared to have using randomised controlled methods, but no details of random sequence generation or allocation concealment. Performance bias, attrition bias and reporting bias were assessed as high risk
[2] Only one published study was included. However, the result was negative
[3] Only one published study was included

BACKGROUND

Description of the condition

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a systemic dysfunction of mineral and bone metabolism in people with chronic kidney disease (CKD). CKD-MBD results from abnormalities in calcium, phosphorus, parathyroid hormone (PTH), or vitamin D metabolism levels; bone turnover, mineralization, volume, linear growth or strength, vascular or other soft tissue calcification (KDIGO 2009). In its early stages, CKD-MBD is characterised by bone fractures, bone pain, skeletal deformities in growing children, reduced velocity in bone growth, abnormal height, vascular and other soft tissue calcification (Mejía 2011). Developments in dialysis technology have meant that fewer patients with CKD die from uraemia and have longer rates of survival. However, CKD-MBD is a significant contributor to decreased quality of life and increased mortality and morbidity risks, and progression of CKD (Moe 2006; Moe 2007).

Phosphate retention plays an important role in the development of CKD-MBD. As kidney function declines, excretion of phosphate becomes more difficult. Phosphate retention stimulates PTH and fibroblast growth factor (FGF)-23 function before hyperphosphataemia is detected during the early stages of CKD. In general, FGF-23 and PTH can suppress renal reabsorption of phosphorus. However as CKD develops, kidney response to these hormones decreases (Razzaque 2011). In contrast, residual kidney function is challenged in converting 25(OH)D to $1,25(OH)_2D$, which may reduce intestinal calcium absorption and increase PTH and FGF-23 levels (Komaba 2008).

Recent research has also indicated that the Klotho gene, which encodes a transmembrane co-receptor specific for FGF-23, declines in people with CKD. The Klotho gene also causes FGF-23 resistance and stimulates PTH (Kuro-O 2011). Both FGF-23 and PTH increase as CKD progresses, eventually leading to renal osteodystrophy, cardiovascular and soft issue calcification. CKD-MBD has been associated with both renal bone disease and higher mortality (Moe 2007; Tentori 2008).

Description of the intervention

Phosphate retention usually begins early in the course of CKD.

Dietary phosphate restriction and use of phosphate binders are two principal measures for the management of elevated phosphate levels. It has been shown that if serum phosphorus can be decreased in relation to the glomerular filtration rate (GFR), plasma PTH elevation could be prevented (Slatopolsky 1973).

Small sample research has also demonstrated that prolonged limiting of dietary phosphate intake is effective in suppressing secondary hyperparathyroidism, and was recommended for implementation at all stages of kidney disease (McCrory 1987; Takeda 2007).

However, challenges persist in the treatment of hyperphosphataemia. At present, calcium-containing and non-calcium containing phosphate binders, such as sevelamer and lanthanum, are the major drugs used to lower phosphate levels. Calcium-containing phosphate binders may increase the risk of positive calcium balance, and lead to cardiovascular and soft tissue calcification, particularly when associated with vitamin D therapy. Sevelamer for reducing serum phosphorus has been demonstrated to decrease progression of coronary artery calcification compared with calcium salts. However, high treatment cost of sevelamer limits its use, and the same is true for lanthanum.

Pelletier 2010 compared older and younger haemodialysis patients and reported better control of serum phosphorus with less phosphate binder and cinacalcet. This study indicated that phosphate binders may not be the determinant in maintaining serum phosphorus. Moreover, the increasing number of patients with CKD requires a large number of conventional drugs which imposes a significant burden for both patients and society (Navaneethan 2009). Thus, searching for interventions that are both efficient and affordable is a pivotal target for preventing and treating CKD-MBD.

Compared with drug therapies, dietary interventions seem to be simple, inexpensive and feasible. Dietary phosphate restriction is recommended in many guidelines. The KDOQI 2003 guidelines suggest that dietary phosphorus should be restricted to 800 to 1000 mg/day when plasma levels of intact PTH are elevated above the target range of the CKD stage. The KDIGO 2009 guidelines recommend that patients with CKD stages 3 to 5D limit their dietary phosphate intake for the treatment of hyperphosphataemia, alone or in combination with other treatments; however, there is currently little evidence to support this recommendation.

Because phosphate intake usually parallels protein intake, dietary phosphate restriction is often achieved by restricting protein intake. Cianciaruso 2008 and Klahr 1994 conducted studies to investigate the effects of different protein diets on metabolic control and CKD progression. Sullivan 2009 focused on the effects of food additives on hyperphosphataemia in people with end-stage kidney disease and reported benefits when phosphorus-containing food additives were avoided. Soroka 1998 investigated feasibility low phosphate diets and showed that a low-phosphorus vegan diet in which only an appropriate cereal-legume mixture was consumed could achieve the same goal as a conventional low-protein diet. Patients not only avoided protein malnutrition, but also reduced phosphate intake, which is an abundant mineral in animal-based foods.

How the intervention might work

Phosphate retention plays a significant role in the development of CKD-MBD. Lowering dietary phosphate by restricting food additives, processed foods and protein, and sometimes in combination with phosphate binders, should therefore be the first step to protect people with CKD from developing mineral and bone disorder.

Why it is important to do this review

Although dietary interventions are well recognised as an important way to help prevent and treat CKD-MBD, there has been no systematic review of these interventions. The safety and efficacy of dietary interventions for people with CKD-MBD remain unknown.

OBJECTIVES

Our objective was to assess the benefits and harms of any dietary intervention for preventing and treating CKD-MBD.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at dietary interventions for preventing or treating CKD-MBD were included. The first periods of randomised cross-over studies were also eligible for inclusion.

Types of participants

People with CKD stages 3 to 5D as defined by the KDOQI 2003 guidelines (stage 3: GFR 30 to 59 mL/min/1.73 m^2; stage 4: GFR 15 to 29 mL/min/1.73 m^2, stage 5: GFR < 15 mL/min/1.73 m^2 or dialysis) were included. Children and kidney transplant recipients were also included.

Types of interventions

1. Any dietary intervention versus placebo, no treatment, another dietary intervention or any other interventions
2. Any dietary intervention in combination with other interventions versus placebo, no treatment, another dietary intervention or any other interventions.

Dietary interventions included protein restricted diets and phosphate restricted diets.

Types of outcome measures

- Outcome data of four weeks intervention or longer were included because it seemed impossible to evaluate the effect of dietary interventions over a shorter time
- Fracture at any site measured by radiographic examination
- Cardiovascular events measured by records of symptoms, any ultrasonic, electrocardiogram or heart intervention
- Vascular calcification or soft tissue calcification measured by CT, X-ray or ultrasonic imaging
- Incidence of calciphylaxis measured by symptoms, X-ray or biopsy
- Bone density (assessed by dual-energy X-ray absorptiometry using Z-scores at the lumbar spine, femoral neck or radius)
- Bone turnover (by bone histomorphometry)
- Potential adverse events included protein energy malnutrition, gastrointestinal symptoms, hypophosphataemia, hyper- or hypocalcaemia
- Other outcomes measured by blood examination at the end of the interventions.

Primary outcomes

- Mortality
- Cardiovascular events
- Fracture.

Secondary outcomes

- Biochemical parameters
  - Serum phosphorus (mmol/L, mg/dL)
  - Serum calcium (mmol/L, mg/dL)
  - Calcium × phosphate product
  - PTH (iPTH) (pmol/L, pg/mL)
  - Alkaline phosphatase (µkat/L, U/L)
  - Urinary phosphorus excretion (mmol/L, mg/dL)
  - Serum FGF-23 (pg/mL)
- Vascular calcification
- Soft tissue calcification
- Left ventricular mass
- Incidence of calciphylaxis
- Bone density (assessed by dual-energy X-ray absorptiometry using Z-scores at the lumbar spine, femoral neck or radius)
- Bone turnover (by bone histomorphometry)
- Bone micro-architecture by high-resolution peripheral computed tomography (HR-pQCT)
- Longitudinal growth in children
- Adverse events.

Search methods for identification of studies

Electronic searches

We searched Cochrane Kidney and Transplant's Specialised Register to 27 August 2015 through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Specialised Register contains studies identified from the following sources.

1. Quarterly searches of the Cochrane Central Register of Controlled Trials CENTRAL
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register were identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about Cochrane Kidney and Transplant.

We also searched:

1. The Chinese Biomedicine Database (CBM) (1976 to August 2015)
2. Chinese National Knowledge Infrastructure (CNKI) (1979 to August 2015)
3. VIP Database for Chinese Technical Periodicals (VIP) (1989 to August 2015).

See Appendix 1 for search terms.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.

2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that might relevant to the review. The titles and abstracts were screened independently by two authors, who discarded studies that were not applicable. However, studies and reviews that might include relevant data or information on studies were retained initially. Two authors independently assessed retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria. There were no disagreements.

Data extraction and management

Data extraction was carried out independently by two authors using standard data extraction forms. We grouped reports of the same study together and only the publication with the most complete data was used in the analyses. There were no disagreements.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Were reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

There were no reports of dichotomous outcomes (such as mortality, cardiovascular events, fracture, adverse events and so forth). Where continuous scales of measurement was used to assess the effects of treatment (such as serum phosphorus, serum calcium, Ca × P product, PTH (iPTH), alkaline phosphatase), the mean difference (MD) with 95% confidence intervals (CI) were used. We analysed final measurement outcomes data for meta-analysis if available.

Unit of analysis issues

Only data from the first period of cross-over studies were included. For multiple intervention groups, we pooled all relevant experimental intervention groups into a single group, and likewise pooled all relevant control intervention groups into a single control group.

Dealing with missing data

Further information required from the original author was requested by written correspondence (e-mailing and/or writing to corresponding author/s) and relevant information obtained in this manner was included in the review.

