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KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)

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KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD)

Sv	Tables and figures
Svii	Disclaimer
Sviii	Work Group membership
Six	KDIGO Board Members
Sx	Abbreviations and acronyms
Sxi	Reference Keys
Sxii	Abstract
S1	Foreword
S3	Chapter 1: Introduction and definition of CKD–MBD and the development of the guideline statements
S9	Chapter 2: Methodological approach
S22	Chapter 3.1: Diagnosis of CKD–MBD: biochemical abnormalities
S32	Chapter 3.2: Diagnosis of CKD–MBD: bone
S44	Chapter 3.3: Diagnosis of CKD–MBD: vascular calcification
S50	Chapter 4.1: Treatment of CKD–MBD targeted at lowering high serum phosphorus and maintaining serum calcium
S70	Chapter 4.2: Treatment of abnormal PTH levels in CKD–MBD
S90	Chapter 4.3: Treatment of bone with bisphosphonates, other osteoporosis medications, and growth hormone
S100	Chapter 5: Evaluation and treatment of kidney transplant bone disease
S111	Chapter 6: Summary and research recommendations
S115	Biographic and disclosure information
S120	Acknowledgments
S121	References

TABLES

- S4 Table 1. KDIGO classification of CKD-MBD and renal osteodystrophy
- S10 Table 2. Grading of recommendations
- S12 Table 3. Screening criteria for systematic review topics
- S13 Table 4. Questions for topics not related to treatments
- S15 Table 5. Literature search yield of primary articles for systematic review topics
- S18 Table 6. Grading of study quality for an outcome
- S19 Table 7. GRADE system for grading quality of evidence for an outcome
- S19 Table 8. Final grade for overall quality of evidence
- S19 Table 9. Balance of benefits and harm
- S20 Table 10. Implications of the strength of a recommendation
- S20 Table 11. Determinants of the strength of a recommendation
- S26 Table 12. Suggested frequencies of serum calcium, phosphorus, and PTH measurements according to CKD stage
- S27 Table 13. Sources and magnitude of the variation in the measurement of serum calcium, phosphorus, PTH, and vitamin D sterols
- S30 Table 14. Vitamin D₂ and D₃ and their derivatives
- S36 Table 15. Changes in bone histomorphometric measurements from patients in placebo groups of clinical trials or longitudinal studies
- S40 Table 16. Relationship between fractures and PTH in patients with CKD-MBD
- S41 Table 17. Positive predictive value for iPTH and b-ALP to predict bone turnover in patients with CKD stage 5
- S41 Table 18. Correlation between PTH or other serum markers and BMD
- S52 Table 19. Phosphate-binding compounds
- S63 Table 20. RCTs of phosphate binders in children with CKD
- S63 Table 21. Summary table of RCTs examining the treatment of CKD-MBD with sevelamer-HCl vs calcium-containing phosphate binders in CKD stages 3–5—description of population at baseline
- S63 Table 22. Summary table of RCTs examining the treatment of CKD-MBD with sevelamer-HCl vs calcium-containing phosphate binders in CKD stages 3–5—intervention and results
- S64 Table 23. Evidence matrix for sevelamer-HCl vs calcium-containing phosphate binders in CKD stage 5D
- S65 Table 24. Evidence profile for the treatment of CKD-MBD with sevelamer-HCl vs calcium-containing phosphate binders in CKD stage 5D
- S67 Table 25. Evidence matrix for lanthanum carbonate vs other phosphate binders in CKD stage 5D
- S68 Table 26. Evidence profile of lanthanum carbonate vs other phosphate binders in CKD stages 5D
- S69 Table 27. Summary table of RCT examining alternate HD regimens in CKD stage 5D—description of population at baseline
- S69 Table 28. Summary table of RCT examining alternate HD regimens in CKD stage 5D—intervention and results
- S69 Table 29. Adverse events of alternate HD regimens in CKD stage 5D
- S82 Table 30. RCTs of calcitriol or other vitamin D analogs in children with CKD
- S83 Table 31. Evidence matrix of calcitriol or vitamin D analogs vs placebo in CKD stages 3–5
- S84 Table 32. Evidence profile of treatment of CKD-MBD with calcitriol or vitamin D analogs vs placebo in CKD stages 3–5
- S85 Table 33. Evidence matrix for calcitriol vs vitamin D analogs in CKD stage 5D
- S86 Table 34. Evidence profile for calcitriol vs vitamin D analogs in CKD stage 5D
- S87 Table 35. Evidence matrix for calcimimetics in CKD stage 5D
- S88 Table 36. Evidence profile for calcimimetics in CKD stage 5D
- S98 Table 37. Evidence matrix of bisphosphonates vs placebo/control in CKD stages 3–5
- S99 Table 38. Evidence profile of bisphosphonates vs placebo/control in CKD stages 3–5
- S106 Table 39. RCTs of treatments for CKD-MBD in children with CKD stages 1–5T
- S107 Table 40. Evidence matrix of calcitriol or vitamin D analogs vs placebo or calcium alone in CKD stages 1–5T
- S108 Table 41. Evidence profile of calcitriol or vitamin D analogs vs placebo or calcium alone in CKD stages 1–5T
- S109 Table 42. Evidence matrix of bisphosphonates vs control in CKD stages 1–5T
- S110 Table 43. Evidence profile for the treatment of CKD-MBD with bisphosphonates vs control in CKD stages 1–5T
- S111 Table 44. Summary of cumulative evidence matrix with patient-centered outcomes, other surrogate outcomes, and biochemical outcomes

S112 Table 45. Cumulative evidence matrix for all treatment studies by outcome

S113 Table 46. Grading of recommendations

FIGURES

S5 Figure 1. Interpreting a surrogate outcome trial

S10 Figure 2. Evidence model

S17 Figure 3. Parameters of bone turnover, mineralization, and volume

S24 Figure 4. Prevalence of abnormal mineral metabolism in CKD

S25 Figure 5. Changes in serum calcium, phosphorus, and iPTH with time in hemodialysis patients of DOPPS countries

S28 Figure 6. PTH assays

S35 Figure 7. Prevalence of types of bone disease as determined by bone biopsy in patients with CKD-MBD

S35 Figure 8. Prevalence of histologic types of renal osteodystrophy in children with CKD stages 5-5D

S35 Figure 9. Types of renal osteodystrophy before and after 1995

S36 Figure 10. Prevalence of bone histology types by symptoms in patients with CKD stage 5D receiving HD treatment

S37 Figure 11. Distribution of osteoporosis, osteopenia, and normal bone density by creatinine clearance in general US population

S38 Figure 12. Overlap between osteoporosis and CKD stages 3-4

S38 Figure 13. Bone mineral density in patients with CKD stage 5D

S40 Figure 14. Correlation coefficients between bone formation rate as seen on bone biopsies and serum markers of PTH, bone-specific ALP (BAP), osteocalcin (OC), and collagen cross-linking molecules (x-link) in patients with CKD stages 5-5D

S76 Figure 15. Comparison of PTH levels to underlying bone histology in chronic hemodialysis patients

S77 Figure 16. Risk of all-cause mortality associated with combinations of baseline serum phosphorus and calcium categories by PTH level

Additional information in the form of supplementary tables can be found online at <http://www.nature.com/ki>

Disclaimer

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based on the best information available as of March 2009, with a final updated literature search of December 2008. It is designed to provide information and assist decision-making. It is not intended to define a standard of care, and should not be construed as one, nor should it be interpreted as prescribing an exclusive course of management.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health-care professional making use of these recommendations is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.

SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group.

All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived or actual conflicts of interest. This document is updated annually and information is adjusted accordingly. All reported information is published in its entirety at the end of this document in the Work Group members' Biographical and Disclosure Information section, and is kept on file at the KDIGO administration office.

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Abbreviations and acronyms

1,25(OH) ₂ D	1,25-Dihydroxyvitamin D	KDOQI	Kidney Disease Outcomes Quality Initiative
25(OH)D	25-Hydroxyvitamin D	KDQOL	Kidney Disease Quality of Life Instrument
ACC/AHA	American College of Cardiology/American Heart Association	LDL-C	Low-density lipoprotein cholesterol
AE	Adverse event	MGP	Matrix Gla protein
ALP	Alkaline phosphatases	MDRD	Modification of Diet in Renal Disease
b-ALP	Bone-specific alkaline phosphatase	MLT	Mineralization lag time
BMD	Bone mineral density	MSCT	Multislice computed tomography
BRIC	Bone Relationship with Inflammation and Coronary Calcification	N	Number of subjects
BV	Bone volume	NAPRTCS	North American Renal Trials and Cooperative Studies
CAC	Coronary artery calcification	NHANES	National Health and Nutrition Examination Survey
CaR	Calcium-sensing receptor	NKF	National Kidney Foundation
Ca × P	Calcium-phosphorus product	NTX	Aminoterminal cross-linking telopeptide of bone collagen
CI	Confidence interval	OC	Osteocalcin
CKD	Chronic kidney disease	OPG	Osteoprotegerin
CKD-MBD	Chronic kidney disease-mineral and bone disorder	OR	Odds ratio
CrCl	Creatinine clearance	PD	Peritoneal dialysis
CT	Computed tomography	PICP	Procollagen type I C propeptide
CTX	Carboxyterminal cross-linking telopeptide of bone collagen	PINP	Procollagen type I N propeptide
CVD	Cardiovascular disease	PTH	Parathyroid hormone
DCOR	Dialysis in Clinical Outcomes Revisited	PWV	Pulse wave velocity
DOPPS	Dialysis Outcomes and Practice Pattern Study	qCT	Quantitative computed tomography
DPD	Deoxypyridinoline	QOL	Quality of life
DXA	Dual energy X-ray absorptiometry	qUS	Quantitative ultrasonography
EBCT	Electron beam computed tomography	RANK-L	Receptor Activator for Nuclear Factor κB Ligand
eGFR	Estimated glomerular filtration rate	RCT	Randomized controlled trial
ELISA	Enzyme-linked immunosorbent assay	rhGH	Recombinant human growth hormone
ERT	Evidence review team	RIA	Radioimmunoassay
FDA	Food and Drug Administration	RIND	Renagel in New Dialysis
FGF	Fibroblast growth factor	RR	Relative risk
GFR	Glomerular filtration rate	s.d.	Standard deviation
HD	Hemodialysis	SDS	Standard deviation score
HDL-C	High-density lipoprotein cholesterol	SEEK	Study to Evaluate Early Kidney Disease
HPLC	High-performance liquid chromatography	SERM	Selective estrogen receptor modulator
HPT	Hyperparathyroidism	SF-36	Medical Outcomes Study Short Form 36
HR	Hazard ratio	t-ALP	Total alkaline phosphatases
IMT	Intimal-medial thickness	TMV	Turnover, mineralization, volume
IP	Intraperitoneal	TRAP	Tartrate-resistant acid phosphatase
iPTH	Intact parathyroid hormone	TV	Tissue volume
IRMA	Immunoradiometric assay	US	Ultrasonography
IU	International Unit	VDR	Vitamin D receptor
IV	Intravenous	WHO	World Health Organization
KDIGO	Kidney Disease: Improving Global Outcomes		

Reference Keys

Stages of chronic kidney disease

Stage	Description	GFR (ml/min per 1.73 m ²)	Treatment
1	Kidney damage with normal or ↑ GFR	≥90	
2	Kidney damage with mild ↓ GFR	60-89	
3	Moderate ↓ GFR	30-59	1-5T if kidney transplant recipient
4	Severe ↓ GFR	15-29	
5	Kidney failure	<15 (or dialysis)	5D if dialysis (HD or PD)

CKD, chronic kidney disease; GFR, glomerular filtration rate; ↑, increased; ↓, decreased.

Conversion factors of metric units to SI units

	Metric Unit	Conversion Factor	SI Units
Albumin	g/dl	10	g/l
Bicarbonate	mEq/l	1	mmol/l
Calcitonin	pg/ml	1	ng/l
Calcium, total	mg/dl	0.2495	mmol/l
Calcium, ionized	mg/dl	0.25	mmol/l
Ca × P	mg ² /dl ²	0.0807	mmol ² /l ²
Cholesterol, total	mg/dl	0.02586	mmol/l
Creatinine	mg/dl	88.4	μmol/l
High-density lipoprotein cholesterol	mg/dl	0.02586	mmol/l
Low-density lipoprotein cholesterol	mg/dl	0.02586	mmol/l
Parathyroid hormone	pg/ml	0.106	pmol/l
Phosphorus (as inorganic phosphate)	mg/dl	0.3229	mmol/l
Protein, total	g/dl	10	g/l
Triglycerides	mg/dl	0.01129	mmol/l
Urea nitrogen	mg/dl	0.357	mmol/l
Vitamin D, 1,25-dihydroxyvitamin D	pg/ml	2.6	pmol/l
Vitamin D, 25-hydroxyvitamin D	ng/ml	2.496	nmol/l

Note: Metric units × conversion factor=SI units.

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Each chapter contains recommendations that are graded as **level 1** or **level 2**, and by the quality of the supporting evidence **A, B, C**, or **D** as shown. In addition, the Work Group could also make ungraded statements (see Chapter 2 section on ungraded statements).

