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Phosphate binders for preventing and treating bone disease in chronic kidney disease patients (Protocol)

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[Intervention Protocol]

Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

1. The efficacy of the available aluminium salts, calcium salts, sevelamer hydrochloride, lanthanum carbonate, iron salts and magnesium-based phosphate binders in treatment of hyperphosphataemia.
2. To assess their impact on the development of SHPT or low bone turnover based on surrogate markers (PTH, bone specific alkaline phosphatase, osteocalcin or other bone turnover markers) and the serum calcium, phosphate, the calcium by phosphate product, PTH levels. In addition, the influence of these drugs would be assessed in relation to lipid profile, tissue calcification and common symptoms such as pruritis and bone or muscle pain.
3. To study the impact of these agents on BMD assessed by dual-energy X-ray absorptiometry (DXA) or quantitative computerised tomography (QCT) and on bone turnover and mineralization based on histomorphometry and fracture rates.
4. To assess other patient-based 'hard' endpoints such as incidence of cardiovascular events, number of hospital admissions and all-cause mortality rates.
5. To assess the impact of various phosphate binders on metastatic calcification rates.
6. To assess cost effectiveness and quality of life.
7. Patient compliance with therapy and the incidence and nature of side effects.

BACKGROUND

The incidence of chronic kidney disease (CKD) has been increasing worldwide and in the year 2002, about 25 billion dollars has been spent on the care of end-stage renal disease (ESRD) (dialysis) patients in the United States alone (USRDS 2004). Five-year survival rates of dialysis patients have improved secondary to the introduction of treatment options for various complications related to the renal failure including management of anaemia, hyperphosphataemia and cardiovascular disease (USRDS 2004). Early diagnosis and regular monitoring of high-risk patients with CKD may also delay the need for commencing dialysis therapy (Jungers 1997).

Renal bone disease is a common metabolic disorder seen early in the course of CKD secondary to disturbed calcium, phosphorus and vitamin D metabolism. The symptoms range from bone pain to incidence of fractures. The histomorphometric patterns vary from high bone turnover associated with high levels of PTH to low bone turnover or adynamic bone disease, often associated with low or normal PTH levels and defects of mineralization (osteomalacia). Secondary hyperparathyroidism (SHPT) develops early in the course of CKD. With progressive reduction of the glomerular filtration rate (GFR), the development of hyperphosphataemia exerts a direct stimulatory effect on PTH secretion and parathyroid cell proliferation. In addition hyperphosphataemia can induce hypocalcaemia and decreases production of calcitriol, which potentiate further release of PTH.

Approximately 50% of dialysis patients have low bone mineral density, although Z-scores are reported to be similar to (age-matched) controls (Taal 1999). Nevertheless, a higher incidence of hip fracture is reported in patients with ESRD than in the general population (Alem 2000; Ball 2002; Baszko-Blaszyk 2001). The reduced total hip bone mass has been found to be an independent predictor of all cause mortality in these population (Taal 2003) with a nearly doubled risk of mortality for hip fractures (Mittalhenkle 2004). Similarly, 62% of pre-dialysis patients had abnormal bone histology and 50% had low bone mineral density (BMD) similar to dialysis patients (Lobao 2004; Spasovski 2003) placing these patients at increased risk of fractures.

Poor phosphate control is associated with increased morbidity and mortality, increased hospitalisation, premature death, reduced quality of life and increased cost of care in CKD (Block 1998; Delmez 1992; Lowrie 1990). Hyperphosphataemia and hyperparathyroidism has also been shown to increase the fracture related hospitalisation in haemodialysis patients (Block 2004). Patients with phosphorus levels of > 6.5 mg/dL had a 27% higher all-cause mortality risk in comparison to patients with 2.4 to 6.5 mg/dL (Block 2000a). Also calcium-phosphorus product of > 72 mg/dL is associated with higher risk ratio (RR) of death (Block 2000b).These findings have been re-established in the DOPPS study (Young 2005) where phosphorus, calcium, calcium-phosphorus product, PTH are independently and significantly associated with all-cause mortality in dialysis patients. Despite these observations only 30% of dialysis patients are found to maintain phosphorus in suggested target range thereby worsening the hyperparathyroidism.