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

We were unable to construct funnel plots to assess and presence of reporting bias because of the small number of included studies.

Data synthesis

Only data from Di Iorio 2003 and Herselman 1995 were pooled using the random-effects model. We were unable to conduct pooled analyses because of the range of interventions reported.

Subgroup analysis and investigation of heterogeneity

We were unable to perform subgroup analysis because of the small number of included studies.

Sensitivity analysis

We were unable to perform sensitivity analyses because of the small number of included studies.

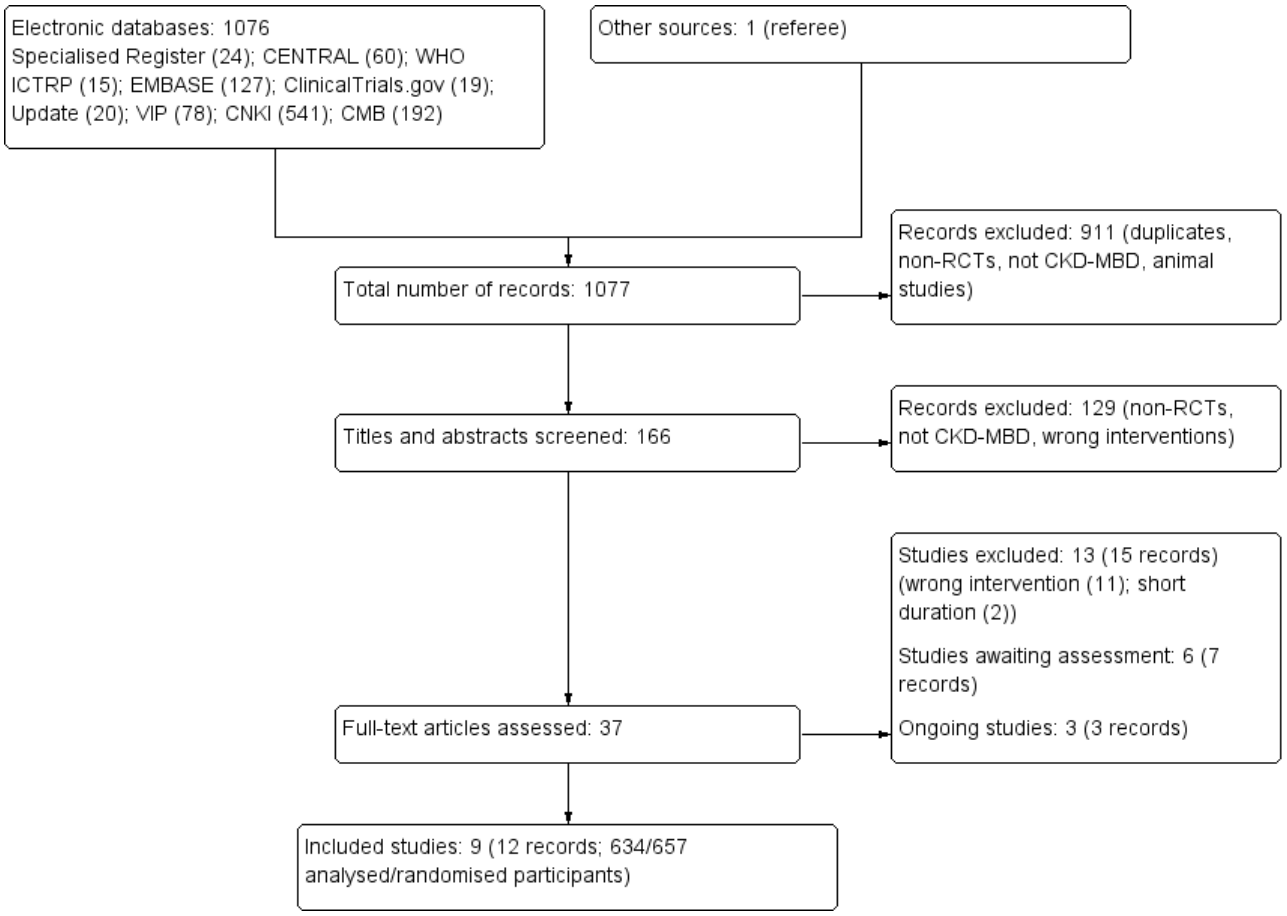
RESULTS

Description of studies

Results of the search

We identified 1077 records. After initial screening we excluded 911 records (duplicates, animal studies, not randomised, wrong population). After title and abstract review we excluded an additional 129 records. We obtained the full-text of 37 records. We included nine studies (12 records) and excluded 12 studies (15 records). Six studies are awaiting assessment and there are three ongoing studies (Figure 1).

Figure 1. Study flow diagram



Included studies

We included nine studies (634/657 analysed/randomised patients) that investigated six types of dietary interventions (Babarykin 2004; Bunio 2004; Di Iorio 2003; Herselman 1995; Isakova 2013; Li 2011c; Lou 2012; Sharma 2002c; Sullivan 2009).

Babarykin 2004 compared calcium-enriched bread diet with calcium acetate. Di Iorio 2003 and Herselman 1995 compared very low protein intake with low protein intake. Herselman 1995 compared 0.6 g protein/kg/day with 0.4 g protein/kg/day supplemented with essential amino acids. Di Iorio 2003 compared 0.6 g protein/kg/day with 0.3 g protein/kg/day of vegetable origin, supplemented with a mixture of keto analogues and essential amino acids. Bunio 2004 compared hypolipaemic diet with statin/lovastatin 20 mg/day. Li 2011c compared low protein intake (0.8 g/kg ideal body weight/day, with keto acid-supplementation) with normal protein intake (1 to 1.2 g/kg ideal body weight/day). Isakova 2013, Lou 2012 and Sullivan 2009 studied phosphorus restricted diets for CKD. Isakova 2013 compared low phosphorus intake (900 mg phosphorus/day) plus lanthanum carbonate/placebo with ad libitum plus lanthanum carbonate/placebo. Lou 2012 compared low phosphorus diet (800 to 900 mg phosphorus/day) with normal diet. Sullivan 2009 also compared low phosphorus diet (education on avoiding foods with phosphorus additives) with usual diet. Sharma 2002c compared post-haemodialysis supplementation (home-prepared or commercially available formula providing 500 Kcal and 15 g protein) with normal diet.

Excluded studies

We excluded 13 studies. Of these, 11 investigated non-dietary interventions (ACTRN12611000500954; Ambrus 2003; Ashurst 2003; Cheng 2008; Chertow 2003; Clark 2010; Morey 2008; NCT01665651; Olivero 2006; Padhi 2007; Young 2009a) and two were of shorter duration than specified in our inclusion criteria (Moe 2011; Spiegel 2012). (See Characteristics of excluded studies).

Studies awaiting assessment

Karavetian 2012 was available only as an abstract, and the details of the nutritional therapy investigated were unclear. Garini 1992 was published in Italian. We unable to translate it and the details of the study were unknown.

Prior to publication a search of the Specialised Register identified four potential studies (Akizawa 2014a; Block 2013; Hill 2013; Karavetian 2013). These studies will be assessed in a future update of this review.

Ongoing studies

Three studies are ongoing and will be assessed in a future update of this review (NCT00755690; NCT01865526; NCT02005302).

Risk of bias in included studies

Overall, study quality was suboptimal. There was insufficient reporting of design and methodological aspects among the

included studies to enable robust assessment of risk of bias. (See Characteristics of included studies; Figure 2; Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