Grade	Implications		
	Patients	Clinicians	Policy
Level 1 'We recommend'	Most people in your situation would want the recommended course of action and only a small proportion would not	Most patients should receive the recommended course of action	The recommendation can be adopted as a policy in most situations
Level 2 'We suggest'	The majority of people in your situation would want the recommended course of action, but many would not	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences	The recommendation is likely to require debate and involvement of stakeholders before policy can be determined

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C	Low	The true effect may be substantially different from the estimate of the effect
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth

Abstract

The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on the management of chronic kidney disease–mineral and bone disorder (CKD–MBD) is intended to assist the practitioner caring for adults and children with CKD stages 3–5, on chronic dialysis therapy, or with a kidney transplant. The guideline contains recommendations on evaluation and treatment for abnormalities of CKD–MBD. This disease concept of CKD–MBD is based on a prior KDIGO consensus conference. Tests considered are those that relate to the detection and monitoring of laboratory, bone, and cardiovascular abnormalities. Treatments considered are interventions to treat hyperphosphatemia, hyperparathyroidism, and bone disease in patients with CKD stages 3–5D and 1–5T. The guideline development process followed an evidence based approach and treatment recommendations are based on systematic reviews of relevant treatment trials. Recommendations for testing used evidence based on diagnostic accuracy or risk prediction and linked it indirectly with how this would be expected to achieve better outcomes for patients through better detection, evaluation or treatment of disease. Critical appraisal of the quality of the evidence and the strength of recommendations followed the GRADE approach. An ungraded statement was provided when a question did not lend itself to systematic literature review. Limitations of the evidence, especially the lack of definitive clinical outcome trials, are discussed and suggestions are provided for future research.

Keywords: Guideline; KDIGO; chronic kidney disease; dialysis; kidney transplantation; mineral and bone disorder; hyperphosphatemia; hyperparathyroidism

CITATION

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Foreword

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Clinical practice guidelines serve many purposes. First and foremost, guidelines help clinicians and other caregivers deal with the exponential growth in medical literature. It is impossible for most busy practitioners to read, understand, and apply a rapidly changing knowledge base to daily clinical practice. Guidelines can help fill this important need. Guidelines can also help to expose gaps in our knowledge, and thereby suggest areas where additional research is needed. Only when evidence is sufficiently strong to conclude that additional research is not needed should guidelines be used to mandate specific medical practices with, for example, clinical performance measures.

Methods for developing and implementing clinical practice guidelines are still relatively new and many questions remain unanswered. How should it be determined when a clinical practice guideline is needed? Who should make that determination? Who should develop guidelines? Should specialists develop guidelines for their practice, or should unbiased, independent clinicians and scientists develop guidelines for them? Is it possible to avoid conflicts of interest when most experts in a field conduct research that has been funded by industry (often because no other funding is available)? Should guidelines offer guidance when strong evidence is lacking, should they point out what decisions must be made in the absence of evidence or guidance, or should they just ignore these questions altogether, that is, make no statements or recommendations?

Professional societies throughout the world have decided that there is a need for developing clinical practice guidelines for patients with chronic kidney disease (CKD). Along with this perceived need has come the realization that developing high-quality guidelines requires substantial resources and expertise. An uncoordinated and parallel or repetitive development of guidelines on the same topics reflects a waste of resources. In addition, there is a growing awareness that CKD is an international problem. Therefore, *Kidney Disease: Improving Global Outcomes* (KDIGO) was established in 2003 as an independent, nonprofit foundation, governed by an international board of directors, with its stated mission to 'improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines.'

To date, KDIGO guideline initiatives have originated in discussions among the KDIGO Executive Committee members and the KDIGO Board of Directors. In some instances, topic areas have been vetted at KDIGO 'Controversies Conferences.' If there is then a consensus that guideline development should go forward, two Work Group chairs are

appointed, and with the help of these chairs, other Work Group members are selected. Efforts are made to include a broad and diverse expertise in the Work Group, and to have international representation. Work Groups then meet and work with a trained, professional evidence review team to develop evidence-based guidelines. These guidelines are reviewed by the KDIGO Board of Directors, and a revision is then sent out for public comment. Only then is a final, revised version developed and published.

The mineral and bone disorder of CKD (CKD-MBD) has been an area of intense interest and controversy. In 2005, KDIGO sponsored a controversies conference 'Definition, Evaluation and Classification of Renal Osteodystrophy.' The results of this conference were summarized in a position statement that was published in 2006. The consensus of the attendees at this conference was that a new set of international guideline on CKD-MBD was indeed warranted.

Therefore, KDIGO invited Sharon Moe, MD, and Tilman Drüeke, MD, to co-chair a Work Group to develop a CKD-MBD guideline. The Work Group was supported by the Evidence Review Team at the Tufts Center for Kidney Disease Guideline Development and Implementation at Tufts Medical Center, Boston, MA, with Katrin Uhlig, MD, MS, as the Evidence Review Team's Project Director. The Work Group met on five separate occasions over a period of 2 years, reviewing evidence and drafting guideline recommendations. The KDIGO Board reviewed a preliminary draft, and ultimately the final document. Importantly, the guideline was also subjected to public review and comment.

During the development of the CKD-MBD guideline, KDIGO continued to develop a system for rating the strength of recommendations and the overall quality of evidence supporting those recommendations. A task force had been formed that ultimately made recommendations to the KDIGO Board. After extensive discussion and debate, the KDIGO Board of Directors in 2008 unanimously approved a modification of the Grading of Recommendations Assessment, Development, and Evaluation system. The system that was adopted allows provision of guidance even if the evidence base is weak, but makes the quality of the available evidence transparent and explicit. It is described in detail in the present CKD-MBD guideline (Chapter 2).

The strength of each recommendation is rated 1 or 2, with 1 being a 'We recommend ...' statement implying that most patients should receive the course of action, and 2 being a 'We suggest ...' statement implying that different choices will be appropriate for different patients with the suggested course of action being a reasonable choice. In addition, each

statement is assigned an overall grade for the quality of evidence, A (high), B (moderate), C (low), or D (very low). The grade of each recommendation depends on the quality of the evidence, and also on additional considerations.

A key issue is whether to include guideline statements on topics that cannot be subjected to a systematic evidence review. KDIGO has decided to meet this need by including some statements that are not graded. Typically, ungraded statements provide guidance that is based on common sense, for example, reminders of the obvious and/or recommendations that are not sufficiently specific enough to allow the application of evidence. Examples include the frequency of laboratory testing and the provision of routine medical care.

The CKD-MBD guideline encompasses many aspects of care for which there is little or no evidence to inform recommendations. Indeed, there are only three recommendations in the CKD-MBD guideline for which the overall quality of evidence was graded 'A,' whereas 12 were graded 'B,' 23 were graded 'C,' and 11 were graded 'D.' Although there are reasons other than quality of evidence to make a grade 1 or 2 recommendation, in general, there is a correlation between the quality of overall evidence and the strength of the recommendation. Thus, there are 10 recommendations graded '1' and 39 graded '2.' There were two recommendations graded '1A,' five were '1B,' three were '1C,' and none were '1D.' There was one graded '2A,' seven were '2B,' 20 were '2C,' and 11 were '2D.' There were 12 statements that were not graded.

The grades should be taken seriously. The lack of recommendations that are graded '1A' suggests that there are few opportunities for developing clinical performance

measures from this guideline. The preponderance of '2' recommendations suggests that patient preferences and other circumstances should be strongly considered when implementing most recommendations. The lack of 'A' and 'B' grades of overall quality of evidence is a result of the lack of patient-centered outcomes as end points in the majority of trials in this field, and thus suggests strongly that additional research is needed in CKD-MBD. Indeed, the extensive review that led to this guideline often exposed significant gaps in our knowledge. The Work Group made a number of specific recommendations for future research needs. This will hopefully be of interest to future investigators and funding agencies.

All of us working with KDIGO hope that the guidelines developed by KDIGO will in some small way help to fulfill its mission to improve the care and outcomes of patients with kidney disease. We understand that these guidelines are far from perfect, but we are confident that they are an important step in the right direction. A tremendous amount of work has gone into the development of the KDIGO CKD-MBD guideline. We sincerely thank Sharon Moe, MD, and Tilman Drüeke, MD, the Work Group chairs, for the tremendous amount of time and effort that they put into this challenging, but important, guideline project. They did an outstanding job. We also thank the Work Group members, the Evidence Review Team, and the KDIGO staff for their tireless efforts. Finally, we owe a special debt of gratitude to the founding KDIGO Co-Chairs, Norbert Lameire, MD, and especially Garabed Eknoyan, MD, for making all of this possible.

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Chapter 1: Introduction and definition of CKD-MBD and the development of the guideline statements

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INTRODUCTION AND DEFINITION OF CKD-MBD

Chronic kidney disease (CKD) is an international public health problem affecting 5–10% of the world population.¹ As kidney function declines, there is a progressive deterioration in mineral homeostasis, with a disruption of normal serum and tissue concentrations of phosphorus and calcium, and changes in circulating levels of hormones. These include parathyroid hormone (PTH), 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D (1,25(OH)₂D), and other vitamin D metabolites, fibroblast growth factor-23 (FGF-23), and growth hormone. Beginning in CKD stage 3, the ability of the kidneys to appropriately excrete a phosphate load is diminished, leading to hyperphosphatemia, elevated PTH, and decreased 1,25(OH)₂D with associated elevations in the levels of FGF-23. The conversion of 25(OH)D to 1,25(OH)₂D is impaired, reducing intestinal calcium absorption and increasing PTH. The kidney fails to respond adequately to PTH, which normally promotes phosphaturia and calcium reabsorption, or to FGF-23, which also enhances phosphate excretion. In addition, there is evidence at the tissue level of a downregulation of vitamin D receptor and of resistance to the actions of PTH. Therapy is generally focused on correcting biochemical and hormonal abnormalities in an effort to limit their consequences.

The mineral and endocrine functions disrupted in CKD are critically important in the regulation of both initial bone formation during growth (bone modeling) and bone structure and function during adulthood (bone remodeling). As a result, bone abnormalities are found almost universally in patients with CKD requiring dialysis (stage 5D), and in the majority of patients with CKD stages 3–5. More recently, there has been an increasing concern of extraskeletal calcification that may result from the deranged mineral and bone metabolism of CKD and from the therapies used to correct these abnormalities.

Numerous cohort studies have shown associations between disorders of mineral metabolism and fractures, cardiovascular disease, and mortality (see Chapter 3). These observational studies have broadened the focus of CKD-related mineral and bone disorders (MBDs) to include cardiovascular disease (which is the leading cause of death in patients at all stages of CKD). All three of these processes (abnormal mineral metabolism, abnormal bone, and extraskeletal calcification) are closely interrelated and together make a major contribution to the morbidity and mortality of patients with CKD.

The traditional definition of renal osteodystrophy did not accurately encompass this more diverse clinical spectrum,

based on serum biomarkers, noninvasive imaging, and bone abnormalities. The absence of a generally accepted definition and diagnosis of renal osteodystrophy prompted Kidney Disease: Improving Global Outcomes (KDIGO) to sponsor a controversies conference, entitled ‘Definition, Evaluation, and Classification of Renal Osteodystrophy,’ held on 15–17 September 2005 in Madrid, Spain. The principal conclusion was that the term ‘CKD–Mineral and Bone Disorder (CKD–MBD)’ should be used to describe the broader clinical syndrome encompassing mineral, bone, and calcific cardiovascular abnormalities that develop as a complication of CKD (Table 1). It was also recommended that the term ‘renal osteodystrophy’ be restricted to describing the bone pathology associated with CKD. The evaluation and definitive diagnosis of renal osteodystrophy require a bone biopsy, using an expanded classification system that was developed at the consensus conference based on parameters of bone turnover, mineralization, and volume (TMV).²

The KDIGO CKD-MBD Clinical Practice Guideline Document

KDIGO was established in 2003 as an independently incorporated nonprofit foundation governed by an international board of directors with the stated mission to ‘improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines.’ The 2005 consensus conference sponsored by KDIGO was seen as an initial step in raising awareness of the importance of this disorder. The next stage was to develop an international clinical practice guideline that provides guidance on the management of this disorder.

CHALLENGES IN DEVELOPING THIS GUIDELINE

The development of this guideline proved challenging for a number of reasons. First, the definition of CKD-MBD was new and had not been applied to characterize populations in published clinical studies. Thus, each of the three components of CKD-MBD had to be addressed separately. Second, the complexity of the pathogenesis of CKD-MBD make it difficult to completely differentiate a consequence of the disease from a consequence of its treatment. Moreover, different stages of CKD are associated with different features and degrees of severity of CKD-MBD. Third, differences exist throughout the world in nutrient intake, availability of medications, and clinical practice. Fourth, many of the local guidelines that already exist are based largely on expert opinion rather than on strong evidence, whereas KDIGO

Table 1 | KDIGO classification of CKD-MBD and renal osteodystrophy**Definition of CKD-MBD**

A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism.
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength.
- Vascular or other soft-tissue calcification.

Definition of renal osteodystrophy

- Renal osteodystrophy is an alteration of bone morphology in patients with CKD.
- It is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy.

CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; KDIGO, Kidney Disease: Improving Global Outcomes; PTH, parathyroid hormone. Adapted with permission from Moe *et al.*²

aims to base its guidelines on an extensive and systematic analysis of the available evidence. Finally, this is a disorder unique to CKD patients, meaning that there are no randomized controlled trials in the non-CKD population that can be generalized to CKD patients, and only a few large studies involving CKD patients.

COMPOSITION OF THE WORK GROUP AND PROCESSES

A Work Group of international experts charged with developing the present guideline was chosen by the Work Group Chairs, who in turn were chosen by the KDIGO Executive Committee. The Work Group defined the questions and developed the study inclusion criterion *a priori*. When it came to evaluating the impact of therapeutic agents, the Work Group agreed *a priori* to evaluate only randomized controlled trials of a 6-month duration with a sample size of at least 50 patients. An exception was made for studies involving children or using bone biopsy criterion as an end point, in which smaller sample sizes were accepted because of the inherent difficulties in conducting these studies.

Defining end points

End points were categorized into three levels for evaluation: those of direct importance to patients (for example, mortality, cardiovascular disease events, hospitalizations fracture, and quality of life), intermediate end points (for example, vascular calcification, bone mineral density (BMD), and bone biopsy), and biochemical end points (for example, serum calcium, phosphorus, alkaline phosphatases, and PTH). Importantly, the Work Group acknowledged that these intermediate and biochemical end points are not validated surrogate end points for hard clinical events unless such a connection had been made in a prospective treatment trial (Figure 1).