Further, cardiovascular disease accounts for the majority of deaths in dialysis patients and arterial stiffness is thought to be one of the major contributory factors (Guerin 2001; Stevens 2004). Vascular calcification occurs frequently in these patients and the changes in mineral metabolism accounts for the higher incidence of vascular calcification and its resultant complications (Cozzolino 2005; Ribeiro 1998).Thus management of abnormalities in mineral metabolism in these patients should also target to reduce these metastatic calcification rates thereby possibly reducing the cardiovascular disease burden in these patients.

The management of secondary hyperparathyroidism includes the correction of hyperphosphataemia with dietary phosphorous restriction and use of phosphate binders, and correction of hypocalcaemia with the use of calcium supplementation and vitamin D analogues. Phosphate binders have been widely used since 1970 and numerous agents have been introduced. Aluminium-based binders lead to aluminium accumulation, with resulting neural and bone toxicity. Aluminium has been largely replaced by calcium-based phosphate binders, but calcium salts, particularly when used with calcitriol or vitamin D analogues results in positive calcium balance and potentially in metastatic soft tissue calcification (Block 2005; Chertow 2003; Goodman 2000; Raggi 2001). Thus the calcium and aluminium-free phosphate binder sevelamer hydrochloride was introduced. Sevelamer reduced phosphorus in a similar manner to calcium salts but with a reduced incidence of hypercalcaemia (Bleyer 1999). A case control study had shown that sevelamer resulted in lower risk of hospitalisation and medical care costs in comparison to calcium based therapy (Collins 2000). The rare earth metal, lanthanum carbonate has recently received US and European marketing approval. Long term safety is currently unreported with this agent (D'Haese 2003).

Numerous randomised controlled trials (RCTs) and prospective studies have assessed the efficacy of various phosphate binders in patients with CKD (Asmus 2005; Bleyer 1999; Chertow 1999; Hervas 2003; Schaefer 1991). NKF/K-DOQI guidelines recommend the use of calcium based binders in CKD stage 3 (GRF 30-59 mL/min) and stage 4 patients (GFR: 15-29 mL/min) and both calcium based and calcium aluminium-free binders in dialysis patients (CKD stage 5) with hyperphosphataemia (K-DOQI 2003). Whilst not evidence based, these guidelines also recommend that total daily calcium intake from diet plus calcium based phosphate binders should not exceed 1.5 to 2 g. If followed this would severely limit the use of such binders. A recently published systematic review analysed the efficacy of sevelamer hydrochloride in ESRD patients and its economic impact (Manns 2004). This review did not analyse the efficacy of other phosphate binders and proposed that 781 million dollars would be needed if sevelamer were used for all US dialysis patients. Similarly, another review analyzed the efficacy of sevelamer hydrochloride alone (Burke 2003). With the introduction of lanthanum carbonate, the most appropriate phosphate binder/s are likely to vary with the stage of CKD, age and concomitant illnesses of the patient and of course the efficacy and potential side effects of the compound chosen in relation to other available, appropriate drugs. These issues have not been adequately addressed by systematic reviews to this point.

OBJECTIVES

1. The efficacy of the available aluminium salts, calcium salts, sevelamer hydrochloride, lanthanum carbonate, iron salts and magnesium-based phosphate binders in treatment of hyperphosphataemia.