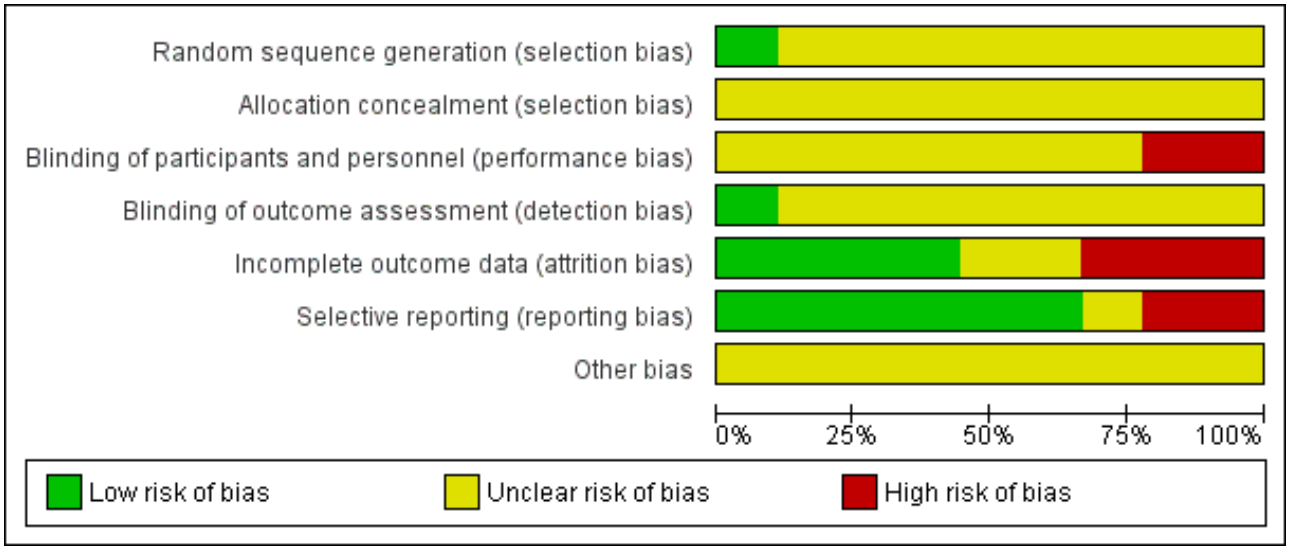
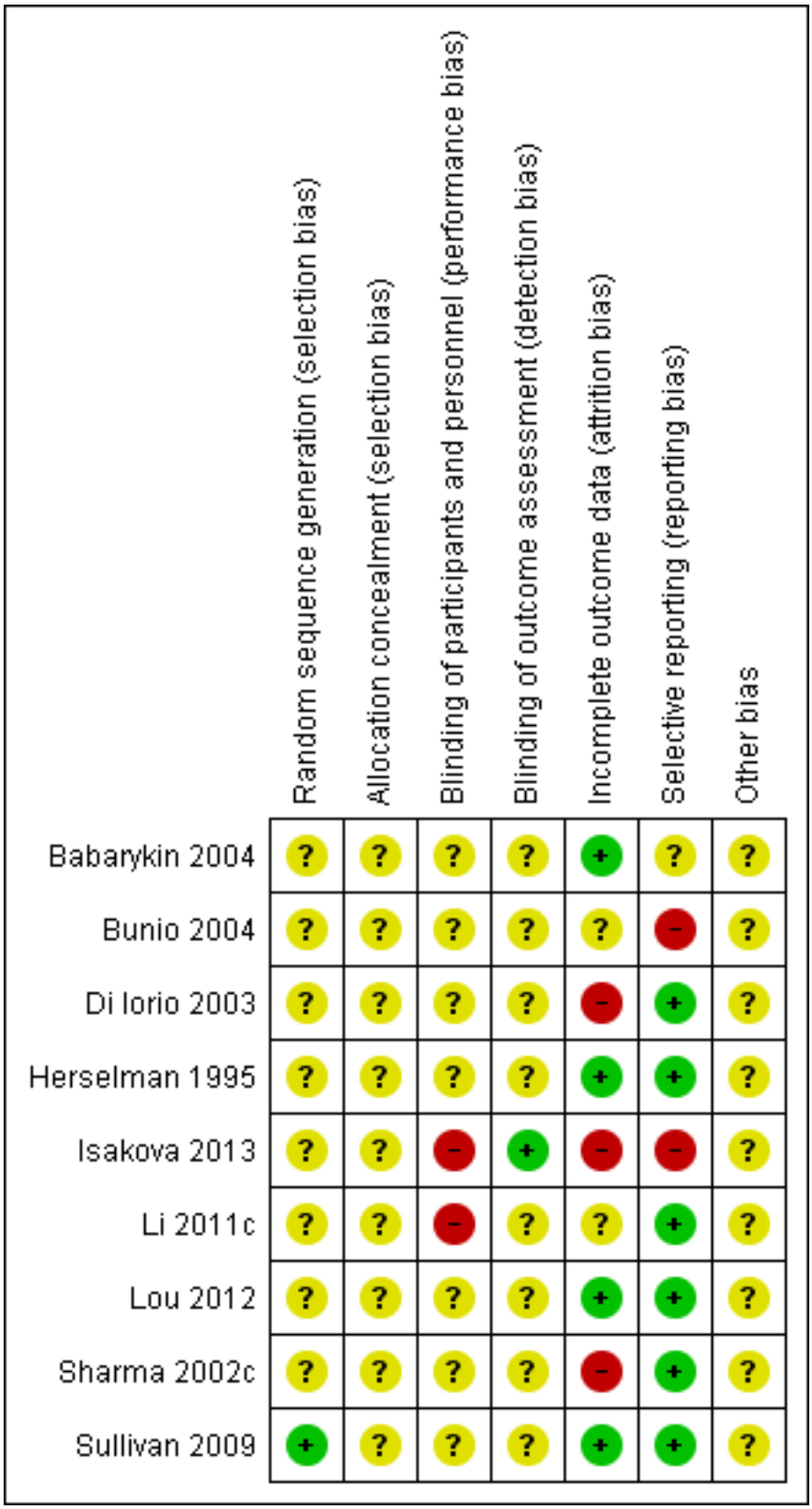


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

Although the included studies reported applying randomised controlled methods, only one study reported specific randomisation method(Sullivan 2009). None adequately reported random sequence generation or allocation concealment.

Blinding

Li 2011c, an open-label study, was assessed at high risk of performance bias. Isakova 2013 was assessed as low risk of detection bias because the investigators remained blinded to the dietary group. However, dietitian and participants were unblinded to the assigned dietary counselling group and the performance bias was assessed as high risk. All other studies (Babarykin 2004; Bunio 2004; Di Iorio 2003; Herselman 1995; Lou 2012; Sharma 2002c; Sullivan 2009) were assessed as unclear risk of performance and detection bias.

Incomplete outcome data

Missing data did not balance between groups in Sharma 2002c and Isakova 2013. In Di Iorio 2003 follow-up duration differed significantly between intervention and control groups; and most control group participants withdrew after 18 months, which meant that participant data did not balanced at the end of the study (24 months). We assessed Di Iorio 2003, Isakova 2013 and Sharma 2002c at high risk of attrition bias. Sullivan 2009 was assessed as low risk of attrition bias because missing outcome data had similar reasons and balanced in numbers across intervention groups. Multiple imputations were also used to account for missing data. Bunio 2004 was abstract only and details of outcome data were unknown. Li 2011c was assessed as unclear risk of attrition bias because detailed control group data were not reported. Babarykin 2004, Herselman 1995 and Lou 2012 were assessed at low risk of attrition bias.

Selective reporting

Bunio 2004 and Isakova 2013 did not report on specified outcomes, and we therefore assessed these studies at high risk of reporting bias. There were insufficient data to assess reporting bias in Babarykin 2004. All other included studies were assessed at low risk of reporting bias (Di Iorio 2003; Herselman 1995; Li 2011c; Lou 2012; Sharma 2002c; Sullivan 2009).

Other potential sources of bias

There was insufficient information to determine if there were any other potential sources of bias present.

Effects of interventions

See: **Summary of findings for the main comparison** Calcium-enriched bread versus calcium acetate for people with CKD-MBD; **Summary of findings 2** Very low versus low protein diet for people with CKD-MBD; **Summary of findings 3** Low phosphorus versus normal diet for people with CKD-MBD; **Summary of findings 4** Post-haemodialysis dietary supplement versus normal diet for people with CKD-MBD; **Summary of findings 5** Low phosphorus intake (avoiding food additives) versus normal diet for people with CKD-MBD; **Summary of findings 6** Low phosphorus intake plus placebo versus ad libitum diet plus placebo for people with CKD-MBD; **Summary of findings 7** Low phosphorus intake plus lanthanum carbonate versus ad libitum diet plus lanthanum carbonate for people with CKD-MBD

Primary outcomes

Only Sullivan 2009 reported death. None of the included studies reported cardiovascular events or fracture.

Death

Sullivan 2009 reported no significant difference in the number of patients who died between low phosphorus intake and normal diet (Analysis 3.1 (279 participants): RR 0.18, 95% CI 0.01 to 3.82).

We inferred from end-of-study data that no deaths occurred in four studies (Babarykin 2004; Herselman 1995; Li 2011c; Sharma 2002c). We were unsure about mortality rates in the other studies because of participant withdrawals and poor reporting of losses to follow-up (Bunio 2004; Di Iorio 2003; Isakova 2013; Lou 2012).

Secondary outcomes

Serum phosphorus

Serum phosphorus was reported in seven studies (Babarykin 2004; Di Iorio 2003; Herselman 1995; Isakova 2013; Lou 2012; Sharma 2002c; Sullivan 2009).

Babarykin 2004 reported calcium-enriched bread significantly reduced serum phosphorus levels compared to calcium acetate (Analysis 1.1 (53 participants): MD -0.41 mmol/L, 95% CI -0.51 to -0.31).

There was no significant difference in serum phosphorus between low protein and very low protein intake (Analysis 2.1 (2 studies, 41 participants): MD -0.12 mmol/L, 95% CI -0.50 to 0.25; I^2 = 80%) (Di Iorio 2003; Herselman 1995). Heterogeneity was high and this may be due to the different amounts of protein given to the very low protein group (0.3 g/kg/d versus 0/4 g/kg/d) and the duration of treatment (24 months versus 9 months)

Serum phosphorus was significantly reduced with a low phosphorus intake compared to a normal diet (Analysis 3.2 (2 studies, 359 participants): MD -0.18 mmol/L, 95% CI -0.29 to -0.07; I^2 = 0%) (Lou 2012; Sullivan 2009).

Sharma 2002c reported neither home-prepared (Analysis 4.1.1 (23 participants): MD 0.06 mmol/L, 95% CI -0.57 to 0.69) nor commercially available diet supplements (Analysis 4.1.2 (17 participants): MD 0.19 mmol/L, 95% CI -0.46 to 0.84) showed significant changes in serum phosphorus levels compared with normal diet (pooled result - Analysis 4.1 (40 participants): MD 0.12 mmol/L, 95% CI -0.33 to 0.58; I^2 = 0%).

Isakova 2013 reported no significant difference in serum phosphorus between either low phosphorus intake plus placebo compared with ad libitum diet plus placebo (Analysis 5.1.1 (20 participants): MD 0.10 mg/dL, 95% CI -0.48 to 0.68) or low phosphorus intake plus lanthanum carbonate compared with ad libitum diet plus placebo (Analysis 5.1.2 (19 participants): MD 0.10 mg/dL, 95% CI -0.38 to 0.58).

Serum calcium

Babarykin 2004 reported calcium-enriched bread significantly increased serum calcium levels compared to calcium acetate (Analysis 1.2 (53 participants): MD 0.16 mmol/L, 95% CI 0.09 to 0.23).

Herselman 1995 reported no significant difference in calcium levels between very low protein intake (0.4 g protein/kg/d) and low protein intake (0.6 g protein/kg/d) (Analysis 2.2 (22 participants): MD 0.00 mmol/L, 95% CI -0.17 to 0.17).