CONTENT OF THE GUIDELINE

The guideline includes detailed evidence-based recommendations for the diagnosis and evaluation of the three components of CKD-MBD—abnormal biochemistries, vascular calcification, and disorders of the bone (Chapter 3)—and recommendations for the treatment of CKD-MBD (Chapter 4). In preparing Chapter 3, studies that assessed

the diagnosis, prevalence, natural history, and risk relationships of CKD-MBD were evaluated. Unfortunately, there was frequently no high-quality evidence to support recommendations for specific diagnostic tests, thresholds for defining disease, frequency of testing, or precisely which populations to test. Multiple studies were reviewed that allowed the generation of overview tables listing a selection of pertinent studies. For the treatment questions, systematic reviews were undertaken of randomized controlled trials and the bodies of evidence were appraised following the Grades of Recommendation Assessment, Development, and Evaluation approach.

Public review version

The initial version of the CKD-MBD guideline was developed by using very rigorous standards for the quality of evidence on which clinical practice recommendations should be based. Thus, the Work Group limited its recommendations to areas that it felt were supported by high- or moderate-quality evidence rather than areas in which the recommendation was based on low- or very-low-quality evidence and predominantly expert judgment. The Work Group was most sensitive to the potential misuse and misapplication of recommendations, especially, as pertains to targets and treatment recommendations. The Work Group believed strongly that patients deserved treatment recommendations based on high-quality evidence and physicians should not be forced to adhere to targets and use treatments without sound evidence showing that benefits outweigh harm. The Work Group recognized that there had already been guidelines developed by different entities throughout the world that did not apply these criteria. In the public review draft, the Work Group provided discussions under ‘Frequently Asked Questions’ at the end of each chapter to provide practical guidance in areas of indeterminate evidence or to highlight areas of controversy.

The public review overwhelmingly agreed with the guideline recommendations. Interestingly, most reviewers requested more specific guidance for the management of CKD-MBD, even if predominantly based on expert judgment, whereas others found the public review draft to be a refreshingly honest appraisal of our current knowledge base in this field.

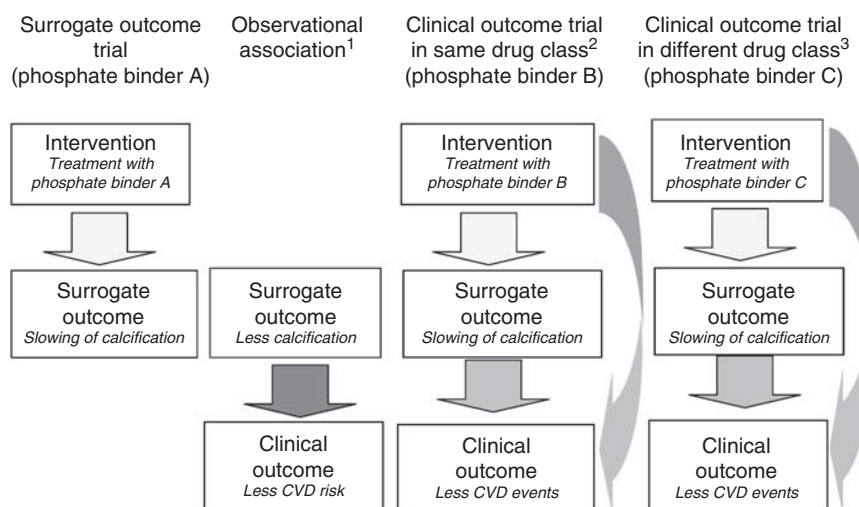


Figure 1 | Interpreting a surrogate outcome trial. When interpreting the validity of a surrogate outcome trial, consider the following questions: 1. Is there a strong, independent, consistent association between the surrogate outcome and the clinical outcome? This is a necessary but not, by itself, sufficient prerequisite. 2. Is there evidence from randomized trials in the same drug class that improvements in the surrogate outcome have consistently led to improvements in the clinical outcome? 3. Is there evidence from randomized trials in other drug classes that improvement in the surrogate outcome has consistently led to improvement in the clinical outcome? Both 2 and 3 should apply. This figure illustrates principles outlined in Users' Guide for Surrogate Endpoint Trial³ and the legend is modified after this reference. Phosphate binders, calcification, and CVD are chosen as an example. CVD, cardiovascular disease.

Responses to review process and modifications

In response to the public review of the CKD–MBD guideline, and in the context of a changing field of guideline development, grading systems, and the need for guidance in complex areas of CKD management, the KDIGO Board in its Vienna session in December 2008 refined its remit to KDIGO Work Groups. It confirmed its charge to the Work Groups to critically appraise the evidence, but encouraged the Work Groups to issue practical guidance in areas of indeterminate evidence. This practical guidance rests on a combination of the evidentiary base that exists (biological, clinical, and other) and the judgment of the Work Group members, which is directed to ensuring 'best care' in the current state of knowledge for the patients.

In the session of December 2008, the KDIGO Board also revised the grading system for the strength of recommendations to align it more closely with Grades of Recommendation Assessment, Development, and Evaluation (GRADE), an international body committed to the harmonization of guideline grading across different speciality areas. The full description of this grading system is found in Chapter 2, but can be summarized as follows: there are two levels for the strength of recommendation (level 1 or 2) and four levels for the quality of overall evidence supporting each recommendation (grade A, B, C, or D) (see Chapter 2). In addition to graded recommendations, ungraded statements in areas in which guidance was based on common sense and/or the question was not specific enough to undertake a systematic evidence review are also presented. This grading system allows the Work Group to be transparent in its appraisal of the evidence, yet provides practical guidance. The simplicity of the grading system also permits the clinician, patient, and policy maker to understand the statement in the context of the evidentiary base more clearly.

In response to feedback by the KDIGO Board of Directors, the CKD–MBD Work Group reconvened in January 2009, revised some recommendations, and formulated some additional recommendations or ungraded statements, integrating suggestions for patient care previously expressed in the Frequently Asked Questions section. Approval of the final recommendations and rating of their strength and the underlying quality of evidence were established by voting, with two votes taken, one including and one excluding those Work Group members who declared potential conflicts of interest. (Note that the financial relationships of the Work Group participants are listed at the end of this document.) The two votes generally yielded a >90% agreement on all the statements. When an overwhelming agreement could not be reached in support of a recommendation, the issue was instead discussed in the rationale.

Finally, the Work Group made numerous recommendations for further research to improve the quality of evidence for future recommendations in the field of CKD–MBD.

Summary and future directions

The wording has been carefully selected for each statement to ensure clarity and consistency, and to minimize the possibility of misinterpretation. The grading system offers an additional level of transparency regarding the strength of recommendation and quality of evidence at a glance. We strongly encourage the users of the guideline to ensure the integrity of the process by quoting the statements verbatim, and by including the grades assigned after the statement when quoting/reproducing or using the statements, as well as by explaining the meaning of the code that combines an Arabic number (to indicate that the recommendation is 'strong' or 'weak') and an uppercase letter (to indicate

that the quality of the evidence is ‘high’, ‘moderate’, ‘low’, or ‘very low’).

We hope that as a reader and user, you appreciate the rigor of the approach we have taken. More importantly, we strongly urge the nephrology community to take up the challenge of expanding the evidence base in line with our research recommendations. Given the current state of knowledge, clinical equipoise, and the need for accumulating data, we strongly encourage clinicians to enroll patients into ongoing and future studies, to participate in the development of registries locally, nationally, and internationally, and to encourage funding organizations to support these efforts, so that, over time, many of the current uncertainties can be resolved.

SUMMARY OF RECOMMENDATIONS

Chapter 3.1: Diagnosis of CKD-MBD: biochemical abnormalities

- 3.1.1. We recommend monitoring serum levels of calcium, phosphorus, PTH, and alkaline phosphatase activity beginning in CKD stage 3 (1C). In children, we suggest such monitoring beginning in CKD stage 2 (2D).
- 3.1.2. In patients with CKD stages 3–5D, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (not graded).

Reasonable monitoring intervals would be:

- in CKD stage 3: for serum calcium and phosphorus, every 6–12 months; and for PTH, based on baseline level and CKD progression.
- In CKD stage 4: for serum calcium and phosphorus, every 3–6 months; and for PTH, every 6–12 months.
- In CKD stage 5, including 5D: for serum calcium and phosphorus, every 1–3 months; and for PTH, every 3–6 months.
- In CKD stages 4–5D: for alkaline phosphatase activity, every 12 months, or more frequently in the presence of elevated PTH (see Chapter 3.2).

In CKD patients receiving treatments for CKD-MBD, or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for trends and treatment efficacy and side-effects (not graded).

- 3.1.3. In patients with CKD stages 3–5D, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and therapeutic interventions (2C). We suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).
- 3.1.4. In patients with CKD stages 3–5D, we recommend that therapeutic decisions be based on trends rather than on a single laboratory value, taking into account all available CKD-MBD assessments (1C).

- 3.1.5. In patients with CKD stages 3–5D, we suggest that individual values of serum calcium and phosphorus, evaluated together, be used to guide clinical practice rather than the mathematical construct of calcium–phosphorus product ($\text{Ca} \times \text{P}$) (2D).
- 3.1.6. In reports of laboratory tests for patients with CKD stages 3–5D, we recommend that clinical laboratories inform clinicians of the actual assay method in use and report any change in methods, sample source (plasma or serum), and handling specifications to facilitate the appropriate interpretation of biochemistry data (1B).

Chapter 3.2: Diagnosis of CKD-MBD: bone

- 3.2.1. In patients with CKD stages 3–5D, it is reasonable to perform a bone biopsy in various settings including, but not limited to: unexplained fractures, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and prior to therapy with bisphosphonates in patients with CKD-MBD (not graded).
- 3.2.2. In patients with CKD stages 3–5D with evidence of CKD-MBD, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B).
- 3.2.3. In patients with CKD stages 3–5D, we suggest that measurements of serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover (2B).
- 3.2.4. In patients with CKD stages 3–5D, we suggest not to routinely measure bone-derived turnover markers of collagen synthesis (such as procollagen type I C-terminal propeptide) and breakdown (such as type I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline) (2C).
- 3.2.5. We recommend that infants with CKD stages 2–5D should have their length measured at least quarterly, while children with CKD stages 2–5D should be assessed for linear growth at least annually (1B).

Chapter 3.3: Diagnosis of CKD-MBD: vascular calcification

- 3.3.1. In patients with CKD stages 3–5D, we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence or absence of valvular calcification, as reasonable alternatives to computed tomography-based imaging (2C).
- 3.3.2. We suggest that patients with CKD stages 3–5D with known vascular/valvular calcification be considered at highest cardiovascular risk (2A). It is reasonable to use this information to guide the management of CKD-MBD (not graded).

Chapter 4.1: Treatment of CKD-MBD targeted at lowering high serum phosphorus and maintaining serum calcium

- 4.1.1. In patients with CKD stages 3–5, we suggest maintaining serum phosphorus in the normal range (2C). In patients with CKD stage 5D, we suggest lowering elevated phosphorus levels toward the normal range (2C).
- 4.1.2. In patients with CKD stages 3–5D, we suggest maintaining serum calcium in the normal range (2D).
- 4.1.3. In patients with CKD stage 5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (2D).
- 4.1.4. In patients with CKD stages 3–5 (2D) and 5D (2B), we suggest using phosphate-binding agents in the treatment of hyperphosphatemia. It is reasonable that the choice of phosphate binder takes into account CKD stage, presence of other components of CKD-MBD, concomitant therapies, and side-effect profile (not graded).
- 4.1.5. In patients with CKD stages 3–5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia (1B).
In patients with CKD stages 3–5D and hyperphosphatemia, we suggest restricting the dose of calcium-based phosphate binders in the presence of arterial calcification (2C) and/or adynamic bone disease (2C) and/or if serum PTH levels are persistently low (2C).
- 4.1.6. In patients with CKD stages 3–5D, we recommend avoiding the long-term use of aluminum-containing phosphate binders and, in patients with CKD stage 5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication (1C).
- 4.1.7. In patients with CKD stages 3–5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (2D).
- 4.1.8. In patients with CKD stage 5D, we suggest increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia (2C).

Chapter 4.2: Treatment of abnormal PTH levels in CKD-MBD

- 4.2.1. In patients with CKD stages 3–5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH (iPTH) above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency (2C).
It is reasonable to correct these abnormalities with any or all of the following: reducing dietary phosphate intake and administering phosphate binders, calcium supplements, and/or native vitamin D (not graded).
- 4.2.2. In patients with CKD stages 3–5 not on dialysis, in whom serum PTH is progressively rising and remains

persistently above the upper limit of normal for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs (2C).

- 4.2.3. In patients with CKD stage 5D, we suggest maintaining iPTH levels in the range of approximately two to nine times the upper normal limit for the assay (2C).
We suggest that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range (2C).
- 4.2.4. In patients with CKD stage 5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH (2B).
- It is reasonable that the initial drug selection for the treatment of elevated PTH be based on serum calcium and phosphorus levels and other aspects of CKD-MBD (not graded).
 - It is reasonable that calcium or non-calcium-based phosphate binder dosage be adjusted so that treatments to control PTH do not compromise levels of phosphorus and calcium (not graded).
 - We recommend that, in patients with hypercalcemia, calcitriol or another vitamin D sterol be reduced or stopped (1B).
 - We suggest that, in patients with hyperphosphatemia, calcitriol or another vitamin D sterol be reduced or stopped (2D).
 - We suggest that, in patients with hypocalcemia, calcimimetics be reduced or stopped depending on severity, concomitant medications, and clinical signs and symptoms (2D).
 - We suggest that, if the intact PTH levels fall below two times the upper limit of normal for the assay, calcitriol, vitamin D analogs, and/or calcimimetics be reduced or stopped (2C).
- 4.2.5. In patients with CKD stages 3–5D with severe hyperparathyroidism (HPT) who fail to respond to medical/pharmacological therapy, we suggest parathyroidectomy (2B).