2. To assess their impact on the development of SHPT or low bone turnover based on surrogate markers (PTH, bone specific alkaline phosphatase, osteocalcin or other bone turnover markers) and the serum calcium, phosphate, the calcium by phosphate product, PTH levels. In addition, the influence of these drugs would be assessed in relation to lipid profile, tissue calcification and common symptoms such as pruritis and bone or muscle pain.
3. To study the impact of these agents on BMD assessed by dual-energy X-ray absorptiometry (DXA) or quantitative computerised tomography (QCT) and on bone turnover and mineralization based on histomorphometry and fracture rates.
4. To assess other patient-based 'hard' endpoints such as incidence of cardiovascular events, number of hospital admissions and all-cause mortality rates.
5. To assess the impact of various phosphate binders on metastatic calcification rates.
6. To assess cost effectiveness and quality of life.
7. Patient compliance with therapy and the incidence and nature of side effects.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) of phosphate binders used for the control of hyperphosphataemia and secondary hyperparathyroidism in CKD patients, alone or in combination with other (non randomised) co interventions (e.g. vitamin D analogues) will be included. The first period of randomised cross-over studies shall also be included. There will be no language restrictions.

Types of participants

Inclusion criteria

CKD patients in stage 3, 4, and 5 as defined by NKF/K-DOQI guidelines (stage 3: GFR 30-59 mL/min; stage 4: GFR 16-29 mL/min; stage 5: GFR < 15 mL/min) greater than 18 years of age.

Exclusion criteria

Studies that included transplant patients as the occurrence of bone disease may be affected other factors such as use of steroids.

Types of interventions

The use of any phosphate binders (aluminium hydroxide, aluminium carbonate calcium acetate, calcium carbonate, calcium ketoglutarate, calcium gluconate, sevelamer hydrochloride, lanthanum carbonate, magnesium carbonate) with or without vitamin D analogues compared to a placebo, or to a different phosphate binder or dose given for at least eight weeks. Comparisons will be:

1. Any phosphate binder with or without vitamin D (25(OH) D) versus placebo.
2. Phosphate binder versus other phosphate binder with or without vitamin D co-intervention.
3. Different doses of the same phosphate binder with or without vitamin D therapy co-intervention.
4. Combination therapy with different phosphate binders versus placebo with or without vitamin D co-intervention.

All above mentioned comparison will be done for pre-dialysis and dialysis patients separately if data is available from the studies.

Types of outcome measures

Primary outcome measure

1. The efficacy of the available aluminium salts, calcium salts, sevelamer, lanthanum carbonate and magnesium based phosphate binders in the prevention and treatment of hyperphosphataemia (serum phosphorous level in mg/dL or mmol/L).
2. To assess the impact of treatment with these drugs on the development of/impact on:
   a. SHPT or low bone turnover based on surrogate markers (PTH, the PTH (1-84)/non-PTH (1-84) ratio, BSALP, osteocalcin or other bone turnover markers).
   b. Serum calcium (in mg/dL or mmol/L), phosphate (mg/dL or mmol/L), the calcium by phosphate product (mmol2/L2 or mg2/dL2), PTH (intact-PTH or PTH (1-84) in pmol/L and pg/mL).
   c. The effect of these agents on lipid parameters (in mg/dL or mmol/L) or calcitriol levels.
   d. The incidence of vascular calcification (as measured by electron beam tomography, ultrasound or other techniques), other soft tissue or valvular calcification and calciphylaxis.
   e. To assess associations of treatment with pruritus, bone or muscular pain as mentioned in the studies.
3. To study the impact of these agents on BMD assessed by DXA or QCT (assessed as change in BMD using Z scores or percent change in g/cm2 at the lumbar spine, femoral neck and radius when reported).
4. To assess 'hard' patient-based endpoints, including:
   a. Bone turnover and mineralization based on histomorphometry and histology.
   b. Fracture (incidence of fracture at any site, vertebral compression fractures, fracture of femur, hip and any long bones identified by radiographic studies.).
   c. Cardiovascular events.
   d. Hospital admission (measured as number of patients who are hospitalised or mean number of days of hospitalisation).
   e. Cardiovascular, vascular, fracture-related and all-cause mortality.
   f. Need for parathyroidectomy.
5. Utilities and cost-effectiveness: life years gained, or quality-adjusted life years gained, or as specified in the studies.
6. Patient compliance with therapy.
7. Incidence and nature of adverse effects, including gastrointestinal (gastritis, diarrhoea, constipation, abdominal bloating), electrolyte imbalance (hypermagnesaemia, hyperkalaemia), accumulation of drugs as demonstrated by bone biopsies (especially for aluminium hydroxide and lanthanum carbonate), and worsening anaemia.