Calcium × phosphate product

Babarykin 2004 reported calcium-enriched bread significantly reduced calcium × phosphate product compared to calcium acetate (Analysis 1.3 (53 participants): MD -0.62 $mmol^2/L^2$, 95% CI -0.77 to -0.47).

Alkaline phosphatase activity

Babarykin 2004) reported no significant difference in alkaline phosphatase activity between calcium-enriched bread and calcium acetate (Analysis 1.4 (53 participants): MD 10.00 IU/L, 95% CI -2.70 to 22.70).

Herselman 1995 reported no significant difference in alkaline phosphatase activity between very low and low protein intake (Analysis 2.3 (22 participants): MD -22.00 U/L, 95% CI -78.25 to 34.25).

Parathyroid hormone

PTH was significantly lower with very low protein intake compared to low protein intake (Analysis 2.4 (2 studies, 41 participants): MD -69.64 pmol/L, 95% CI -139.83 to 0.54; I^2 = 57%) (Di Iorio 2003; Herselman 1995).

Isakova 2013 reported PTH was significantly lower with low phosphorous intake compared to ad libitum diet (Analysis 5.2.1 (20 participants): MD 25.60 pg/mL, 95% CI 5.13 to 46.07), however there was no significant difference in PTH between low phosphorous intake plus lanthanum carbonate compared to ad libitum diet plus lanthanum carbonate (Analysis 5.2.2 (19 participants): MD 31.60 pg/mL, 95% CI -29.82 to 93.02).

Fibroblast growth factor 23

Isakova 2013 reported no significant difference in FGF-23 with low phosphorous intake compared to ad libitum diet (Analysis 5.3.1 (20 participants): MD 2.30 RU/mL, 95% CI -13.18 to 17.78), however there was a significant decrease in FGF-23 in the low phosphorous intake plus lanthanum carbonate group compared to ad libitum diet plus lanthanum carbonate (Analysis 5.3.2 (19 participants): (MD -333.80 RU/mL, 95% CI -526.60 to -141.00).

Adverse events

Lou 2012 reported clinical complications (3) and kidney transplantation (3), but participants' groups were not reported.

Isakova 2013 reported five participants (three who received lanthanum carbonate and two who received lanthanum carbonate placebo) had gastrointestinal adverse effects. Two participants in low phosphate diet plus lanthanum carbonate group had nausea and vomiting.

The included studies did not report on any other of the secondary outcomes of interest for this review.

DISCUSSION

Summary of main results

Evidence from the included studies was low quality and insufficiently powered to inform clinical decision making about the value of dietary modification for people with CKD-MBD. None of the included studies reported on the primary outcomes of cardiovascular events or fracture; only one study reported adverse events and another reported mortality. Most studies focused on chemical parameters, particularly serum phosphorus levels.

There was limited, low quality evidence to indicate that calcium-enriched bread may increase serum calcium, decrease serum phosphorus and the calcium × phosphate product (Babarykin 2004). Elsewhere, it was reported that reduced phosphorus intake may decrease serum phosphorus level (Lou 2012; Sullivan 2009). Low phosphorus intake plus lanthanum carbonate showed benefit in decreasing FGF-23 level compared with ad libitum diet plus lanthanum carbonate (Isakova 2013). Very low protein intake was not superior to conventional low protein diet in terms of effect on serum phosphorus, serum calcium, and alkaline phosphatase levels (Di Iorio 2003; Herselman 1995), however PTH levels were significantly lower with very low protein diets. Low protein intake supplemented with keto-acids may decrease serum phosphorus compared with normal protein intake in people undergoing haemodialysis (Li 2011c). No changes in PTH and alkaline phosphatase were observed when haemodialysis patients adopted a hypolipaemic diet compared with statins (Bunio 2004). Compared with a normal diet, post-haemodialysis diet supplements did not increase serum phosphorus levels (Sharma 2002c).

Restricting protein or phosphorus, taking calcium-enriched bread in the diet may have positive effects for people with CKD. It mainly showed in chemical parameters. However, none of the included studies reported cardiovascular events and fracture, and only one study reported mortality. CKD-MBD guidelines currently suggest not exceeding dietary phosphorus intake of 800 to 1000 mg/day (Bellorin-Font 2013; Goldsmith 2010), but little practical information about how to assess and alter dietary phosphate intake was provided, the same as the included studies. It is worth noting that combined interventions, like calcium-enriched bread served as a phosphate binder, showed another way of decreasing phosphorus level.

Overall completeness and applicability of evidence

The included studies were conducted in America, China, India, Italy, Latvia, Poland, Spain and South Africa. Participant ethnicity was not reported. Herselman 1995, Isakova 2013 and Lou 2012 reported clear age definitions for inclusion (≥ 18 years); all other studies provided mean age. It is unknown if the dietary interventions investigated had similar effects on children. CKD stages among the included studies differed; six included people undergoing haemodialysis (Babarykin 2004; Bunio 2004; Li 2011c; Lou 2012; Sharma 2002c; Sullivan 2009).

Isakova 2013 reported estimated GFR of 15 to 59 mL/min/1.73 m^2. Herselman 1995 reported serum creatinine (150 to 700 µmol/L) but Di Iorio 2003 analysed creatinine clearance (≤ 25 mL/min). A robust conclusion therefore could not be made about the CKD stage at which people may derive benefits from any of the interventions.

Pooled analysis was not conducted because of the range and diversity of interventions explored in the studies. Some dietary interventions were home-prepared and others were commercial preparations (Sharma 2002c); content and manufacturing methods were not reported. Only calorie and calcium content were reported.

Although results showed some positive outcomes, the studies were underpowered and provided low quality evidence. Outcomes should be interpreted with caution.

Quality of the evidence

The methodological quality of the included studies was poor. Although all studies reported assigning randomised controlled methods, only one study reported specific randomisation method (Sullivan 2009). None reported allocation concealment. Isakova 2013 was assessed as at low risk of detection bias because the investigators remained blinded to the dietary group. Overall, the quality of the evidence was assessed as low and insufficiently powered to inform clinical decision making.

Potential biases in the review process

The small number of included studies meant that we were unable to construct a funnel plot to investigate publication bias.

Agreements and disagreements with other studies or reviews

Di Iorio 2012 reported that intensive restriction of protein and phosphate intake decreased FGF-23 and serum phosphorus level compared to low protein diet. Fouque 2009 found that reducing protein intake in people with CKD could reduce renal death rate (defined as dialysis, death, or kidney transplantation) by 32% compared with higher or unrestricted protein intake. These studies supported protein restriction in people with CKD. Other dietary phosphate control interventions included reducing food additives and boiling (Cupisti 2013).

Restricting protein may be contraindicated for people with uraemia. Klahr 1994 found that very low protein diets did not significantly slow progression of kidney disease compared with low protein diets among people with CKD stage 3 (GFR 25 to 55 mL/min/1.73 m^2). Johnson 2006 considered that therapeutic effects of low protein diets were unclear, because of the poor evidence and the high prevalence of malnutrition in people with CKD.

AUTHORS' CONCLUSIONS

Implications for practice

There was limited, low powered and suboptimal quality evidence to suggest that consumption of calcium-enriched bread or low phosphorus and protein intake may provide some benefit for people with CKD-MBD. Very low protein intake, post-haemodialysis diet supplements and hypolipaemic diets were conferred no significant benefit compared with controls. There was insufficient evidence to support the use of these interventions.

Implications for research

Large, well-designed RCTs are needed to evaluate the effect of dietary interventions or combination interventions (including diet) for people with CKD-MBD that report mortality, cardiovascular and fracture-related outcomes and measure impact on quality of life. Adverse events, reasons for participants' withdrawals, and losses to follow-up should be reported.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Babarykin 2004

Methods	• Study design: RCT • Duration of study: 14 weeks
Participants	• Country: Latvia • Setting: university hospital outpatient dialysis unit • Diagnostic criteria: no detailed information • Number: treatment group (27); control group (26) • Mean age ± SD: 49.8 ± 10.1 years • Sex (M/F): 26/27 • Comorbidities: hypophosphataemia, non-diabetic
Interventions	Treatment group • Discontinued the use of calcium acetate for the first 2 weeks, then received 30 to 40 g Ca-bread, which containing 2.5% of elemental calcium (by weight) 3 times a day for the next 8 weeks, then consumed the Ca-bread between their main meals for the next 2 weeks, and returned to the initial diet for the last 2 weeks Control group • Received calcium acetate (Calcium Nephro 700, Medice, Germany) as the principal phosphate binder (5 to 7 capsules of 700 mg calcium acetate or 886 to 1,244 mg elemental calcium was consumed with the patient's main meals on a thrice daily basis)
Outcomes	• Mean serum phosphorus (mmol/L) • Mean serum calcium (mmol/L) • Mean calcium × phosphate product • Total alkaline phosphatase activity (U/L) • iPTH (pmol/L)
Notes	

Babarykin 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Bunio 2004

Methods	• Study design: RCT • Duration of study: 6 months
Participants	• Country: Poland • Setting: not reported • Diagnostic criteria: not reported • Time on HD: 38.7 ± 32.8 mo • Number (included/randomised): 77/62 • Mean age ± SD: 54 ± 13 years • Sex (M/F): 40/37 • Comorbidity: lipid disturbances
Interventions	Treatment group • Hypolipaemic diet Control group • Lovastatin: 20 mg/d
Outcomes	• Bone specific alkaline phosphatase (U/L) • iPTH (pmol/L)
Notes	• Abstract only, unable to obtain full text • Details of hypolipaemic diet were unclear

Bunio 2004 *(Continued)*

- Not included in the meta-analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	High risk	iPTH, bone specific alkaline phosphatase were listed in the methods, but no detailed information provided in the results
Other bias	Unclear risk	Insufficient information to permit judgement