Chapter 4.3: Treatment of bone with bisphosphonates, other osteoporosis medications, and growth hormone

- 4.3.1. In patients with CKD stages 1–2 with osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, we recommend management as for the general population (1A).
- 4.3.2. In patients with CKD stage 3 with PTH in the normal range and osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, we suggest treatment as for the general population (2B).
- 4.3.3. In patients with CKD stage 3 with biochemical abnormalities of CKD-MBD and low BMD and/or

fragility fractures, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy (2D).

- 4.3.4. In patients with CKD stages 4–5D having biochemical abnormalities of CKD–MBD, and low BMD and/or fragility fractures, we suggest additional investigation with bone biopsy prior to therapy with antiresorptive agents (2C).
- 4.3.5. In children and adolescents with CKD stages 2–5D and related height deficits, we recommend treatment with recombinant human growth hormone when additional growth is desired, after first addressing malnutrition and biochemical abnormalities of CKD–MBD (1A).

Chapter 5: Evaluation and treatment of kidney transplant bone disease

- 5.1. In patients in the immediate post-kidney-transplant period, we recommend measuring serum calcium and phosphorus at least weekly, until stable (1B).
- 5.2. In patients after the immediate post-kidney-transplant period, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (not graded).

Reasonable monitoring intervals would be:

- In CKD stages 1–3T, for serum calcium and phosphorus, every 6–12 months; and for PTH, once, with subsequent intervals depending on baseline level and CKD progression.
- In CKD stage 4T, for serum calcium and phosphorus, every 3–6 months; and for PTH, every 6–12 months.
- In CKD stage 5T, for serum calcium and phosphorus, every 1–3 months; and for PTH, every 3–6 months.
- In CKD stages 3–5T, measurement of alkaline phosphatases annually, or more frequently in the presence of elevated PTH (see Chapter 3.2).

In CKD patients receiving treatments for CKD–MBD, or in whom biochemical abnormalities are identified, it is

reasonable to increase the frequency of measurements to monitor for efficacy and side-effects (not graded).

It is reasonable to manage these abnormalities as for patients with CKD stages 3–5 (not graded) (see Chapters 4.1 and 4.2).

- 5.3. In patients with CKD stages 1–5T, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and interventions (2C).
- 5.4. In patients with CKD stages 1–5T, we suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).
- 5.5. In patients with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73 m², we suggest measuring BMD in the first 3 months after kidney transplant if they receive corticosteroids, or have risk factors for osteoporosis as in the general population (2D).
- 5.6. In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73 m² and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidol, or bisphosphonates be considered (2D).
 - We suggest that treatment choices be influenced by the presence of CKD–MBD, as indicated by abnormal levels of calcium, phosphorus, PTH, alkaline phosphatases, and 25(OH)D (2C).
 - It is reasonable to consider a bone biopsy to guide treatment, specifically before the use of bisphosphonates due to the high incidence of adynamic bone disease (not graded).

There are insufficient data to guide treatment after the first 12 months.

- 5.7. In patients with CKD stages 4–5T, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population and BMD does not predict the type of kidney transplant bone disease (2B).
- 5.8. In patients with CKD stages 4–5T with known low BMD, we suggest management as for patients with CKD stages 4–5 not on dialysis, as detailed in Chapters 4.1 and 4.2 (2C).

Chapter 2: Methodological approach

Kidney International (2009) **76** (Suppl 113), S9–S21; doi:10.1038/ki.2009.190

This clinical practice guideline contains a set of recommendations for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD–MBD). The aim of this chapter is to describe the process and methods by which the evidence review was conducted and the recommendations and statements were developed.

The members of the Work Group and of the Evidence Review Team (ERT) collaborated closely in an iterative process of question development, evidence review, and evaluation, culminating in the development of recommendations that have been graded according to an approach developed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group (Table 2).¹⁴ This grading scheme with two levels for the strength of a recommendation was adopted by the KDIGO (Kidney Disease: Improving Global Outcomes) Board in December 2008. The Board also approved the option of an ungraded statement instead of a graded recommendation. This alternative allows a Work Group to issue general advice on the basis of what it considers a reasonable approach for clinical practice. We ask the users of this guideline to include the grades with each recommendation and consider the implications of the respective grade (see detailed description below). The importance of the explicit details provided in this chapter lies in the transparency required of this process, and strives to instill confidence in the reader about the methodological rigor of the approach.

OVERVIEW OF THE PROCESS

The development of the guideline included concurrent steps to:

- appoint the Work Group and ERT, which were responsible for different aspects of the process;
- confer to discuss process, methods, and results;
- develop and refine topics;
- define specific populations, interventions or predictors, and outcomes of interest;
- create and standardize quality assessment methods;
- create data extraction forms;
- develop literature search strategies and run searches;
- screen abstracts and retrieve full articles on the basis of predetermined eligibility criteria;
- extract data and perform a critical appraisal of the literature;
- grade the quality of the outcomes of each study;
- tabulate data from articles into summary tables;

- grade the quality of evidence for each outcome and assess the overall quality of bodies of evidence with the aid of evidence profiles;
- write recommendations and supporting rationale;
- grade the strength of the recommendations on the basis of the quality of evidence and other considerations;
- write the narrative; and
- respond to peer review by the KDIGO Board of Directors in December 2007 and again in early 2009, and public review in 2008 before publication.

The KDIGO Co-Chairs appointed the Co-Chairs of the Work Group, who then assembled the Work Group to be responsible for the development of the guideline. The Work Group consisted of domain experts, including individuals with expertise in adult and pediatric nephrology, bone disease, cardiology, and nutrition. The Tufts Center for Kidney Disease Guideline Development and Implementation at Tufts Medical Center in Boston, MA, USA was contracted to provide expertise in guideline development methodology and systematic evidence review. One Work Group member (Alison MacLeod) also served as an international methodology expert. KDIGO support staff provided administrative assistance and facilitated communication.

The ERT consisted of physicians/methodologists with expertise in nephrology and internal medicine, and research associates and assistants. The ERT instructed and advised Work Group members in all steps of literature review, in critical literature appraisal, and in guideline development. The Work Group and the ERT collaborated closely throughout the project. The Work Group, KDIGO Co-Chairs, ERT, liaisons, and KDIGO support staff met five times for 2-day meetings in Europe and in North America. The meetings included a formal instruction in the state of the art and science of guideline development, and training in the necessary process steps, including the grading of evidence and the strength of recommendations, as well as in the formulation of recommendations. Meetings also provided a forum for general topic discussion and consensus development with regard to both evidence appraisal and specific wording to be used in the recommendations.

The first task was to define the overall topics and goals for the guideline. The Work Group Chairs drafted a preliminary list of topics. The Work Group then identified key clinical questions. The Work Group and ERT further developed and refined each topic specified for a systematic review of

Table 2 | Grading of recommendations

Grade for strength of recommendation ^a	Strength	Wording	Grade for quality of evidence	Quality of evidence
Level 1	Strong	'We recommend...should'	A	High
Level 2	Weak	'We suggest...might'	B	Moderate
			C	Low
			D	Very low

^aIn addition the Work Group could also make ungraded statements (see Chapter 2 section on ungraded statements).

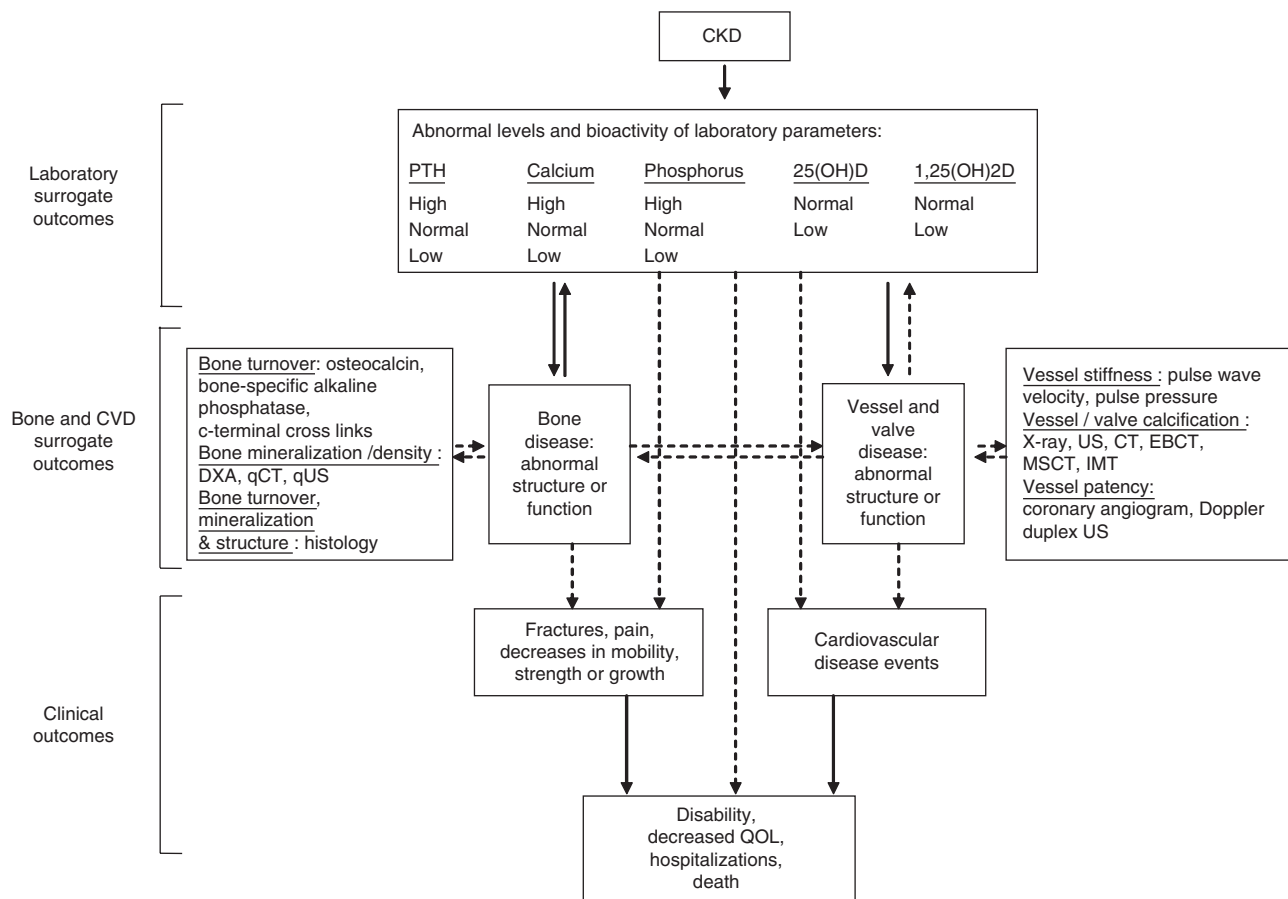


Figure 2 | Evidence model. Arrows represent relationships and correspond to a question or questions of interest. Solid arrows represent well-established associations. Dashed arrows represent associations that need to be established with greater certainty. The relationships between laboratory abnormalities and organ diseases other than bone and cardiovascular diseases are not depicted here. In addition to the laboratory abnormalities shown, there are other factors that are determinants of bone and cardiovascular health, which are not depicted. CKD, chronic kidney disease; CVD, cardiovascular disease; DXA, dual-energy X-ray absorptiometry; EBCT, electron beam computed tomography; IMT, intimal-medial thickness; MSCT, multislice computed tomography; PTH, parathyroid hormone; (q)CT, (quantitative) computed tomography; (q)US, (quantitative) ultrasound; QOL, quality of life.

treatment questions, and summarized the literature for nontreatment topics.

The ERT performed literature searches, and abstract and article screening. The ERT also coordinated the methodological and analytical process of the report. It defined and standardized the method for performing literature searches and data extraction, and for summarizing evidence. Throughout the project, ERT offered suggestions for guideline development, and led discussions on systematic review, literature searches, data extraction, assessment of quality and

applicability of articles, evidence synthesis, and grading of evidence.

The ERT provided suggestions and edits on the wording of recommendations, and on the use of specific grades for the strength of the recommendations and the quality of evidence.

The Work Group took on the primary role of writing the recommendations and rationale, and retained final responsibility for the content of the recommendations and for the accompanying narrative.

DEVELOPMENT OF AN EVIDENCE MODEL

With the initiation of the evidence review process of the KDIGO CKD-MBD guideline, the ERT developed an evidence model and refined it with the Work Group (Figure 2). This was carried out to conceptualize what is known about epidemiological associations, hypothesized causal relationships, and the clinical importance of different outcomes. Ultimately, this model served to clarify the questions for evidence review and to weigh the evidence for different outcomes. The model depicts laboratory abnormalities as a direct consequence of CKD and bone disease, and cardiovascular disease (CVD) as a consequence of laboratory abnormalities as well as due to direct consequences of CKD. Bone disease and CVD are defined as abnormalities in structure and function, which can be seen on imaging tests or tissue examination. Bone disease and CVD are then shown as factors that—together with other direct consequences of CKD—lead to clinical outcomes, such as fractures, pain, and disability on the one hand, and clinical CVD events on the other. All of these contribute to morbidity and mortality. The arrows represent relationships and correspond to a question or questions of interest. Solid arrows represent well-established associations. Dashed arrows represent associations that need to be established with greater certainty. The model suggests a hierarchy with the clinical importance of each condition increasing from top to bottom. The model is incomplete in that it does not show other factors or disease processes that may contribute to, or directly result in, abnormalities at every level. For example, bone abnormalities in a patient with CKD may also be the result of aging and osteoporosis, and abnormalities of CVD will be a result of other traditional and nontraditional CVD risk factors. Thus, the model does not reflect the complexity of the multifactorial processes that result in clinical disease, nor the uncertainty with regard to the relative and absolute risk attributable to each risk factor. However, it does highlight the complexity of the issues facing the Work Group, which evaluated the evidence to make recommendations for the care of patients, but found that the majority of outcomes from clinical trials in this field studied laboratory outcomes.