Search methods for identification of studies

Relevant trials will be obtained from the following sources:-

1) The Cochrane Renal Groups Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, (most recent) which will be searched using the following terms:-
#1. KIDNEY DISEASES
#2. KIDNEY FAILURE CHRONIC
#3. KIDNEY FAILURE
#4. RENAL REPLACEMENT THERAPY
#5. RENAL DIALYSIS
#6. HEMOFILTRATION
#7. ((chronic next kidney) or (chronic next renal))
#8. (ckd or ckf or crd or crf or eskd or esrd or eskf or esrf)
#9. (predialysis or dialysis)
#10. (hemodialysis or haemodialysis)
#11. (capd or ccpd or apd)
#12. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11)
#13. BONE DISEASES
#14. RENAL OSTEODYSTROPHY
#15. (bone next disease*)
#16. (bone* and (atroph* or formation or deform* or destruct* or necrosis or resorption or metabol* or turnover or demineral* or decalcif* or density))
#17. (#13 or #14 or #15 or #16)
#18. (#12 and #17)
#19. ALUMINUM HYDROXIDE
#20. CALCIUM CARBONATE
#21. CALCIUM GLUCONATE
#22. POLYAMINES
#23. ANION EXCHANGE RESINS
#24. ((phosphate next buffer*) or (phosphate next binder*))
#25. ((aluminum next carbonate*) or (aluminium next carbonate*))
#26. (calcium next acetate*)
#27. (calcium next ketoglutarate*)
#28. sevelamer
#29. (lanthanum next carbonate*)
#30. (magnesium next carbonate*)
#31. ((aluminum next hydroxide*) or (aluminium next hydroxide*))
#32. colestimide
#33. phoslo
#34. renagel
#35. fosrenol
#36. (#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35)
#37. (#18 and #36)

CENTRAL and the Renal Groups Specialised Register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective (http://www.cochrane.us/masterlist.asp). Therefore we will not specifically search conference proceedings.

2) MEDLINE (1966 to most recent) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Dickersin 1994) with a specific search strategy developed with input from the Trial Search Coordinator.
1. Kidney Diseases/
2. Kidney Failure, Chronic/
3. Kidney Failure/
4. renal replacement therapy/ or exp renal dialysis/ or exp hemofiltration/
5. (chronic kidney or chronic renal).tw.
6. (CKD or CKF or CRD or CRF or ESKD or ESRD or ESKF or ESRF).tw.
7. (predialysis or dialysis).tw.
8. (hemodialysis or haemodialysis).tw.
9. (CAPD or CCPD or APD).tw.
10. or/1-9
11. exp Bone Diseases/
12. Renal Osteodystrophy/
13. bone disease$.tw.
14. (bone$ and (atroph$ or formation or deform$ or destruct$ or necrosis or resorption or metabol$ or turnover or demineral$ or decalcif$ or density)).tw.
15. (osteo$ or hyperparathyroid$ or hyperphosphat$).tw.
16. or/11-15
17. and/10,16
18. Aluminum Hydroxide/
19. Calcium Carbonate/
20. Calcium Gluconate/
21. Polyamines/
22. Anion Exchange Resins/
23. (phosphate buffer$ or phosphate bind$).tw.
24. alumin?um carbonate$.tw.
25. calcium acetate$.tw.
26. calcium ketoglutarate$.tw.
27. sevelamer.tw.
28. lanthanum carbonate$.tw.
29. magnesium carbonate$.tw.
30. alumin?um hydroxide$.tw.
31. colestimide.tw.
32. phoslo.tw.
33. renagel.tw.
34. fosrenol.tw.
35. or/18-34
36. and/17,35