Di Iorio 2003

Methods	• Study design: RCT • Duration of study: 24 months
Participants	• Country: Italy • Setting: outpatient clinic • Diagnostic criteria: CrCl ≤ 25 mL/min/1.73 m^2 • Number: treatment group (10); control group (10) • Mean age ± SD (years): treatment group (52 ± 15); control group (57 ± 17) • Sex (M/F): treatment group (6/4); control group (6/4) • Comorbidity: not reported • Exclusion criteria: bleeding or diseases potentially affecting EPO response such as neoplastic diseases, infectious diseases, severe malnutrition
Interventions	Treatment group • 35 kcal/kg/d but with 0.3 g/kg/d of protein of vegetable origin, and supplemented with a mixture of keto-analogues and essential amino-acids administered at the dose of 1 tablet/5 kg body weight; each tablet contained calcium keto-isoleucine 67 mg, calcium keto-leucine 101 mg, calcium phenylpyruvate 68 mg, calcium keto-valine 86 mg, calcium hydroxy-methionine 59 mg, L-lysine monoacetate 105 mg, L-threonine 53 mg, L-histidine 38 mg, and L-tyrosine 30 mg Control group

Di Iorio 2003 *(Continued)*

	• 0.6 g protein/kg body weight/d with a caloric intake of 35 kcal/kg/d
Outcomes	• Serum phosphorus (mmol/L) • iPTH (pmol/L)
Notes	• At 18 months only 9 patients analysed in the control group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Most control group participants withdrew after 18 months; missing data were therefore imbalanced at the end of the study (24 months)
Selective reporting (reporting bias)	Low risk	Published reports included all prespecified outcomes
Other bias	Unclear risk	Insufficient information to permit judgement

Herselman 1995

Methods	• Study design: RCT • Duration of study: 9 months
Participants	• Country: South Africa • Setting: outpatient clinic • Diagnostic criteria: history of confirmed CKD for at least 6 months; SCr 150 to 700 µmol/L; no evidence of diabetes mellitus, liver disease, alcoholism, underlying malignancy or psychiatric disorders; no prescription for corticosteroids, cyclophosphamide, angiotensin-converting enzyme inhibitors, calcium entry blockers or other bone toxic drugs • Number: (treatment group (11); control group (11) • Mean age ± SD (years): treatment group (42 ± 13); control group (43 ± 15) • Sex (M/F): treatment group (7/4); control group (5/6)
Interventions	Patients received the same standard of counselling. Each patient was supplied with food scales for the weighing of food, and was visited at home to optimise education. Following the training period of 8 weeks, patients were matched for underlying nephropathy, SCr, creatinine clearance, known duration of disease, age, sex and dietary knowledge, then randomised.

Herselman 1995 *(Continued)*

	Treatment group • 0.4 g protein/kg/d supplemented with essential amino acids Control group • 0.6 g protein/kg/d
Outcomes	• Serum phosphorus (mmol/L) • Serum calcium (mmol/L) • PTH (pmol/L) • Alkaline phosphatase (U/L)
Notes	• Funding: "supported by grants from Kabi Vitrum AB, Stockholm, Sweden; Adcock-Ingram Laboratoris Ltd, South Africa, and Roussel Laboratories (Pty) Ltd, South Africa"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data at nine months follow-up
Selective reporting (reporting bias)	Low risk	Published report included all specified outcomes
Other bias	Unclear risk	Insufficient information to permit judgement

Isakova 2013

Methods	• Study design: RCT • Study time frame: July 2009 to March 2012 • Duration of study: 3 months
Participants	• Country: USA • Setting: clinical research centre • Diagnostic criteria: eGFR of 15-59 mL/min/1.73 m^2 on the basis of the Modification of Diet in Renal Disease equation, and had normal phosphate levels (2.5 to 4.6 mg/dL) • Number: treatment group A (10); control group A (10); treatment group B (8); control group B (11)

Isakova 2013 *(Continued)*

- Mean age ± SD (years): treatment group A (56.2 ± 10.1); control group B (55.1 ± 12.6); treatment group B (56.1 ± 10.0); control group B (54.3 ± 9.8)
- Sex (M/F): treatment group A (7/3); control group A (5/5); treatment group B (5/3); control group B (8/3)
- Comorbidity: not reported
- Exclusion criteria: hyperphosphataemia; rapidly advancing CKD, primary hyper- or hypoparathyroidism or prior parathyroidectomy; malabsorption; malnutrition, liver disease; cholestasis; anaemia; received prior counselling by a nutritionist within 6 months; taking phosphate binders; hospitalised within the previous 4 weeks; pregnant or breastfeeding mothers; unable to provide written informed consent

Interventions	All participants met with the dietitian, who provided personalized dietary recommendations during a 60-minute session at the randomisation visit and at 30-minute follow-up visits during weeks 2, 8, and 12, when adherence with the dietary intervention was reassessed with 3-day food records. Dietitian used the food records to counsel participants to follow a diet tailored to their randomisation group. Treatment group A • 900-mg phosphate diet • Lanthanum carbonate placebo Control group A • ad libitum diet • Lanthanum carbonate placebo Treatment group B • 900 mg phosphate diet • Lanthanum carbonate (1000 mg, 3 times/d with meals) Control group B • ad libitum diet • Lanthanum carbonate (1000 mg, 3 times/d with meals)
Outcomes	• Serum phosphorus (mg/dL) • FGF-23 (RU/mL) • PTH (pg/mL)
Notes	• Funding: "supported by a grant from Shire Pharmaceuticals and by grants from the National Institutes of Health and the National Institute of Diabetes and Digestive and Kidney Diseases: K23DK087858 (T.I.), R01DK076116 (M.W.) and R01DK081374 (M.W.)" • "Shire Pharmaceuticals gave full rights of publication to the investigators. Shire did review the manuscript but did not participate in the conceptual design, data analysis, interpretation of the results, or writing of the manuscript"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	Dietitian and participants were unblinded to the assigned dietary counselling group

Isakova 2013 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators remained blinded to the dietary group
Incomplete outcome data (attrition bias) All outcomes	High risk	Imbalance in numbers and reasons for missing data across intervention groups
Selective reporting (reporting bias)	High risk	Data did not show all of the study's pre-specified primary outcomes
Other bias	Unclear risk	Insufficient information to permit judgement

Li 2011c

Methods	• Study design: RCT • Duration of study: 8 weeks
Participants	• Country: China • Setting: single centre • Diagnostic criteria: not reported • Number: treatment group (20); control group (20) • Mean age ± SD (years): treatment group (52.4 ± 4.9); control group (51.1 ± 5.8) • Sex (M/F): treatment group (10/10); control group (11/9) • Comorbidity: uncontrolled hyperphosphataemia
Interventions	Treatment group • Restriction of dietary protein intake with keto-acid supplementation (0.8 g/kg ideal body weight/day with keto-acids x 12 tablets/d) Control group • Normal dietary protein intake(normal dietary protein intake: 1.0 to 1.2 g/kg ideal body weight/day according to the patient's routine diet)
Outcomes	• Serum phosphorus (mmol/L) • Serum calcium (mmol/L)
Notes	• Phosphorus and calcium control group data not provided in detail at 8 weeks - not included in the meta-analyses • Funding: "supported by a grant from New Century Grant for the Talented People by National Education Committee of China, and Ketosteril Research Award by Fresenius Kabi Deutschland GmbH"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Li 2011c *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Phosphorus and calcium data from control group participants were not provided in detail at the end of 8 weeks
Selective reporting (reporting bias)	Low risk	Published reports included all prespecified outcomes
Other bias	Unclear risk	Insufficient information to permit judgement

Lou 2012

Methods	• Study design: RCT • Duration of study: 6 months
Participants	• Country: Spain • Setting: multicentre • Diagnostic criteria: not reported • Number (randomised/analysed): treatment group (46/41); control group (45/39) • Mean age ± SD (years): treatment group (61.3 ± 15); control group (63 ± 16) • Sex (F): treatment group (46.2%); control group (48.8%)
Interventions	Treatment group • Patients in an initial visit with a registered dietitian received instructions to elaborate menus. The menus were designed to offer about 0.9 to 1 g/kg ideal weight/d of proteins, 30 kcal/kg ideal weight/d, 800 to 900 mg phosphorus/d and 600 mg calcium/d Control group • Usual dietary recommendations for dialysis patients explained at routine medical visits
Outcomes	• Serum phosphorus (mg/dL) • PTH (pg/mL)
Notes	• 91 patients were randomised, 11 patients were lost: clinical complications (3); kidney transplant (3); dialysis unit change (2); consented withdrawals (3)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Lou 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data at the end of the study
Selective reporting (reporting bias)	Low risk	Published reports included all prespecified outcomes
Other bias	Unclear risk	Insufficient information to permit judgement

Sharma 2002c

Methods	• Study design: RCT • Duration of study: 1 month
Participants	• Country: India • Setting: HD unit • Diagnostic criteria: Not reported • Number (randomised/analysed): 47/40; treatment group 1 (16) treatment group 2 (10); control group (14) • Mean age ± SD (years): treatment group 1 (32.7 ± 7.9); treatment group 2 (29.6 ± 8); control group (31.9 ± 6.9) • Sex (M/F): 35/5
Interventions	Treatment group 1 • Home-prepared formula 500 Kcal and 15 g protein as a milkshake post-HD for 1 month Treatment group 2 • Commercial formula 500 Kcal and 15 g protein as a milkshake post-HD for 1 month Control • Diet included protein intake of 1.2 g/kg/d and 35 to 45 kcal/kg/d of energy. Dietary potassium restricted to 60 mEq/L, fluid to 500 to 1500 mL depending on native urine output, sodium to 2 to 4 g/d, and phosphorus to 1 g/d
Outcomes	• Serum phosphorus (mg/dL)
Notes	• 7 patients not analysed (groups not stated)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported

Sharma 2002c *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Seven patients did not complete the study; data for these participants were not reported
Selective reporting (reporting bias)	Low risk	The published reports included all expected outcomes that were pre-specified
Other bias	Unclear risk	Insufficient information to permit judgement