REFINEMENT OF TOPICS, QUESTIONS, AND DEVELOPMENT OF MATERIALS

The Work Group Co-Chairs prepared the first draft of the scope-of-work document as a series of open-ended questions to be considered by Work Group members. At their first 2-day meeting, members added further questions until the initial working document included all topics of interest to the Work Group. The inclusive, combined set of questions formed the basis for the deliberation and discussion that followed. The Work Group strove to ensure that all topics deemed clinically relevant and worthy of review were identified and addressed.

For questions of treatments, systematic reviews of the literature, which met prespecified criteria, were undertaken

(Table 3). For these topics, the ERT created forms to extract relevant data from articles, and extracted information for baseline data on populations, interventions, and study design. Work Group experts extracted the results of included articles and provided an assessment of the quality of evidence. The ERT reviewed and revised data extraction for results and quality grades performed by Work Group members. In addition, the ERT tabulated studies in summary tables, and assigned grades for the quality of evidence in consultation with the Work Group.

For nontreatment questions, that is, questions related to prevalence, evaluation, natural history, and risk relationships, the ERT conducted systematic searches, screened the yield for relevance, and provided lists of citations to the Work Group (Table 4). The Work Group took primary responsibility for reviewing and summarizing this literature in a narrative format.

On the basis of the list of topics, the Work Group and ERT developed a list of specific research questions for which systematic review would be performed. For each systematic review topic, the Work Group Co-Chairs and the ERT formulated well-defined systematic review research questions using a well-established system.⁴ For each question, clear and explicit criteria were agreed upon for the population, intervention or predictor, comparator, and outcomes of interest (Table 3). Each criterion was defined as comprehensively as possible. A list of outcomes of interest was generated and the Work Group was advised to rank patient-centered clinical outcomes (such as death or cardiovascular events) as being more important than intermediate outcomes (such as bone mineral density) or laboratory outcomes (such as phosphorus level), and not to include experimental biomarkers. In addition, study eligibility criteria were decided on the basis of study design, minimal sample size, minimal follow-up duration, and year of publication, as indicated (Table 3). The specific criteria used for each topic are explained below in the description of review topics. In general, eligibility criteria were determined on the basis of clinical value, relevance to the guideline and clinical practice, a determination on whether a set of studies would affect recommendations or the quality of evidence, and practical issues such as available time and resources.

LITERATURE SEARCH

A MEDLINE search was carried out to capture all abstracts and articles relevant to the topic of CKD and mineral metabolism, bone disorders, and vascular/valvular calcification. This search encompassed original articles, systematic reviews, and meta-analyses. The entire search was updated through 17 December 2007; the search for randomized controlled trials (RCTs) was updated through November 2008, and articles (including RCTs in press) identified by Work Group members were included through December 2008. The starting point of the literature search was the reference lists from the KDOQI (the Kidney Disease Outcomes Quality Initiative) Bone Guidelines for Adults and Children,^{5,6} which

Table 3 | Screening criteria for systematic review topics

Intervention	Screening criteria	Articles in summary tables		
		CKD stages 3–5	CKD stage 5D	CKD stages 1–5T
Treatment targets	Treatment to different targets of phosphorus; or treatment to different targets of PTH CKD stages 3–5, 5D, or 1–5T RCTs ^a <i>N</i> ≥ 25 per arm (≥ 10 per arm for bone biopsy) F/U ≥ 6 months	0	0	0
Phosphate binders	Any P Binder vs placebo/active control (except Ca vs placebo) ^b CKD stages 3–5, 5D, or 1–5T RCTs ^a <i>N</i> ≥ 25 per arm (≥ 10 per arm for bone biopsy) F/U ≥ 6 months	1	19 reports of 11 studies	0
Vitamin D	Vitamin D, calcitriol, or vitamin D analogs vs placebo/active control CKD stages 3–5, 5D, or 1–5T RCTs ^{a,c} <i>N</i> ≥ 25 per arm (≥ 10 per arm for bone biopsy) F/U ≥ 6 months	7	3	5
Calcimimetics	Calcimimetics vs placebo/active control CKD stages 3–5, 5D, or 1–5T RCTs ^a <i>N</i> ≥ 25 per arm (≥ 10 per arm for bone biopsy) F/U ≥ 6 months	1	5 reports of 3 studies	0
Calcium supplementation	Calcium supplementation vs active or control medical treatment CKD stages 3–5 RCTs ^{a,c} <i>N</i> ≥ 25 per arm (≥ 10 per arm for bone biopsy) F/U ≥ 6 months	0	0	0
Bisphosphonates, calcitonin, estrogen, progesterone, SERMs, intermittent PTH	Treatment vs placebo/active control CKD stages 3–5, 5D, or 1–5T RCTs ^{a,c} <i>N</i> ≥ 25 per arm (≥ 10 per arm for bone biopsy) F/U ≥ 6 months	3 Bisphosphonates 1 Teriparatide	1 Raloxifene	3 Bisphosphonates
Diet	Dietary phosphate restriction vs standard diet (must quantify phosphate intake) CKD stages 3–5, 5D, or 1–5T RCTs ^a <i>N</i> ≥ 10 per arm F/U ≥ 1 month for biochemical ≥ 6 months for bone outcomes	0	0	0
PTx	PTx vs medical management CKD stages 3–5, 5D, or 1–5T RCTs ^a <i>N</i> ≥ 25 per arm (≥ 10 per arm for bone biopsy) F/U ≥ 6 months	0	0	0
Pediatric	Same interventions as for adults (see above) CKD stages 3–5, 5D, or 1–5T RCTs ^a <i>N</i> as specified above for adult studies (Studies with <i>N</i> ≥ 5 are discussed in narrative) F/U as specified above for adult studies	0	2	0
Outcomes of interest for all questions of interventions				
Biochemical outcomes	Ca, P, PTH, 25(OH)D ^d , 1,25(OH) ₂ D ^d , ALP, b-ALP, Bicarbonate			
Other surrogate outcomes	Bone histology, BMD Vascular and valvular calcification imaging Measures of GFR			
Patient-centered outcomes	Mortality, cardiovascular and cerebrovascular events, hospitalization, QOL, kidney or kidney graft failure, fracture, PTx, pain, clinical AEs For studies in pediatric populations: growth and development, including school performance			

1,25(OH)₂D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; AE, adverse event; ALP, alkaline phosphatases; b-ALP, bone-specific alkaline phosphatase; BMD, bone mineral density; Ca, calcium; CKD, chronic kidney disease; F/U, minimum duration of follow-up; GFR, glomerular filtration rate; *N*, number of subjects; P, phosphorus; PTH, parathyroid hormone; PTx, parathyroidectomy; QOL, quality of life; RCT, randomized controlled trial; RR, relative risk; SERM, Selective Estrogen Receptor Modulators.

^aObservational studies of treatment effects would have been included if they examined a clinical outcome and had a RR of >2.0 or <0.5.

^bThe question of Ca-based P binders vs placebo was reviewed in the 2003 KDOQI (Kidney Disease Outcomes Quality Initiative) bone guidelines.⁵

^cLarge RCTs of interventions and comparisons of interest in the general population that reported results on more than 500 patients with CKD stages 3–5 were included.

^d25(OH)D and 1,25(OH)₂D included as outcomes of interest in patients not receiving vitamin D supplementation.

Table 4 | Questions for topics not related to treatments

Topic	Question	Screening criteria
Natural history of bone and CVD abnormalities	What is the natural history of bone abnormalities, and vascular and valvular calcification in CKD, after transplantation and after PTx?	CKD stages 3–5D and T Prospective, longitudinal F/U ≥ 6 months N ≥ 50 Predictors: bone biopsy; DXA; qCT; Vascular/Valvular calcification by echo, EBCT, MSCT, qCT, carotid IMT, aortic X-ray Outcomes: change in predictor over time, with or without interim transplantation or PTx
	What is the association between calcium, phosphorus, CaXP, and PTH, and (a) morbidity and mortality, (b) bone abnormalities (histology, DXA, qCT), and (c) vascular and valvular calcification? How do these vary by CKD stage?	CKD stages 3–5D and T Prospective, longitudinal F/U ≥ 6 months N ≥ 100, for bone biopsy N ≥ 20 Predictors: serum calcium (ionized, correct, total), serum phosphorus, CaXP, second, third generation or ratio PTH Outcomes: mortality, bone outcomes, CVD outcomes
Evaluation of biochemical markers	What is the association between additional biomarkers of bone turnover, and (a) morbidity and mortality, (b) bone abnormalities, and (c) vascular and valvular calcification?	CKD stages 3–5D and T Prospective, longitudinal F/U ≥ 6 months N ≥ 100, for bone biopsy N ≥ 20 Predictors: total alkaline phosphatase, bone-specific alkaline phosphatase, TRAP, OC, OPG, C-terminal cross links Outcomes: mortality, bone outcomes, CVD outcomes
	What is the association between vitamin D (25(OH)D and 1,25(OH) ₂ D), and (a) morbidity and mortality, (b) bone abnormalities, and (c) vascular and valvular calcification in individuals not treated with vitamin D replacement?	CKD stages 3–5D and T, naïve to treatment with vitamin D Prospective, longitudinal F/U ≥ 6 months N ≥ 100, for bone biopsy N ≥ 20 Predictors: vitamin D, 25(OH)D for all, 1,25 (OH) ₂ D for non-dialysis Outcomes: mortality, bone outcomes, CVD outcomes
Evaluation of bone	How do bone biopsy and DXA, and other bone imaging tests, including plain radiographs, qCT, and quantitative US predict (a) clinical outcomes and (b) surrogate outcomes for bone and CVD?	CKD stages 3–5D and T Prospective, longitudinal F/U ≥ 1 year, ≥ 6 months for transplant N ≥ 50, for bone biopsy N ≥ 20 Predictors: bone biopsy, DXA, DXA in combination with biochemical markers, change in DXA over 1 year, bone imaging by qCT (spine, wrist), qUS (heel) Outcomes: mortality, bone outcomes, CVD outcomes
	How do imaging tests and physiological/hemodynamical measures of vascular stiffening or calcification predict (a) clinical outcomes and (b) surrogate outcomes for bone and CVD?	CKD stages 3–5D and T, or subgroups with CKD in general population studies Prospective, longitudinal F/U ≥ 6 months N ≥ 50, for vascular histology N ≥ 20; for general population studies N ≥ 800, at least 50 with CKD Predictors: imaging techniques – X-ray, US, echo, EBCT, MSCT (separately by site), fistulogram; Physiological measures – PWV, PP, PWA, AIX, applanation tonometry Outcomes: mortality, bone outcomes, CVD outcomes
Evaluation of vascular and valvular calcification	What is the sensitivity and specificity of the imaging tests (plain radiograph, US, echo) for detecting vascular and valvular calcification by EBCT or MSCT?	CKD stages 3–5D and T Diagnostic test study, cross-sectional N ≥ 50 Index test: vascular or valvular calcification – X-ray, US, echo, EBCT, MSCT Comparison test: vascular or valvular calcification (respectively) by EBCT and MSCT Outcomes: sensitivity, specificity, ROC curves
	How do physiological/hemodynamical measures of vascular stiffening (PWV, PP) correlate with vascular or valvular calcifications by imaging tests?	CKD stages 3–5D and T Cross-sectional correlations N ≥ 50 Determinant: physiological measures PWV, PWA, AIX, PP, applanation tonometry Outcome: vascular and valvular calcification measures by EBCT, MSCT

Table 4 | Continued

Topic	Question	Screening criteria
	What is the correlation between imaging tests of valvular calcification and imaging tests of vascular calcification?	CKD stages 3–5D and T Cross-sectional correlations $N \geq 50$ Determinant: valvular calcification by echo, EBCT Outcome: vascular calcification by EBCT, MSCT

1,25(OH)₂D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; AIX, augmentation index; CaXP, calcium-phosphorus product; CKD, chronic kidney disease; CVD, cardiovascular disease; Dx, diagnostic; DXA, dual energy X-ray absorptiometry; EBCT, electron-beam computed tomography; echo, echocardiogram; F/U, follow-up; IMT, intimal-media thickness; MSCT, multislice computed tomography; N, number of subjects; OC, osteocalcin; OPG, osteoprotegerin; PP, pulse pressure; PTH, parathyroid hormone; PTx, parathyroidectomy; PWA, pulse wave analysis; PWV, pulse wave velocity; qCT, quantitative computed tomography; ROC, receiver operating characteristic; TRAP, tartrate-resistant acid phosphatase; US, ultrasonography.

were based on a systematic search of MEDLINE (1966–31 December 2000). This was supplemented by a MEDLINE search for relevant terms, including kidney, kidney disease, renal replacement therapy, bone, calcification, and specific treatments. The search was limited to English language publications since 1 January 2001 (*Supplementary Table 1*). Additional pertinent articles were added from the reference lists of relevant meta-analyses and systematic reviews.^{7–11}

During citation screening, journal articles reporting original data were used. Editorials, letters, abstracts, unpublished reports, and articles published in non-peer-reviewed journals were not included. The Work Group also decided to exclude publications from journal supplements because of potential differences in the process of how they get solicited, selected, reviewed, and edited compared with peer-reviewed publications in main journals. However, one article published in a supplement¹² was used for the clarification of adverse events (AEs) related to a study for which primary results were reported elsewhere.¹³ Selected review articles and key meta-analyses were retained from the searches for background material. An attempt was made to build on or use existing Cochrane or other systematic reviews on relevant topics (*Supplementary Table 2*).

EXCLUSION/INCLUSION CRITERIA FOR ARTICLE SELECTION FOR TREATMENT QUESTIONS

Search results were screened by members of the ERT for relevance, using predefined eligibility criteria in the following paragraphs. For questions related to treatment, the systematic search aimed at identifying RCTs with sample sizes and follow-up periods as described in (**Table 3**).