3) EMBASE (1980 to most recent) using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of RCTs (Lefebvre 1996) together with a specific search strategy developed with input from the Trial Search Coordinator.
1. Kidney Disease/
2. Kidney Failure/
3. Chronic Kidney Failure/
4. exp hemodialysis/
5. (hemodialysis or haemodialysis).tw.
6. dialysis.tw.
7. (CAPD or CCPD or APD).tw.
8. predialysis.tw.
9. (chronic renal or chronic kidney).tw.
10. (CKD or CKF or CRD or CRF or ESKD or ESRD or ESKF or ESRF).tw.
11. or/1-10
12. exp Bone Disease/
13. bone disease$.tw.
14. (bone$ and (atroph$ or formation or deform$ or destruct$ or necrosis or resorption or metabol$ or turnover or demineral$ or decalcif$ or density)).tw.
15. (osteo$ or hyperparathyroid$ or hyperphosphat$).tw.
16. or/12-15
17. Aluminum Hydroxide/
18. Calcium Carbonate/

19. Gluconate Calcium/
20. Polyamine/
21. Anion Exchange Resin/
22. Sevelamer/
23. Lanthanum Carbonate/
24. Magnesium Carbonate/
25. Aluminum Carbonate/
26. Calcium Acetate/
27. Phosphate Binding Agent/
28. Aluminum Hydroxide/
29. Colestilan/
30. (phosphate buffer$ or phosphate bind$).tw.
31. alumin?um carbonate$.tw.
32. calcium acetate$.tw.
33. calcium ketoglutarate$.tw.
34. sevelamer.tw.
35. colestimide.tw.
36. phoslo.tw.
37. renagel.tw.
38. fosrenol.tw.
39. lanthanum carbonate$.tw.
40. magnesium carbonate$.tw.
41. alumin?um hydroxide$.tw.
42. or/17-41
43. and/11,16,42

4) Reference lists of nephrology textbooks, review articles and relevant trials.
5) Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous trials.

Data collection and analysis

Included and excluded studies

The review will be undertaken by seven authors (SN, PC, GS, SP, JC, and GE). The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts will be screened independently by (SN) and (PC), who will discard studies that are not applicable, however studies and reviews that might include relevant data or information on trials will be retained initially. Reviewers (SN), (PC) will independently assess retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria. Data extraction will be carried out by the same reviewers independently using standard data extraction forms. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one trial exists, only the publication with the most complete data will be included. Any further information required from the original author will be requested by written correspondence and any relevant information obtained in this manner will be included in the review. Disagreements will be resolved in consultation with GS, GE and JC who will also provide methodological assistance through the review process.

Study quality

The quality of studies to be included will be assessed independently by (SN), and (PC) without blinding to authorship or journal using the checklist developed for the Cochrane Renal Group. Discrepancies will be resolved by discussion with GS. The quality items to be assessed are allocation concealment, intention-to-treat analysis, completeness to follow-up and blinding of investigators, participants, outcome assessors and data analysis.

Quality checklist

Allocation concealment

- Adequate (A): Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study
- Unclear (B): Randomisation stated but no information on method used is available
- Inadequate (C): Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group

Blinding

- Blinding of investigators: Yes/No/not stated
- Blinding of participants: Yes/No/not stated
- Blinding of outcome assessor: Yes/No/not stated
- Blinding of data analysis: Yes/No/not stated

The above are considered not blinded if the treatment group can be identified in > 20% of participants because of the side effects of treatment.

Intention-to-treat

- Yes: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
- Yes: Not stated but confirmed on study assessment
- No: Not reported and lack of intention-to-treat analysis confirmed on study assessment. (Patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation)
- No: Stated but not confirmed upon study assessment
- Not stated

Completeness to follow-up

Per cent of participants excluded or lost to follow-up.

Statistical assessment

For dichotomous outcomes (Incidence of fractures, all-cause mortality and fracture related mortality, bone pain and adverse effects of treatment, number of patients who are hospitalized) results will be expressed as RR with 95% confidence intervals (CI). Data will be pooled using the random effects model but the fixed effects model will also be analysed to ensure robustness of the model chosen and susceptibility to outliers. Where continuous scales of measurement are used to assess the effects of treatment (changes in bone mineral density by DEXA scanning, serum phosphorus, calcium and intact PTH levels, calcium x phosphorus product, days of hospitalization), the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used. Heterogeneity will be analysed using a chi squared 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).