Sullivan 2009

Methods	• Study design: RCT • Duration of study: 3 months
Participants	• Country: USA • Setting: multicentre • Diagnostic criteria: HD patients • Number: treatment group (145); control group (134) • Mean age ± SD (years): treatment group (54 ± 13); control group (52 ± 13) • Sex (M/F): treatment group (83/62); control group (88/46) • Comorbidity: hyperphosphataemia
Interventions	Intervention • A study coordinator provided approximately 30 minutes of education regarding phosphorus-containing additives and provided each intervention participant with a small magnifier in a plastic case. The names of common phosphorus-containing additives were printed on the case. The coordinator instructed participants to avoid purchasing any items whose ingredient lists include phosphorus-containing additives. A handout that listed specific menu items to be avoided was also given because they contained phosphorus additives. The study coordinator telephoned intervention participants during the second month of the study to reinforce the instructions and to answer any questions. Control • Participants continued to receive care from their dietitians and nephrologists. A study coordinator telephoned control participants during the second month of the study
Outcomes	• Serum phosphorus (mg/dL)
Notes	• Funding: "supported by grant DK51472 from the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland, and by the Leonard C. Rosenberg Renal Research Foundation, Cleveland, Ohio. Role of the Sponsor: The funding organizations had no role in the design and conduct

Sullivan 2009 *(Continued)*

of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	a random number generator was used
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data had similar reasons and balanced in numbers across intervention groups. Multiple imputation was used to account for missing data.
Selective reporting (reporting bias)	Low risk	The published reports included all expected outcomes that were pre-specified
Other bias	Unclear risk	Insufficient information to permit judgement

CKD - chronic kidney disease; CrCl - creatinine clearance; FGF-23 fibroblast growth factor 23; HD - haemodialysis; M/F - male/female; PTH - parathyroid hormone; RCT - randomised controlled trial; SCr - serum creatinine

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12611000500954	Wrong intervention
Ambrus 2003	Wrong intervention
Ashurst 2003	Wrong intervention
Cheng 2008	Wrong intervention
Chertow 2003	Wrong intervention
Clark 2010	Wrong intervention
Moe 2011	Study duration was shorter than our inclusion criteria
Morey 2008	Wrong intervention
NCT01665651	Wrong intervention

Study	Reason for exclusion
Olivero 2006	Wrong intervention
Padhi 2007	Wrong intervention
Spiegel 2012	Study duration was shorter than our inclusion criteria
Young 2009a	Wrong intervention

Characteristics of studies awaiting assessment *[ordered by study ID]*

Akizawa 2014a

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Block 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Garini 1992

Methods	• Study design: RCT • Duration of study: not reported
Participants	• Country: Italy • Setting: not reported • Diagnostic criteria: not reported • Number: 21 • Age: not reported • Sex: not reported • Comorbidity: not reported
Interventions	Treatment group

Garini 1992 *(Continued)*

	• 0.4 g of protein/kg/d, supplemented with a mixture of essential amino acids which contained HIS, TYR and a high proportion of branched chain amino acids Control group • 0.6 g of protein/kg/d
Outcomes	• Not reported
Notes	• Published in Italian; English language abstract only

Hill 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Karavetian 2012

Methods	• Study design: RCT (block randomisation) • Duration of study: 6 months • Blinding: single-blind
Participants	• Country: Lebanon • Setting: not reported • Diagnostic criteria: not reported • Number: 750 • Age: not reported • Sex: not reported • Comorbidity: not reported
Interventions	Treatment group 1 • Medical nutritional therapy for 6 months as 2 hours/patient/mo, delivered by externally recruited dietitians, fully dedicated to the unit Treatment group 2 • Medical nutritional therapy was delivered by the hospital dietitian after HD-specific nutritional training Control group • Control
Outcomes	• Serum phosphorus (mg/dL)

Karavetian 2012 *(Continued)*

Notes	• Abstract only available. We were unable to obtain full text and the details of medical nutritional therapy were unclear

Karavetian 2013

Methods
Participants
Interventions
Outcomes
Notes

DATA AND ANALYSES

Comparison 1. Calcium-enriched bread versus calcium acetate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum phosphorus	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Serum calcium	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Calcium × phosphate product	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Alkaline phosphatase activity	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Calcium-enriched bread versus calcium acetate, Outcome 1 Serum phosphorus.

Study or subgroup	Calcium-enriched bread		Calcium acetate		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Babarykin 2004	27	1.7 (0.2)	26	2.1 (0.2)		-0.41[-0.51,-0.31]

Analysis 1.2. Comparison 1 Calcium-enriched bread versus calcium acetate, Outcome 2 Serum calcium.

Study or subgroup	Calcium-enriched bread N	Calcium-enriched bread Mean(SD)	Calcium acetate N	Calcium acetate Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Babarykin 2004	27	2.3 (0.1)	26	2.1 (0.2)		0.16[0.09,0.23]

Higher with calcium acetate | -0.5 | -0.25 | 0 | 0.25 | 0.5 | Higher with calcium-enriched bread

Analysis 1.3. Comparison 1 Calcium-enriched bread versus calcium acetate, Outcome 3 Calcium × phosphate product.

Study or subgroup	Calcium-enriched bread N	Calcium-enriched bread Mean(SD)	Calcium acetate N	Calcium acetate Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Babarykin 2004	27	3.8 (0.3)	26	4.4 (0.3)		-0.62[-0.77,-0.47]

Lower with calcium-enriched bread | -1 | -0.5 | 0 | 0.5 | 1 | Lower with calcium acetate

Analysis 1.4. Comparison 1 Calcium-enriched bread versus calcium acetate, Outcome 4 Alkaline phosphatase activity.

Study or subgroup	Calcium-enriched bread N	Calcium-enriched bread Mean(SD)	Calcium acetate N	Calcium acetate Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Babarykin 2004	27	105 (26)	26	95 (21)		10[-2.7,22.7]

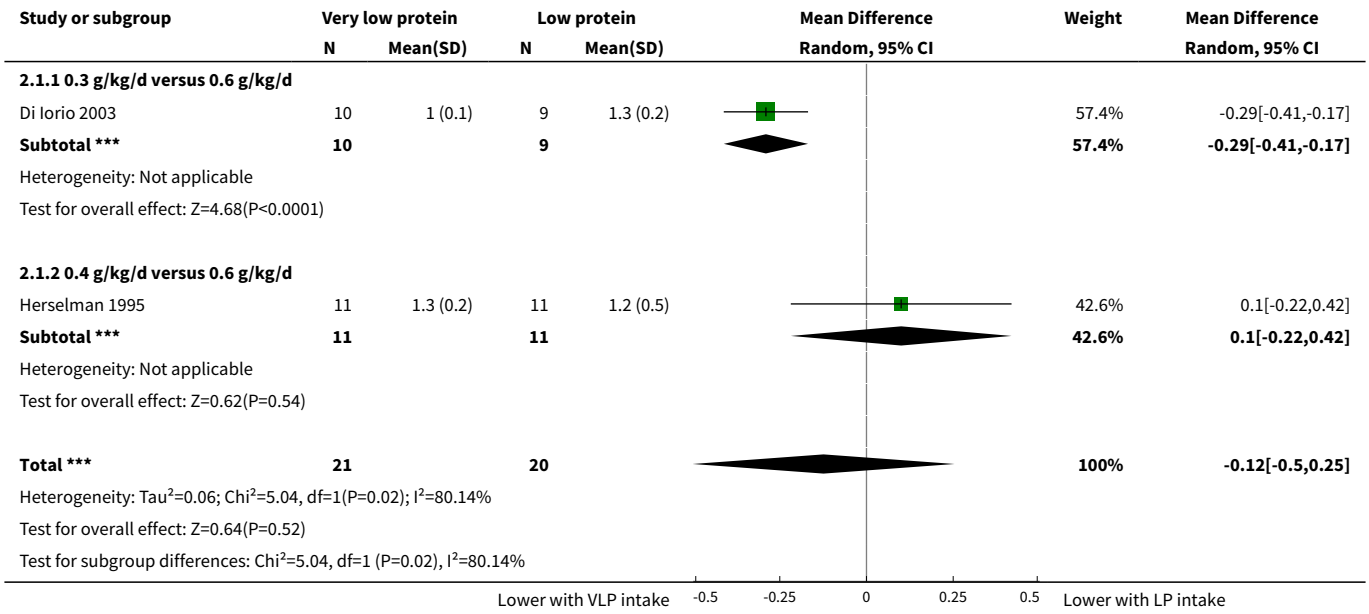
Higher with calcium-enriched bread | -50 | -25 | 0 | 25 | 50 | Higher with calcium acetate

Comparison 2. Very low versus low protein intake

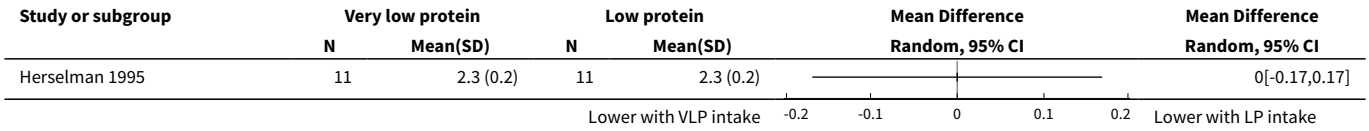
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum phosphorus	2	41	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.50, 0.25]
1.1 0.3 g/kg/d versus 0.6 g/kg/d	1	19	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.41, -0.17]
1.2 0.4 g/kg/d versus 0.6 g/kg/d	1	22	Mean Difference (IV, Random, 95% CI)	0.10 [-0.22, 0.42]
2 Serum calcium	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Alkaline phosphatase	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 PTH	2	41	Mean Difference (IV, Random, 95% CI)	-69.64 [-139.83, 0.54]
4.1 0.3 g/kg/d versus 0.6 g/kg/d	1	19	Mean Difference (IV, Random, 95% CI)	-94.0 [-121.17, -66.83]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 0.4 g/kg/d versus 0.6 g/kg/d	1	22	Mean Difference (IV, Random, 95% CI)	-17.0 [-112.42, 78.42]

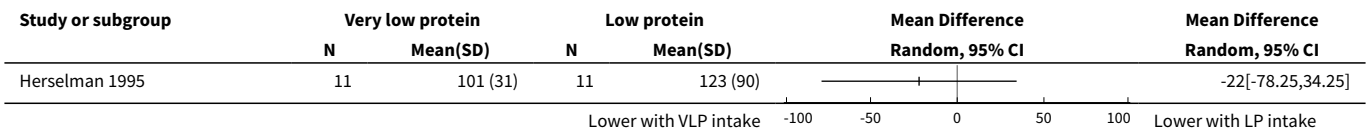
Analysis 2.1. Comparison 2 Very low versus low protein intake, Outcome 1 Serum phosphorus.