Restrictions by sample size and duration of follow-up were based on methodological and clinical considerations. Generally, trials with fewer than 25 people per arm would be unlikely to have sufficient power to find significant differences in patient-centered outcomes in individuals with CKD. This is especially true for dichotomous outcomes, such as deaths, cardiovascular clinical events, or fractures. However, for specific topics in which little data were available, lower sample-size thresholds were used to provide some information for descriptive purposes.

The minimum mean duration of follow-up of 6 months was chosen on the basis of clinical reasoning, accounting for

the hypothetical mechanisms of action. For treatments of interest, the proposed effects on patient-centered outcomes require long-term exposure and typically would not be evident before several months of follow-up.

Any study not meeting the inclusion criteria for a detailed review could nevertheless be cited in the narrative.

Interventions of interest are listed in (**Table 3**). For dietary phosphate restriction, the literature search identified no RCTs comparing assignment to different levels of dietary phosphate intake and outcomes of CKD–MBD. There were studies that compared assignment to different levels of protein restriction, and some of them quantified phosphate intake as a result of the dietary protein intervention. The question of dietary protein restriction, however, has been systematically reviewed previously.⁵ Thus, the Work Group chose a narrative format to review this topic. For the question of how alternative dialysis schedules affect serum calcium and phosphorus and parathyroid hormone, the Work Group chose to restrict itself to describing only the effects of RCTs, comparing different dialysis schedules on these laboratory outcomes. A complete review of all outcomes from these studies was deemed to be beyond the scope of this guideline.

Interventions of interest for children included all interventions reviewed in the adult population as well as growth hormone.

The use of observational studies for questions on the efficacy of interventions is a topic of ongoing methodological debate, given the many potential biases in the observational studies of treatment effects. The decision on how to incorporate this type of evidence in the development of this guideline was guided by concepts outlined in the GRADE approach.¹⁴ Observational studies of treatment effects start off as ‘low quality’. Their quality, however, can be upgraded if they show a consistent and independent, strong association. For the strength of the association, GRADE defines two arbitrary thresholds: one for a relative risk of > 2 or < 0.5 to upgrade the quality of evidence by one level, and the second for a relative risk of > 5 and < 0.2 to upgrade by two levels.¹⁴ As the quality of observational studies can be downgraded for methodological limitations or indirectness, they can yield high- or moderate-quality evidence only if they have no serious methodological limitations and show a strong or very strong association for a patient-relevant clinical outcome.

Thus, the Work Group was asked to identify the observational studies of treatment effects that were relevant to the guideline questions and that showed a relative risk of >2.0 or <0.5 for patient-relevant clinical outcomes. This process for identifying observational studies was used instead of systematic searches on the basis of the assumption that high-quality observational studies of patient-relevant clinical outcomes with large effect sizes would be well known to experts in the field. No observational studies meeting these criteria were identified. Observational studies with smaller estimates of treatment effects for clinical outcomes could be discussed and referenced in the rationale. The ERT cautioned against interpreting observational studies with smaller effect sizes for treatments as high-quality evidence, especially in areas in which RCTs are feasible.

EXCLUSION/INCLUSION CRITERIA FOR ARTICLE SELECTION FOR NONTREATMENT QUESTIONS

For studies related to questions of diagnosis, prevalence, and natural history (Table 4), the ERT completed a search in March 2007, screened the literature yield, and screened abstracts for relevance on the basis of the list of topics and questions. The yield of abstracts was tabulated by citation, population, number of individuals, follow-up time, study design (cross-sectional or longitudinal, prospective or retrospective), and by predictors and outcomes of interest. These lists were reviewed by the Work Group at the second Work Group meeting on 6 March 2007. The Work Group, in subgroups, made decisions to eliminate studies for a number of reasons (including publication prior to 1995, study size, poor study design, or not contributing pertinent information). The Work Group, with the assistance of the ERT, made the final decision for the inclusion or exclusion of all articles. These articles were either reviewed in a narrative form by the Work Group members or were tabulated into overview tables by the ERT and interpreted by the Work Group members. Articles pertinent to these nontreatment questions could be added by the Work Group members after the literature search date of March 2006. This hybrid process of a systematic search and selection of pertinent articles by experts was used to find information that was relevant and deemed important by the Work Group for the specific questions. The final yield of studies for these topics cannot be considered to be

comprehensive and thus does not constitute a systematic review. The articles were not data extracted or graded.

The following sections apply to studies included in the systematic reviews of treatment questions.

LITERATURE YIELD FOR SYSTEMATIC REVIEW TOPICS

The literature searches up to December 2007 yielded 15,921 citations. For treatment topics, 92 articles were reviewed in full, of which 49 publications of 38 trials were extracted and included in summary tables. The remaining 43 articles were rejected by the ERT after a review of the full text. Details of the yield can be found in Table 5. An updated search for RCTs was conducted in November 2008. It yielded an extension study of an earlier RCT¹⁵, which was added as an annotation to the respective summary table. Two other RCTs in press were added by the Work Group.

There were no RCTs comparing treatment to different targets of phosphorus or parathyroid hormone levels. Thus, observational studies were reviewed for data on risk relationship to define extreme ranges of risk, rather than treatment targets.

For the question related to parathyroidectomy vs medical management for secondary or tertiary hyperparathyroidism, a search was run for 'parathyroidectomy' and 'kidney disease' published from 2001 to 2008. These dates were used to capture citations published after the final search for the 2003 KDOQI bone guidelines. This search did not reveal any RCTs. Observational studies also did not meet criteria in terms of relative risk or odds ratio; therefore, a list of potential observational studies comparing these two modalities was provided to the Work Group as references for a narrative review.

For the question of calcium supplementation vs other active or control treatments for preventing the development of hyperparathyroidism, the search did not yield any RCTs that met the inclusion criteria. This question had not been specifically addressed in the 2003 KDOQI Bone Guidelines; thus, the literature search with key words pertaining to 'kidney', 'calcium', and 'parathyroid hormone' was not limited to a specific publication year (i.e., 1950 onward).

For the question of bisphosphonates as a treatment for CKD-MBD, one RCT was identified that evaluated the use of bisphosphonates for the prevention of glucocorticoid-induced bone loss in patients with glomerulonephritis.¹⁶

Table 5 | Literature search yield of primary articles for systematic review topics

Intervention	Articles included in summary tables ^a		
	CKD stages 3-5	CKD stage 5D	CKD stages 1-5T
Phosphate binders	1 ^b	19 ^b	0
Vitamin D	7	3	5
Calcimimetics	1	5	0
Other bone treatments ^c	4	1	3

Ca, calcium; CKD, chronic kidney disease; PTH, parathyroid hormone; SERM, Selective Estrogen Receptor Modulators.

^aExcludes articles in tables other than summary tables; includes each report for a particular study.

^bNot all reports of the Treat to Goal Study will be included in the summary tables.

^cBisphosphonates, calcitonin, estrogen, progesterone, SERMs, intermittent PTH, Ca supplement, growth hormone, and diet.

As this study predominately included patients with CKD stages 1–2, and therefore, by definition, did not evaluate CKD–MBD, it was not included in the systematic review table of this topic.

For treatment topics in the pediatric population, 30 articles were reviewed in full. A total of 11 RCTs were identified. If treatment studies in children met the same criteria as those for adult studies, including sample size and follow-up, they were added to adult summary tables.^{17,18} Otherwise, they were described in the corresponding section in the narrative. Separate evidence profiles for studies in children were not generated.

For the topic of growth hormone, a Cochrane meta-analysis update published in January 2007¹⁹ was found to include all studies identified by the ERT through to 16 July 2007. In this meta-analysis, RCTs were identified from the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE through to July 2005, as well as from article reference lists, and through contact with local and international experts in the field. The screening criteria were similar to the criteria established by the ERT and Work Group, but were more inclusive in that studies with less than five individuals per arm were included. The ERT and the Work Group decided that a summary of this meta-analysis was adequate for the question of growth hormone treatment in children with CKD.

DATA EXTRACTION

The ERT designed data extraction forms to capture information on various aspects of primary studies. Data fields for all topics included study setting, patient demographics, eligibility criteria, stage of kidney disease, numbers of individuals randomized, study design, study-funding source, description of mineral bone disorder parameters, descriptions of interventions, description of outcomes, statistical methods, results, quality of outcomes (as described in the following paragraphs), limitations to generalizability, and free-text fields for comments and assessment of biases.

The ERT extracted the baseline data. The Work Group extracted results, including AEs, graded the quality of the data, and listed the limitations to generalizability. Training of the Work Group members to extract data from primary articles occurred during Work Group meetings and by e-mail. The ERT reviewed and checked the data extraction carried out by the Work Group. Discrepancies in grading were resolved with the relevant Work Group members or with the entire Work Group during Work Group meetings. The ERT subsequently condensed the information from the data extraction forms. These condensed forms as well as the original articles were posted on a shared web site that all Work Group members could access to review the evidence. Data extraction of bone histology outcomes was carried out by two Work Group members specialized in that field (Susan Ott and Vanda Jorgetti). The ERT could not proof the results or evidence grades for this outcome. The method applied for assessing bone histomorphometry data

by the Work Group experts is described in detail in the next section.

DATA EXTRACTION AND METHODS FOR CATEGORIZING BONE HISTOMORPHOMETRY DATA

The KDIGO position statement about renal osteodystrophy² recommended that bone biopsy results should be reported on a unified classification system that includes parameters of turnover, mineralization, and volume. The clinical trials with bone histology outcomes reviewed for this guideline, however, were written before this statement, and the bone histomorphometry results were presented in a wide variety of ways. After reviewing the studies that met the inclusion criteria, two Work Group members chose a method that could be applied to most of the reported data. Most reports presented enough information to determine whether patients had changed from one category to another; sometimes this required extrapolation from figures or graphs. The categories are defined in Chapter 3.1, page S34.

The Work Group defined an improvement in turnover as a change from any category to normal, from adynamic or osteomalacia to mild or mixed, from osteitis fibrosa to mild, or from mixed to mild. Worsening bone turnover was defined as a change from normal to any category, from any category to adynamic or osteomalacia, from adynamic or osteomalacia to osteitis fibrosa, or from mild to osteitis fibrosa. These changes are shown in Figure 3, left side.

The average change in the bone formation rate could not be used to determine improvement, because a patient with a high bone-formation rate improves when it decreases, whereas a patient with adynamic bone disease must increase bone-formation rate to show improvement. A categorical approach, however, is also not ideal, because a patient could have substantial improvement but remain within a category, whereas another patient with a baseline close to the threshold between categories may change into another category with a small change. Another problem is variable definitions of the mixed category. A better method would be to report the mean change toward normal.^{20,21} Most of the reports, however, did not provide enough detail to analyze biopsies in this manner.

With some treatments, an overall index of improvement does not convey all the important information, because the results have to be interpreted in the context of the original disease. For example, a medicine that decreased bone turnover could be beneficial if the original disease was osteitis fibrosa, but harmful if the patient had adynamic disease.

Assessing mineralization was more straightforward. An increase in mean osteoid volume, osteoid thickness or mineralization lag time indicates a worsening of mineralization. An increase indicates a worsening of mineralization. Using categories, an improvement would be a change from mixed or osteomalacia to normal, adynamic, or osteitis fibrosa; worsening would be a change to the osteomalacia or mixed categories (Figure 3, right side).

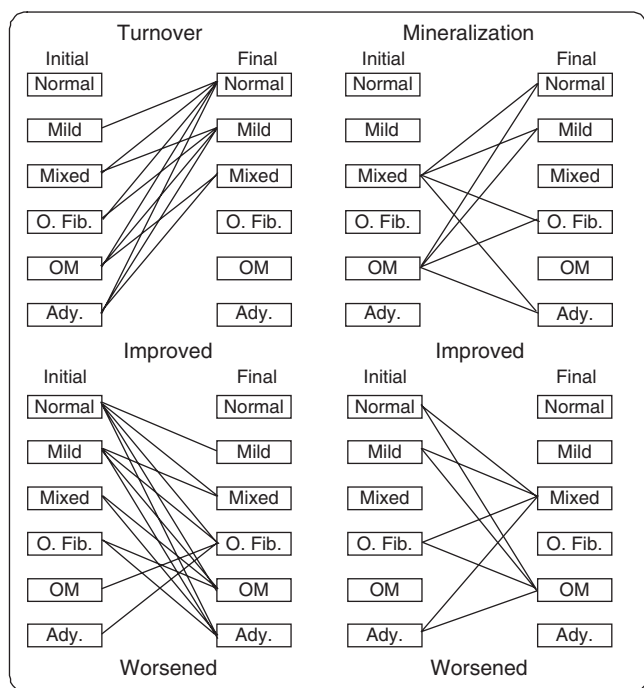


Figure 3 | Parameters of bone turnover, mineralization, and volume. Ady, adynamic bone disease; O. Fib, osteitis fibrosa; OM, osteomalacia.

For bone volume, an increase is usually an indication of improvement. Exceptions would be when patients develop osteosclerosis, but this is unusual. Most reports did not take bone volume into account. The studies also did not usually report differences in cortical vs cancellous bone, or report other structural parameters.

SUMMARY TABLES

Summary tables were developed to tabulate data from studies pertinent for each treatment question. Each summary contains three sections: a 'Baseline Characteristics Table', an 'Intervention and Results Table', and an 'Adverse Events Table'. Baseline Characteristics Tables include a description of the study size, the study population at baseline, demographics, country of residence, duration on dialysis, calcium concentration in the dialysis bath, diabetes status, previous use of aluminum-based phosphate binders, and findings on baseline MBD laboratory, bone, and calcification tests. Intervention and Results Tables describe the studies according to four dimensions: study size, follow-up duration, results, and methodological quality. Adverse Events Tables include study size, type of AEs, numbers of patients who discontinued treatment because of AEs, number of patients who died, and those who changed modality (including those who received a kidney transplant). The Work Group specified AEs of interest for each particular intervention (for example, hypercalcemia). Work Group members proofed all summary table data and quality assessments.