Subgroup analysis will be used to explore possible sources of heterogeneity (e.g. participants, treatments and study quality). Heterogeneity among participants could be related to age, stage of kidney disease and modalities of dialysis used. Heterogeneity in treatments could be related to prior agent(s) used and the agent, dose and duration of various phosphate binders and the use of vitamin D analogues. Subgroup analyses will be performed based on the presence or absence of concomitant illness (such as cardiovascular disease, cerebrovascular disease) and the type of dialysis (haemodialysis versus peritoneal dialysis). Adverse effects will be tabulated and assessed with descriptive techniques, as they are likely to be different for the various agents used. Where possible, the risk difference with 95% CI will be calculated for each adverse effect, either compared to no treatment or to another agent.

Trials of at least eight weeks duration will be selected for the purposes of this systematic review. If possible, the effect of short- and long-term follow-up as a source of significant heterogeneity between trials will be analysed. Plausible explanation for variations in treatment effect will be explored using subgroup analysis based on study quality, length of follow-up, population characteristics (pre-dialysis versus dialysis patients) and use of different phosphate binders. Separate analyses would be done for individual phosphate binders used.

If sufficient RCTs are identified, an attempt will be made to examine for publication bias using a funnel plot (Egger 1997).

REFERENCES

Additional references

Alem 2000

Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, et al. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney International* 2000;**58**(1):396-9. [MEDLINE: 10886587]

Asmus 2005

Asmus HG, Braun J, Krause R, Brunkhorst R, Holzer H, Schulz W, Neumayer HH, Raggi P, Bommer J. Two year comparison of sevelamer and calcium carbonate effects on cardiovascular calcification and bone density. *Nephrology Dialysis Transplantation* 2005;**20**(8):1653-61. [MEDLINE: 15930018]

Ball 2002

Ball AM, Gillen DL, Sherrard D, Weiss NS, Emerson SS, Seliger SL, et al. Risk of hip fracture among dialysis and renal transplant recipients. *JAMA* 2002;**288**(23):3014-8. [MEDLINE: 12479766]

Baszko-Blaszyk 2001

Baszko-Blaszyk D, Grzegorzewska AE, Horst-Sikorska W, Sowinski J. Bone mass in chronic renal insufficiency patients treated with continuous ambulatory peritoneal dialysis. *Advances in Peritoneal Dialysis* 2001;**17**:109-13. [MEDLINE: 11510255]

Bleyer 1999

Bleyer AJ, Burke SK, Dillon M, Garrett B, Kant KS, Lynch D, et al. A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients. *American Journal of Kidney Diseases* 1999;**33**(4):694-701. [MEDLINE: 10196011]

Block 1998

Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *American Journal of Kidney Diseases* 1998;**31**(4):607-17. [MEDLINE: 9531176]

Block 2000a

Block GA, Port FK. Re-evaluation of risks associated with hyperphosphatemia and hyperparathyroidism in dialysis patients: recommendations for a change in management. *American Journal of Kidney Diseases* 2000;**35**(6):1226-37. [MEDLINE: 10845841]

Block 2000b

Block GA. Prevalence and clinical consequences of elevated Ca x P product in hemodialysis patients. *Clinical Nephrology* 2000;**54**(4):318-24. [MEDLINE: 11076108]

Block 2004

Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *Journal of the Amercian Society of Nephrology* 2004;**15**(8):2208-18. [MEDLINE: 15284307]

Block 2005

Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh J, Dreisbach A, et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney International* 2005;**68**(4):1815-24. [MEDLINE: 16164659]

Burke 2003

Burke SK, Dillon MA, Hemken DE, Rezabek MS, Balwit JM. Meta-analysis of the effect of sevelamer on phosphorus, calcium, PTH, and serum lipids in dialysis patients. *Advances in Renal Replacement Therapy* 2003;**10**(2):133-45. [MEDLINE: 12879374]