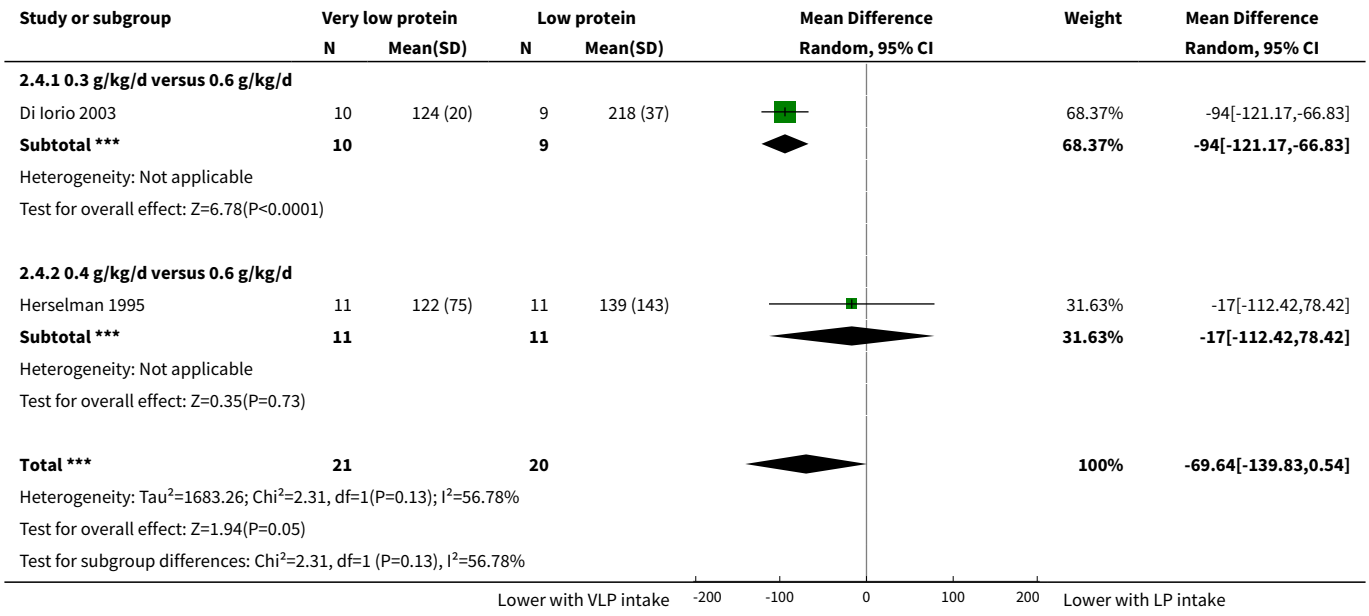
Analysis 2.2. Comparison 2 Very low versus low protein intake, Outcome 2 Serum calcium.



Analysis 2.3. Comparison 2 Very low versus low protein intake, Outcome 3 Alkaline phosphatase.



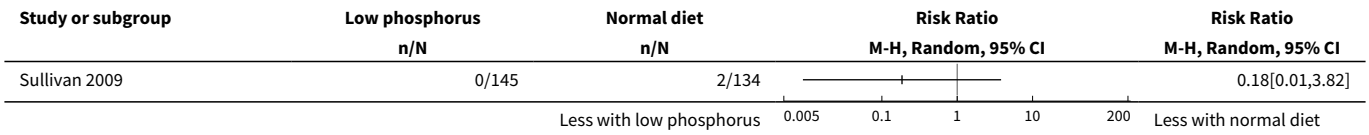
Analysis 2.4. Comparison 2 Very low versus low protein intake, Outcome 4 PTH.



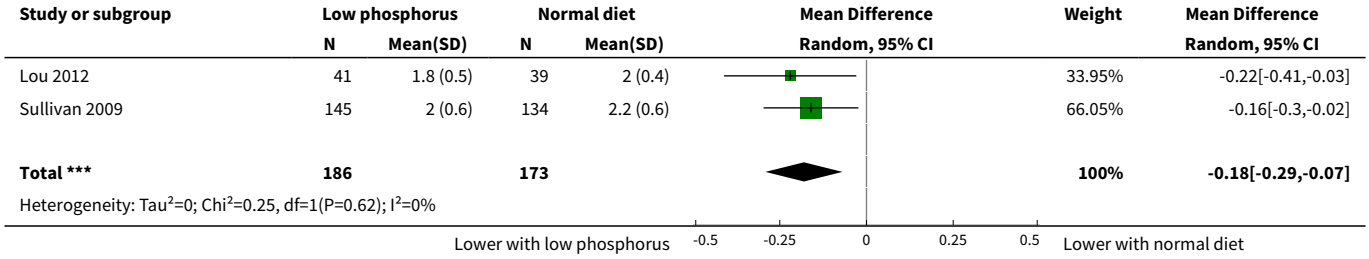
Comparison 3. Low phosphorus intake versus normal diet

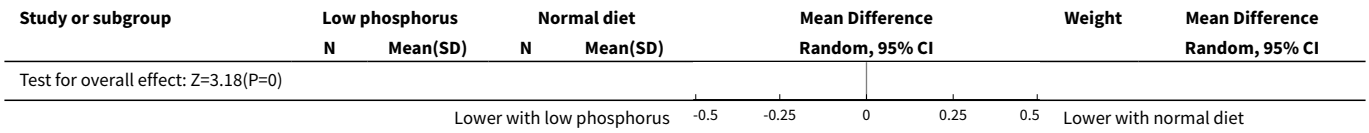
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Serum phosphorus	2	359	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.29, -0.07]

Analysis 3.1. Comparison 3 Low phosphorus intake versus normal diet, Outcome 1 Mortality.



Analysis 3.2. Comparison 3 Low phosphorus intake versus normal diet, Outcome 2 Serum phosphorus.

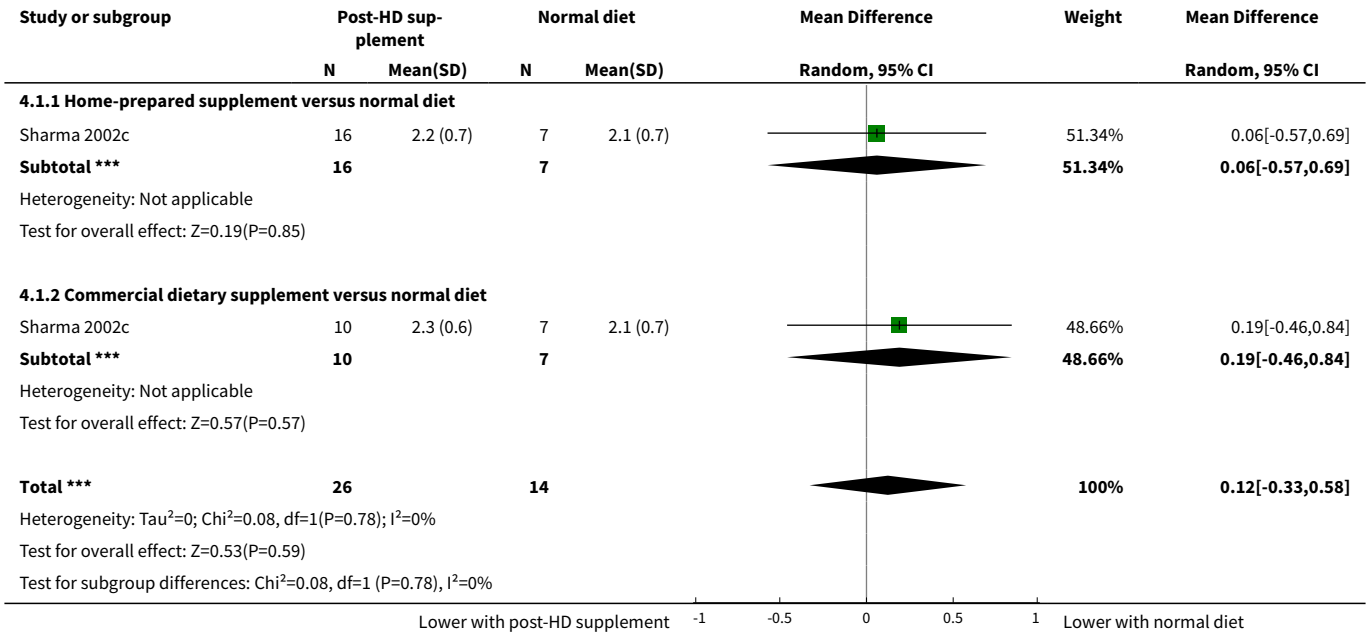




Comparison 4. Post-haemodialysis dietary supplement versus normal diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum phosphorus	1	40	Mean Difference (IV, Random, 95% CI)	0.12 [-0.33, 0.58]
1.1 Home-prepared supplement versus normal diet	1	23	Mean Difference (IV, Random, 95% CI)	0.06 [-0.57, 0.69]
1.2 Commercial dietary supplement versus normal diet	1	17	Mean Difference (IV, Random, 95% CI)	0.19 [-0.46, 0.84]

Analysis 4.1. Comparison 4 Post-haemodialysis dietary supplement versus normal diet, Outcome 1 Serum phosphorus.