To provide consistency throughout the summary tables, data were sometimes converted or estimated. When follow-up times were reported in weeks, the results were converted into months by estimating 1 month as 4 weeks. Conventional units were converted into SI units, with the exception of creatinine clearance.

EVIDENCE PROFILES

Evidence profiles were constructed by the ERT to record decisions with regard to the estimates of effect, quality of evidence for each outcome, and quality of overall evidence across all outcomes. These profiles serve to make transparent to the reader the thinking process of the Work Group in systematically combining evidence and judgments. Each evidence profile was reviewed by Work Group experts. Decisions were taken on the basis of data and results from the primary studies listed in corresponding summary tables, and on judgments of the Work Group. Judgments with regard to the quality, consistency, and directness of evidence were often complex, as were judgments regarding the importance of an outcome or the net effect and quality of the overall quality of evidence across all outcomes. The evidence profiles provided a structured approach to grading, rather than a rigorous method of quantitatively summing up grades. When the body of evidence for a particular question or for a comparison of interest consisted of only one study, the summary table provided the final level of synthesis and an evidence profile was not generated.

EVIDENCE MATRICES

Evidence matrices were generated for each systematic review for a treatment question. The matrix shows the quantity and quality of evidence reviewed for each outcome of interest. Each study retained in the systematic review is tabulated with the description of its authors, year of publication, sample size, mean duration of follow-up, and the quality grade for the respective outcome. Conceptually, information on the left upper corner shows high-quality evidence for outcomes of high importance. Information on the right lower corner shows low-quality evidence for outcomes of lesser importance. Evidence for AEs was not graded for quality, but still tabulated in one column in the matrices.

An evidence matrix was not generated for a systematic review topic when the yield for the topic was only one study that met inclusion criteria, as the entire study is summarized in the summary table that contains all relevant information.

An overall evidence matrix was generated to show the yield of all studies included in summary tables for all interventions of interest. This overall evidence matrix shows the entire yield for all treatment questions, both in terms of outcomes reviewed and the quality of evidence for each outcome in each study. Single studies that did not warrant an individual evidence matrix (that is, they were the only studies for a specific intervention question) were still included in the overall evidence matrix.

Table 6 | Grading of study quality for an outcome

A: Good quality: low risk of bias and no obvious reporting errors; complete reporting of data. Must be prospective. If study of intervention: must be RCT.

B: Fair quality: Moderate risk of bias, but problems with study/paper are unlikely to cause major bias. If study of intervention: must be prospective.

C: Poor quality: High risk of bias or cannot exclude possible significant biases. Poor methods, incomplete data, reporting errors. Prospective or retrospective.

RCT, randomized controlled trial.

GRADING OF QUALITY OF EVIDENCE FOR OUTCOMES IN INDIVIDUAL STUDIES

Study size and duration

The study (sample) size is used as a measure of the weight of evidence. In general, large studies provide more precise estimates. Similarly, longer-duration studies may be of better quality and more applicable, depending on other factors.

Methodological quality

Methodological quality (or internal validity) refers to the design, conduct, and reporting of the outcomes of a clinical study. A three-level classification of study quality was previously devised (Table 6). Given the potential differences in the quality of a study for its primary and other outcomes, study quality was assessed for each outcome.

The evaluation of questions of interventions included RCTs. The grading of the outcomes of these studies included a consideration of the methods (that is, duration, type of blinding, number and reasons for dropouts, etc.), population (that is, does the population studied introduce bias?), outcome definition/measurement, and thoroughness/precision of reporting and statistical methods (that is, was the study sufficiently powered and were the statistical methods valid?).

Results

The type of results used from a study was determined by the study design, the purpose of the study, and the Work Group's question(s) of interest. Decisions were based on screening criteria and outcomes of interest (Table 3).

Approach to grading

A structured approach, modeled after GRADE,^{14,22,23,27} and facilitated by the use of Evidence Profiles and Evidence Matrices, was used to determine a grade that described the quality of the overall evidence and a grade for the strength of a recommendation. For each topic, the discussion on grading of the quality of evidence was led by the ERT, and the discussion regarding the strength of the recommendations was led by the Work Group Chairs.

Grading the quality of evidence for each outcome

The 'quality of a body of evidence' refers to the extent to which our confidence in an estimate of effect is sufficient

to support a particular recommendation (GRADE Working Group, 2008).²⁴ Following GRADE, the quality of a body of evidence pertaining to a particular outcome of interest is initially categorized on the basis of study design. For questions of interventions, the initial quality grade is 'High' if the body of evidence consists of RCTs, or 'Low' if it consists of observational studies, or 'Very Low' if it consists of studies of other study designs. For questions of interventions, the Work Group graded only RCTs. The grade for the quality of evidence for each intervention/outcome pair was then decreased if there were serious limitations to the methodological quality of the aggregate of studies; if there were important inconsistencies in the results across studies; if there was uncertainty about the directness of evidence including a limited applicability of findings to the population of interest; if the data were imprecise or sparse; or if there was thought to be a high likelihood of bias. The final grade for the quality of evidence for an intervention/outcome pair could be one of the following four grades: 'High', 'Moderate', 'Low', or 'Very Low' (Table 7).

Grading the overall quality of evidence

The quality of the overall body of evidence was then determined on the basis of the quality grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each outcome. The resulting four final categories for the quality of overall evidence were 'A', 'B', 'C', or 'D' (Table 8).¹⁴ This grade for overall evidence is indicated behind the strength of recommendations. The summary of the overall quality of evidence across all outcomes proved to be very complex. Thus, as an interim step, the evidence profiles recorded the quality of evidence for each of three outcome categories: patient-centered outcomes, other bone and vascular surrogate outcomes, and laboratory outcomes. The overall quality of evidence was determined by the Work Group and is based on an overall assessment of the evidence. It reflects that, for most interventions and tests, there is no high-quality evidence for net benefit in terms of patient-centered outcomes.

Assessment of the net health benefit across all important clinical outcomes

Net health benefit was determined on the basis of the anticipated balance of benefits and harm across all clinically important outcomes. The assessment of net medical benefit was affected by the judgment of the Work Group and ERT. The assessment of net health benefit is summarized in one of the following statements: (i) There is net benefit from intervention when benefits outweigh harm; (ii) there is no net benefit; (iii) there are tradeoffs between benefits and harm when harm does not altogether offset benefits, but requires consideration in decision making; or (iv) uncertainty remains regarding net benefit (Table 9).

Table 7 | GRADE system for grading quality of evidence for an outcome

Step 1: Starting grade for quality of evidence based on study design	Step 2: Reduce grade	Step 3: Raise grade	Final grade for quality of evidence for an outcome ^a
High for randomized trial	<i>Study quality</i> –1 level if serious limitations –2 levels if very serious limitations	<i>Strength of association</i> +1 level is strong, ^b no plausible confounders, consistent and direct evidence	High
Moderate for quasi-randomized trial	<i>Consistency</i> –1 level if important inconsistency	+2 levels if very strong, ^c no major threats to validity and direct evidence	Moderate
Low for observational study	<i>Directness</i> –1 level if some uncertainty –2 levels if major uncertainty	<i>Other</i> +1 level if evidence of a dose-response gradient	Low
Very Low for any other evidence	<i>Other</i> –1 level if sparse or imprecise data –1 level if high probability of reporting bias	+1 level if all residual plausible confounders would have reduced the observed effect	Very low

GRADE, Grades of Recommendations Assessment, Development, and Evaluation; RR, relative risk.

^aThe highest possible grade is 'high' and the lowest possible grade is 'very low'.

^bStrong evidence of association is defined as 'significant RR of >2 (<0.5)' based on consistent evidence from two or more observational studies, with no plausible confounders.

^cVery strong evidence of association is defined as 'significant RR of >5 (<0.2)' based on direct evidence with no major threats to validity.

Modified with permission from Uhlig (2006),²² and Atkins (2004)¹⁴

Table 8 | Final grade for overall quality of evidence²³

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

GRADING THE STRENGTH OF THE RECOMMENDATIONS

The 'strength of a recommendation' indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. The strength of a recommendation is graded as Level 1 or Level 2.²³

Table 10 shows the nomenclature for grading the strength of a recommendation and the implications of each level for patients, clinicians, and policy makers. Recommendations can be for or against doing something.

Table 11 shows that the strength of a recommendation is determined not just by the quality of evidence, but also by other, often complex judgments regarding the size of the net medical benefit, values and preferences, and costs. Formal decision analyses, including cost analysis, were not conducted. Where there is doubt regarding the balance of benefits and harm with respect to patient centered outcomes, or when the quality of evidence is too low to assess balance, the recommendation is necessarily a 'level 2'.

UNGRADED STATEMENTS

The Work Group felt that having a category that allows it to issue general advice would be useful. For this purpose,

Table 9 | Balance of benefits and harm²³

When there was evidence to determine the balance of medical benefits and harm of an intervention to a patient, conclusions were categorized as follows:

Net benefits	The intervention clearly does more good than harm.
Trade-offs	There are important trade-offs between the benefits and harm.
Uncertain trade-offs	It is not clear whether the intervention does more good than harm.
No net benefits	The intervention clearly does not do more good than harm.

the Work Group chose the category of a recommendation that was not graded. Typically, this type of ungraded statement met the following criteria: it provides guidance on the basis of common sense; it provides reminders of the obvious; and it is not sufficiently specific enough to allow an application of evidence to the issue, and therefore it is not based on a systematic evidence review. Common examples include recommendations regarding the frequency of testing, referral to specialists, and routine medical care. The ERT and Work Group strove to minimize the use of ungraded recommendations.

FORMULATION AND VETTING OF RECOMMENDATIONS

The selection of specific wording for each of the statements was a time-intensive process. In addition to striving for the recommendations to be clear and actionable, the wording also considered grammar, proper English-word usage, and the ability of concepts to be translated accurately into other languages. A final wording of recommendations and the corresponding grades for the strength of the recommendations and the quality of evidence were voted upon by the Work Group, and required a majority to

Table 10 | Implications of the strength of a recommendation

Grade	Implications		
	Patients	Clinicians	Policy
Level 1 'We recommend'	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be adopted as a policy in most situations.
Level 2 'We suggest'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require debate and involvement of stakeholders before policy can be determined.

Table 11 | Determinants of the strength of a recommendation²³

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is warranted. The narrower the gradient, the more likely a weak recommendation is warranted.
Quality of the evidence	The higher the quality of evidence, the more likely a strong recommendation is warranted.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted.
Costs (resource allocation)	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

be accepted. The process of peer review was a serious undertaking. It included an internal review by the KDIGO Board of Directors and an external review by the public to ensure widespread input from numerous stakeholders, including patients, experts, and industry and national organizations, and then another internal review by the KDIGO Board of Directors.

FORMAT FOR CHAPTERS

Each chapter contains one or more specific 'recommendations'. Within each recommendation, the strength of the recommendation is indicated as level 1 or level 2, and the quality of the overall supporting evidence is shown as A, B, C, or D. The recommendations are followed by a section that describes the chain of logic, which consists of declarative sentences summarizing the key points of the evidence base and the judgments supporting the recommendation. This is followed by a narrative that provides the supporting rationale and includes data tables where appropriate. In relevant sections, research recommendations suggest future research to resolve current uncertainties.

COMPARISON WITH OTHER GUIDELINES

The reconciliation of a guideline with other guidelines reduces potential confusion related to variability or discrepancies in guideline recommendations. At the beginning of the guideline process, the ERT searched for other current guidelines on CKD-MBD and compiled them by topic. This information was submitted to the Work Group to highlight those topics that other guidelines had addressed and what recommendations had been issued. However, given the global nature of the KDIGO guidelines, it was felt that judging how any guideline might be applicable in a particular setting would require a process of 'guideline adoption', and that it

would be the task of a local 'guideline adoption group' to review and reconcile the recommendations of the KDIGO guideline with those of other guidelines pertinent and applicable to its country or context. Thus, this KDIGO guideline does not contain a comparison of how the recommendations from this KDIGO Work Group differ from those of other existing guidelines.

LIMITATIONS OF APPROACH

Although the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE was the only database searched, and the search was limited to English language publications. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, important studies known to domain experts, which were missed by the electronic literature searches, were added to the retrieved articles and reviewed by the Work Group. Nonrandomized studies were not systematically reviewed. The majority of the ERT and Work Group resources were devoted to a detailed review of randomized trials, as these were deemed to most likely provide data to support treatment recommendations with higher quality evidence. Where randomized trials are lacking, it was deemed to be sufficiently unlikely that studies previously unknown to the Work Group would result in higher quality evidence. Evidence for patient-relevant clinical outcomes was low. Usually, low-quality evidence required a substantial use of expert judgment in deriving a recommendation from the evidence reviewed.

SUMMARY OF THE PROCESS

Several tools and checklists have been developed to assess the quality of the guideline development process and to enhance

the quality of guideline reporting. These include the Appraisal of Guidelines for Research and Evaluation (AGREE) criteria²⁵ and the Conference on Guideline Standardization (COGS) checklist.²⁶ *Supplementary Table 3* shows the key features of the guideline development process according to the COGS checklist.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Literature search strategy.

Supplementary Table 2. Use of other relevant systematic reviews and meta-analyses.

Supplementary Table 3. Key features of the guideline.

Supplementary material is linked to the online version of the paper at <http://www.nature.com/ki>

Chapter 3.1: Diagnosis of CKD–MBD: biochemical abnormalities

Kidney International (2009) **76** (Suppl 113), S22–S49. doi:10.1038/ki.2009.191

Grade for strength of recommendation ^a	Strength	Wording	Grade for quality of evidence	Quality of evidence
Level 1	Strong	'We recommend...should'	A	High
Level 2	Weak	'We suggest...might'	B	Moderate
			C	Low
			D	Very low

^aIn addition the Work Group could also make ungraded statements (see Chapter 2 section on ungraded statements).