Chertow 1999

Chertow GM, Dillon M, Burke SK, Steg M, Bleyer AJ, Garrett BN, et al. A randomized trial of sevelamer hydrochloride (RenaGel) with and without supplemental calcium. Strategies for the control of hyperphosphatemia and hyperparathyroidism in hemodialysis patients. *Clinical Nephrology* 1999;**51**(1):18-26. [MEDLINE: 9988142]

Chertow 2003

Chertow GM, Raggi P, McCarthy JT, Schulman G, Silberzweig J, Kuhlik A, et al. The effects of sevelamer and calcium acetate on proxies of atherosclerotic and arteriosclerotic vascular disease in hemodialysis patients. *American Journal of Nephrology* 2003;**23**(5):307-14. [MEDLINE: 12915774]

Collins 2000

Collins AJ, St Peter WL, Dalleska FW, Ebben JP, Ma JZ. Hospitalization risks between Renagel phosphate binder treated and non-Renagel treated patients. *Clinical Nephrology* 2000;**54**(4):334-41. [MEDLINE: 11076110]

Cozzolino 2005

Cozzolino M, Brancaccio D, Gallieni M, Slatopolsky E. Pathogenesis of vascular calcification in chronic kidney disease. *Kidney International* 2005;**68**(2):429-36. [MEDLINE: 16014020]

D'Haese 2003

D'Haese PC, Spasovski GB, Sikole A, Hutchison A, Freemont TJ, Sulkova S, et al. A multicenter study on the effects of lanthanum carbonate (Fosrenol) and calcium carbonate on renal bone disease in dialysis patients. *Kidney International - Supplement* 2003, (85):73-8. [MEDLINE: 12753271]

Delmez 1992

Delmez JA, Slatopolsky E. Hyperphosphatemia: its consequences and treatment in patients with chronic renal disease. *American Journal of Kidney Diseases* 1992;**19**(4):303-17. [MEDLINE: 1562018]

Dickersin 1994

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**(6964):1286-91. [MEDLINE: 7718048]

Egger 1997

Egger M, Davey-Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. *BMJ* 1997;**315**(7109):629-34. [MEDLINE: 9310563]

Goodman 2000

Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *New England Journal of Medicine* 2000;**342**(20):1478-83. [MEDLINE: 10816185]

Guerin 2001

Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 2001;**103**(7):987-92. [MEDLINE: 11181474]

Hervas 2003

Hervas JG, Prados D, Cerezo S. Treatment of hyperphosphatemia with sevelamer hydrochloride in hemodialysis patients: a comparison with calcium acetate. *Kidney International - Supplement* 2003, (85):69-72. [MEDLINE: 12753270]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [MEDLINE: 12958120]

Jungers 1997

Jungers P, Skhiri H, Zingraff J, Muller S, Fumeron C, Giatras I, et al. Benefits of early nephrological management in chronic renal failure. *Presse Medicale* 1997;**26**(28):1325-9. [MEDLINE: 9365486]

K-DOQI 2003

National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease patients. *American Journal of Kidney Diseases* 2003;**42**(4 Suppl 3):70-7. [MEDLINE: 14520607]

Lefebvre 1996

Lefebvre C, McDonald S. Development of a sensitive search strategy for reports of randomized controlled trials in EMBASE. Fourth International Cochrane Colloquium, Adelaide Australia, 20-24 October. 1996.

Lobao 2004

Lobao R, Carvalho AB, Cuppari L, Ventura R, Lazaretti-Castro M, Jorgetti V, et al. High prevalence of low bone mineral density in pre-dialysis chronic kidney disease patients: bone histomorphometric analysis. *Clinical Nephrology* 2004;**62**(6):432-9. [MEDLINE: 15630902]

Lowrie 1990

Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *American Journal of Kidney Diseases* 1990;**15**(5):458-82. [MEDLINE: 2333868]

Manns 2004

Manns B, Stevens L, Miskulin D, Owen WF Jr, Winkelmayer WC, Tonelli M. A systematic review of sevelamer in ESRD and an analysis of its potential economic impact in Canada and the United States. *Kidney International* 2004;**66**(3):1239-47. [MEDLINE: 15327423]