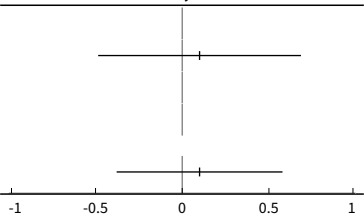


Comparison 5. Low phosphorus intake plus drug/placebo versus ad libitum diet plus drug/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum phosphorus	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Low phosphorus intake plus placebo versus ad libitum diet plus placebo	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Low phosphorus intake plus lanthanum carbonate versus ad libitum diet plus lanthanum carbonate	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 PTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Low phosphorus intake plus placebo versus ad libitum diet plus placebo	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Low phosphorus intake plus lanthanum carbonate versus ad libitum diet plus lanthanum carbonate	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 FGF-23	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Low phosphorus intake plus placebo versus ad libitum diet plus placebo	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Low phosphorus intake plus lanthanum carbonate versus ad libitum diet plus lanthanum carbonate	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

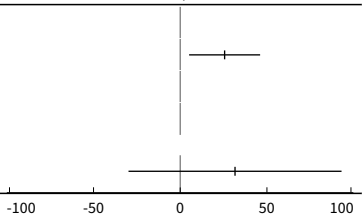
Analysis 5.1. Comparison 5 Low phosphorus intake plus drug/placebo versus ad libitum diet plus drug/placebo, Outcome 1 Serum phosphorus.

Study or subgroup	Low phosphorus N	Low phosphorus Mean(SD)	ad libitum N	ad libitum Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
5.1.1 Low phosphorus intake plus placebo versus ad libitum diet plus placebo						
Isakova 2013	10	3.6 (0.5)	10	3.5 (0.8)		0.1[-0.48,0.68]
5.1.2 Low phosphorus intake plus lanthanum carbonate versus ad libitum diet plus lanthanum carbonate						
Isakova 2013	8	3.4 (0.6)	11	3.3 (0.4)		0.1[-0.38,0.58]



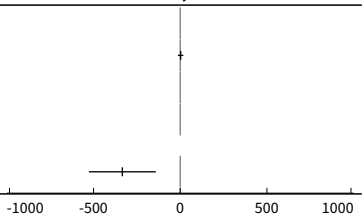
Analysis 5.2. Comparison 5 Low phosphorus intake plus drug/ placebo versus ad libitum diet plus drug/placebo, Outcome 2 PTH.

Study or subgroup	Low phosphorus N	Mean(SD)	ad libitum N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
5.2.1 Low phosphorus intake plus placebo versus ad libitum diet plus placebo						
Isakova 2013	10	75.4 (27.7)	10	49.8 (18)		25.6[5.13,46.07]
5.2.2 Low phosphorus intake plus lanthanum carbonate versus ad libitum diet plus lanthanum carbonate						
Isakova 2013	8	100.5 (80.7)	11	68.9 (43)		31.6[-29.82,93.02]



Analysis 5.3. Comparison 5 Low phosphorus intake plus drug/ placebo versus ad libitum diet plus drug/placebo, Outcome 3 FGF-23.

Study or subgroup	Low phosphorus N	Mean(SD)	ad libitum N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
5.3.1 Low phosphorus intake plus placebo versus ad libitum diet plus placebo						
Isakova 2013	10	-3.3 (21.3)	10	-5.6 (13)		2.3[-13.18,17.78]
5.3.2 Low phosphorus intake plus lanthanum carbonate versus ad libitum diet plus lanthanum carbonate						
Isakova 2013	8	-309.5 (277.6)	11	24.3 (22.4)		-333.8[-526.6,-141]



APPENDICES

Appendix 1. Electronic Search Strategies

Database	Search terms
CENTRAL	1. "renal replacement therapy":ti,ab,kw 2. dialysis:ti,ab,kw 3. (h*emodialysis or h*emofiltration or h*emodiafiltration):ti,ab,kw 4. (CAPD or CCPD or APD):ti,ab,kw 5. "renal insufficiency":ti,ab,kw 6. kidney next disease:ti,ab,kw 7. kidney next failure:ti,ab,kw 8. renal next disease:ti,ab,kw 9. renal next failure:ti,ab,kw 10.(ESRF or ESKF or ESRD or ESKD):ti,ab,kw 11.(CKF or CKD or CRF or CRD):ti,ab,kw 12.(predialysis or pre-dialysis):ti,ab,kw 13.(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12) 14.hyperparathyroidism:ti,ab,kw 15.(bone next disease* or bone next disorder*):ti,ab,kw 16.(#14 OR #15)

(Continued)

	17.(#13 AND #16) 18.renal next osteo*:ti,ab,kw 19.(#17 OR #18) 20.diet:kw 21.((dietary or diet or diets) NEAR/3 (intervention* or change* or changing or modif* or therap*)):ti,ab,kw 22.((phosphate* or protein) NEAR/3 (restrict* or reduc* or low or lower* or modif* or change* or changing)):ti,ab,kw 23.(#20 OR #21 OR #22) 24.(#19 AND #23)
MEDLINE	1. Renal Replacement Therapy/ 2. exp Renal Dialysis/ 3. (hemodialysis or haemodialysis).tw. 4. (hemofiltration or haemofiltration).tw. 5. (hemodiafiltration or haemodiafiltration).tw. 6. dialysis.tw. 7. (CAPD or CCPD or APD).tw. 8. Renal Insufficiency/ 9. exp Renal Insufficiency, Chronic/ 10.Kidney Diseases/ 11.(end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw. 12.(ESRF or ESKF or ESRD or ESKD).tw. 13.(chronic kidney or chronic renal).tw. 14.(CKF or CKD or CRF or CRD).tw. 15.(predialysis or pre-dialysis).tw. 16.or/1-15 17.exp Hyperparathyroidism/ 18.Bone Diseases, Metabolic/ 19.hyperparathyroidism.tw. 20.(bone disease* or bone disorder*).tw. 21.or/17-20 22.and/16,21 23.Renal Osteodystrophy/ 24.renal osteodystrophy.tw. 25.renal bone disease*.tw. 26.or/23-25 27.or/22,26 28.Diet/ 29.Diet, Protein Restricted/ 30.Diet Therapy/ 31.((dietary or diet or diets) adj3 (intervention* or change* or changing or modif* or therap*)).tw. 32.((phosphate* or protein) adj3 (restrict* or reduc* or low or lower* or modif* or change* or changing)).tw. 33.or/28-32 34.and/27,33
EMBASE	1. exp Renal Replacement Therapy/ 2. (hemodialysis or haemodialysis).tw. 3. (hemofiltration or haemofiltration).tw. 4. (hemodiafiltration or haemodiafiltration).tw. 5. dialysis.tw.

(Continued)

6. (PD or CAPD or CCPD or APD).tw.
7. Chronic Kidney Disease/
8. Kidney Failure/
9. Chronic Kidney Failure/
10. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
11. (ESRF or ESKF or ESRD or ESKD).tw.
12. (chronic kidney or chronic renal).tw.
13. (CKF or CKD or CRF or CRD).tw.
14. (predialysis or pre-dialysis).tw.
15. or/1-14
16. exp Hyperparathyroidism/
17. Metabolic Bone Disease/
18. hyperparathyroidism.tw.
19. (bone disease* or bone disorder*).tw.
20. or/16-19
21. and/15,20
22. Renal Osteodystrophy/
23. renal osteo*.tw.
24. renal bone disease*.tw.
25. or/22-24
26. or/21,25
27. Diet/
28. Diet Therapy/
29. Diet Restriction/
30. Renal Diet/
31. Protein Restriction/
32. ((dietary or diet or diets) adj3 (intervention* or change* or changing or modif* or therap*)).tw.
33. ((phosphate* or protein) adj3 (restrict* or reduc* or low or lower* or modif* or change* or changing)).tw.
34. or/27-33
35. and/26,34

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequential-

(Continued)

inadequate concealment of allocations prior to assignment	ly numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse

(Continued)

	effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
16 February 2016	Amended	Clarification of stage of chronic kidney disease in 'Agreements and disagreements with other studies' section

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: LZZ
2. Study selection: MWZ, ZC, GXF
3. Extract data from studies: ZL, XY, LXS
4. Enter data into RevMan: WYF
5. Carry out the analysis: YQC
6. Interpret the analysis: LXS, ZC
7. Draft the final review: LZZ, SGB
8. Disagreement resolution: LXS, GXF
9. Update the review: LZZ, SGB

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Methodological Research Unit, Guangdong Provincial Hospital of Traditional Chinese Medicine, Guangzhou, China.

External sources

- No sources of support supplied

NOTES

16 February 2016: Clarification of stage of chronic kidney disease in Agreements and disagreements with other studies section

INDEX TERMS

Medical Subject Headings (MeSH)

*Bread; Acetates [administration & dosage]; Alkaline Phosphatase [blood]; Bone Density; Bone Diseases, Metabolic [blood] [etiology] [*therapy]; Calcium [blood]; Calcium Compounds [administration & dosage]; Calcium Phosphates [blood]; Calcium, Dietary [*administration & dosage]; Dietary Proteins [administration & dosage]; Fibroblast Growth Factor-23; Hydroxymethylglutaryl-CoA Reductase Inhibitors [administration & dosage]; Phosphorus [administration & dosage] [*blood]; Randomized Controlled Trials as Topic; Renal Insufficiency, Chronic [*complications]

MeSH check words

Humans