Mittalhenkle 2004

Mittalhenkle A, Gillen DL, Stehman-Breen CO. Increased risk of mortality associated with hip fracture in the dialysis population. *American Journal of Kidney Diseases* 2004;**44**(4):672-9. [MEDLINE: 15384018]

Raggi 2001

Raggi P. Imaging of cardiovascular calcifications with electron beam tomography in hemodialysis patients. *American Journal of Kidney Diseases* 2001;**37**(1 Suppl 2):62-5. [MEDLINE: 11158864]

Ribeiro 1998

Ribeiro SR, Brandao A, Rebelo JR, Guerra A, Resina C, Vila-Lobos A, et al. Cardiac valve calcification in haemodialysis patients: Role of calcium-phosphate metabolism. *Nephrology Dialysis Transplantation* 1998;**13**(8):2307-40. [MEDLINE: 9719161]

Schaefer 1991

Schaefer K, Scheer J, Asmus G, Umlauf E, Hagemann J, von Herrath D. The treatment of uraemic hyperphosphataemia with calcium acetate and calcium carbonate: a comparative study. *Nephrology Dialysis Transplantation* 1991;**6**(3):170-5. [MEDLINE: 1866045]

Spasovski 2003

Spasovski GB, Bervoets AR, Behets GJ, Ivanovski N, Sikole A, Dams G, et al. Spectrum of renal bone disease in end-stage renal failure patients not yet on dialysis. *Nephrology Dialysis Transplantation* 2003;**18**(6):1159-66. [MEDLINE: 12748350]

Stevens 2004

Stevens LA, Djurdjev O, Cardew S, Cameron EC, Levin A. Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: evidence for the complexity of the association between mineral metabolism and outcomes. *Journal of the Amercian Society of Nephrology* 2004;**15**(3):770-9. [MEDLINE: 14978180]

Taal 1999

Taal MW, Masud T, Green D, Cassidy MJ. Risk factors for reduced bone density in haemodialysis patients. *Nephrology Dialysis Transplantation* 1999;**14**(8):1922-8. [MEDLINE: 10462272]

Taal 2003

Taal MW, Roe S, Masud T, Green D, Porter C, Cassidy MJ. Total hip bone mass predicts survival in chronic hemodialysis patients. *Kidney International* 2003;**63**(3):1116-20. [MEDLINE: 12631095]

USRDS 2004

Collins AJ, Kasiske B, Herzog C, Chavers B, Foley R, Gilbertson D, et al. Excerpts from the United States Renal Data System 2004 annual data report: Atlas of end-stage renal disease in the United States. *American Journal of Kidney Diseases* 2005;**45**(1 Suppl 1):1-273. [MEDLINE: 15640975]

Young 2005

Young EW, Albert JM, Satayathum S, Goodkin DA, Pisoni RL, Akiba T, et al. Predictors and consequences of altered mineral metabolism: The Dialysis Outcomes and Practice Patterns Study. *Kidney International* 2005;**67**(3):1179-87. [MEDLINE: 15698460]

WHAT'S NEW

Date	Event	Description
13 August 2009	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 2, 2006

Date	Event	Description
12 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Writing of protocol and review - SN, PC, GF, JC, GE, SP
Screening of titles and abstracts - SN, PC
Assessment for inclusion - SN, PC
Quality assessment - SN, PC
Data extraction - SN, PC
Data entry into RevMan - SN
Data analysis - SN
Disagreement resolution - GS

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

Bone Diseases, Metabolic [*drug therapy] [prevention & control]; Calcium [blood]; Calcium Compounds [adverse effects] [*therapeutic use]; Chelating Agents [adverse effects] [*therapeutic use]; Chronic Disease; Hypercalcemia [chemically induced]; Kidney Diseases [blood] [*complications]; Parathyroid Hormone [blood]; Phosphorus [*blood]; Polyamines [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Sevelamer

MeSH check words

Humans