INTRODUCTION

Biochemical abnormalities are common in chronic kidney disease (CKD) and are the primary indicators by which the diagnosis and management of CKD–mineral and bone disorder (CKD–MBD) is made. The two other components of CKD–MBD (bone abnormalities and vascular calcification) are discussed in Chapters 3.2 and 3.3.

RECOMMENDATIONS

3.1.1 We recommend monitoring serum levels of calcium, phosphorus, PTH, and alkaline phosphatase activity beginning in CKD stage 3 (1C). In children, we suggest such monitoring beginning in CKD stage 2 (2D).

3.1.2 In patients with CKD stages 3–5D, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (not graded).

Reasonable monitoring intervals would be:

- In CKD stage 3: for serum calcium and phosphorus, every 6–12 months; and for PTH, based on baseline level and CKD progression.
- In CKD stage 4: for serum calcium and phosphorus, every 3–6 months; and for PTH, every 6–12 months.
- In CKD stages 5, including 5D: for serum calcium and phosphorus, every 1–3 months; and for PTH, every 3–6 months.
- In CKD stages 4–5D: for alkaline phosphatase activity, every 12 months, or more frequently in the presence of elevated PTH (see Chapter 3.2).

In CKD patients receiving treatments for CKD–MBD, or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for trends and treatment efficacy and side-effects (not graded).

3.1.3 In patients with CKD stages 3–5D, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and therapeutic interventions (2C). We suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).

3.1.4 In patients with CKD stages 3–5D, we recommend that therapeutic decisions be based on trends rather than on a single laboratory value, taking into account all available CKD–MBD assessments (1C).

3.1.5 In patients with CKD stages 3–5D, we suggest that individual values of serum calcium and phosphorus, evaluated together, be used to guide clinical practice rather than the mathematical construct of calcium–phosphorus product (Ca × P) (2D).

3.1.6 In reports of laboratory tests for patients with CKD stages 3–5D, we recommend that clinical laboratories inform clinicians of the actual assay method in use and report any change in methods, sample source (plasma or serum), and handling specifications to facilitate the appropriate interpretation of biochemistry data (1B).

Summary of rationale for recommendations

- As the diagnosis of CKD–MBD depends on the measurement of laboratory and other variables, it is important to provide a guide to clinicians regarding when to commence measurement of those variables. Although changes in the biochemical abnormalities of CKD–MBD may begin in CKD stage 3, the rate of change and severity of abnormalities are highly variable among patients.
- Thus, the recommendations and suggestions above indicate that assessment of CKD–MBD should begin at stage 3, but the frequency of assessment needs to take into account the identified abnormalities, the severity and duration of the abnormalities in the context of the degree

and rate of change of glomerular filtration rate (GFR), and the use of concomitant medications. Further testing and shorter time intervals would be dependent on the presence and severity of biochemical abnormalities.

- Furthermore, the interpretation of these biochemical and hormonal values requires an understanding of assay type and precision, interassay variability, blood sample handling, and normal postprandial, diurnal, and seasonal variations in individual parameters.
- The serum phosphorus fluctuates more than the serum calcium. As the mathematical construct of the calcium \times phosphorus product ($\text{Ca} \times \text{P}$) is largely driven by serum phosphorus and generally does not provide any additional information beyond that which is provided by individual measures, it is of limited use in clinical practice.

BACKGROUND

The laboratory diagnosis of CKD-MBD includes the use of laboratory testing of serum PTH, calcium (ideally ionized calcium but most frequently total calcium, possibly corrected for albumin), and phosphorus. In some situations, measuring serum ALPs (total or bone specific) and bicarbonate may be helpful. It is important to acknowledge that the biochemical and hormonal assays used to diagnose, treat, and monitor CKD-MBD have limitations and, therefore, the interpretation of these laboratory values requires an understanding of assay type and precision, interassay variability, blood sample handling, and normal postprandial, diurnal, and seasonal variations. Derivations of these assays compound the problems with precision and accuracy. It is important for the practicing clinician to appreciate the potential variations in laboratory test results to avoid overemphasizing small or inconsistent changes in clinical decision making. Educating patients and primary-care physicians as to these subtleties is also important to ensure the appropriate interpretation by non-nephrologists who may also receive the results of the tests.

This chapter is the result of a comprehensive literature review of selected topics by the Work Group with assistance from the evidence review team to formulate the rationale for clinical recommendations. Thus, it should not be considered as a systematic review.

RATIONALE

3.1.1 We recommend monitoring serum levels of calcium, phosphorus, PTH, and alkaline phosphatase activity beginning in CKD stage 3 (1C). In children, we suggest such monitoring beginning in CKD stage 2 (2D).

Abnormalities in calcium, phosphorus, PTH, and vitamin D metabolism (collectively referred to as disordered mineral metabolism) are common in patients with CKD. Changes in the laboratory parameters of CKD-MBD may begin in CKD stage 3, but the presence of abnormal values, the rate of change, and the severity of abnormalities are highly variable among patients. To make the diagnosis of CKD-MBD, one or more of these laboratory abnormalities must be present.

Thus, measuring them once is essential for diagnosis. Although the initial assessment should begin at this stage, the frequency of assessment is based on the presence and persistence of identified abnormalities, the severity of abnormalities, all in the context of the degree and rate of change of GFR and the use of concomitant medications.

The interpretation of the biochemical and hormonal values also requires an understanding of normal postprandial, diurnal, and seasonal variations, with differences from one parameter to the other. For example, serum phosphorus fluctuates more than serum calcium within an individual, and is affected by diurnal variation more than is serum calcium. Given the complexity of changes within any one parameter, it is important to take into account the trends of changes rather than single values to evaluate changes in the degree of severity of laboratory abnormalities of CKD-MBD.

The best available data to guide diagnostic monitoring consist of that which is obtained from population-based or cohort-based prevalence studies. Although subject to specific biases, these studies do guide the clinician with respect to expected proportions of abnormal test results at specific levels of CKD. However, even this is problematic, given the inconsistent definitions of 'abnormal' (be it insufficient, deficient, or in excess). Moreover, there are additional issues with specific assays, especially for PTH and 25(OH)D, which further complicate and limit our ability to characterize specific levels as pathological.

Limitations of current data sources

Most of the studies describing observational data and relationships between individual parameters and clinical outcomes have been conducted in hemodialysis (HD) populations. Furthermore, those HD population studies are generally from cohorts who did not always receive predialysis care or early identification. In addition, the analysis of the observational data uses cohort-specific cut points or KDOQI recommendations from 2003.

Limited data exist regarding the prevalence of biochemical and hormonal abnormalities in CKD stages 3–5, because of the general absence of registry data, population-based studies, or large cohort studies. There are increasingly recognized differences in referred vs nonreferred populations, and in those with kidney transplants. Data are limited in all of these non-dialysis groups. Even in national dialysis databases, a routine collection of data on MBD is uncommon, and in those databases that do have the information, they are generally available only for a single time point, such as dialysis initiation, or confounded by treatment.

Thus, establishing diagnostic and management criteria on the basis of data obtained from the sources described above, and in the context of individual person and assay variability, is problematic. Nevertheless, utilizing trends, consistency of data direction, and biological plausibility, the Work Group has made recommendations and suggestions for the diagnosis and management of laboratory parameters.

Examples of studies that describe the prevalence of abnormalities

CKD stages 3-5. Levin *et al.*²⁸ have described the prevalence of abnormalities in serum calcium, phosphorus, and PTH in a cross-sectional analysis of 1800 patients with CKD stages 3-5 in North America (Study To Evaluate Early Kidney Disease). Calcium and phosphorus values did not become abnormal until GFR fell below 40 ml/min per 1.73 m², and were relatively stable until GFR fell below 20 ml/min per 1.73 m² (Figure 4). However, 12% of patients with GFR > 80 ml/min per 1.73 m² had a high PTH (defined as >65 pg/ml, the upper limit of normal of the assay used) and nearly 60% of patients with GFR < 60 ml/min per 1.73 m² had elevated PTH levels. Similar findings have been recently reported from a community-based screening program sponsored by the National Kidney Foundation, the Kidney Education and Evaluation Program.²⁹ It is to be noted that both cohorts were primarily nonreferred populations, with a diagnosis of CKD made on the estimated GFR.

CKD stage 5D. The Choices for Healthy Outcomes in Caring for End-Stage Renal Disease study is a large, prospectively collected national cohort of incident dialysis patients with repeated measures of laboratory values. In incident dialysis patients, serum levels of calcium and phosphorus at the start of dialysis were 9.35 mg/dl

(2.34 mmol/l) and 5.23 mg/dl (1.69 mmol/l), respectively. Mean serum levels increased over the initial 6 months of renal replacement therapy (calcium 9.51 mg/dl or 2.38 mmol/l; phosphorus 5.43 mg/dl or 1.75 mmol/l).³⁰

Although there are numerous cross-sectional reports of serum levels of calcium, phosphorus, and PTH in CKD stage 5D population, the international Dialysis Outcomes and Practice Pattern Study provides the most comprehensive global view of the prevalence of disorders of calcium (corrected for albumin), phosphorus, and PTH.³³ Unfortunately, there is no standardization of PTH assays from around the world. Nevertheless, abnormalities were observed in parallel studies from large dialysis providers in the United States with central laboratories. Figure 5 provides a robust depiction of not only the distribution of abnormalities in laboratory values relevant to CKD-MBD but also a visual representation of changes in international practice patterns as well over the three phases of the Dialysis Outcomes and Practice Pattern Study observation (I = 1996-2001, II = 2002-2004, and III = 2005-present).

Recently, elevated serum total ALP (t-ALP) levels have been recognized as a possibly independent variable associated with an increase in the relative risk (RR) of mortality in patients with CKD stage 5D.^{31,32} Regidor *et al.*³¹ have described an association of serum t-ALP levels with mortality

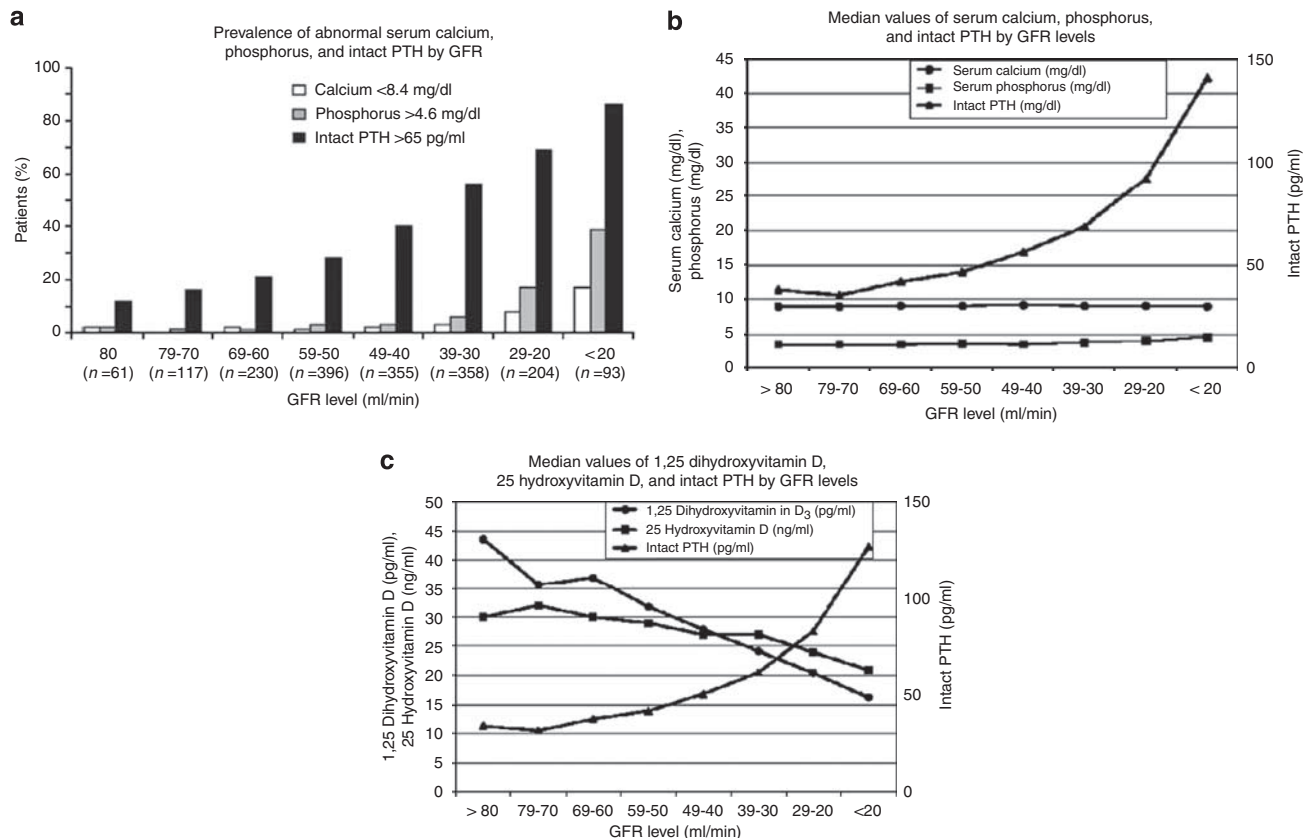


Figure 4 | Prevalence of abnormal mineral metabolism in CKD. (a) The prevalence of hyperparathyroidism, hypocalcemia, and hyperphosphatemia by eGFR levels at 10-ml/min per 1.73 m² intervals. (b) Median values of serum Ca, P, and iPTH by eGFR levels. (c) Median values of 1,25 (OH)₂D₃, 25(OH)D₃, and iPTH by GFR levels. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; iPTH, intact parathyroid hormone. Reprinted with permission from Levin *et al.*²⁸

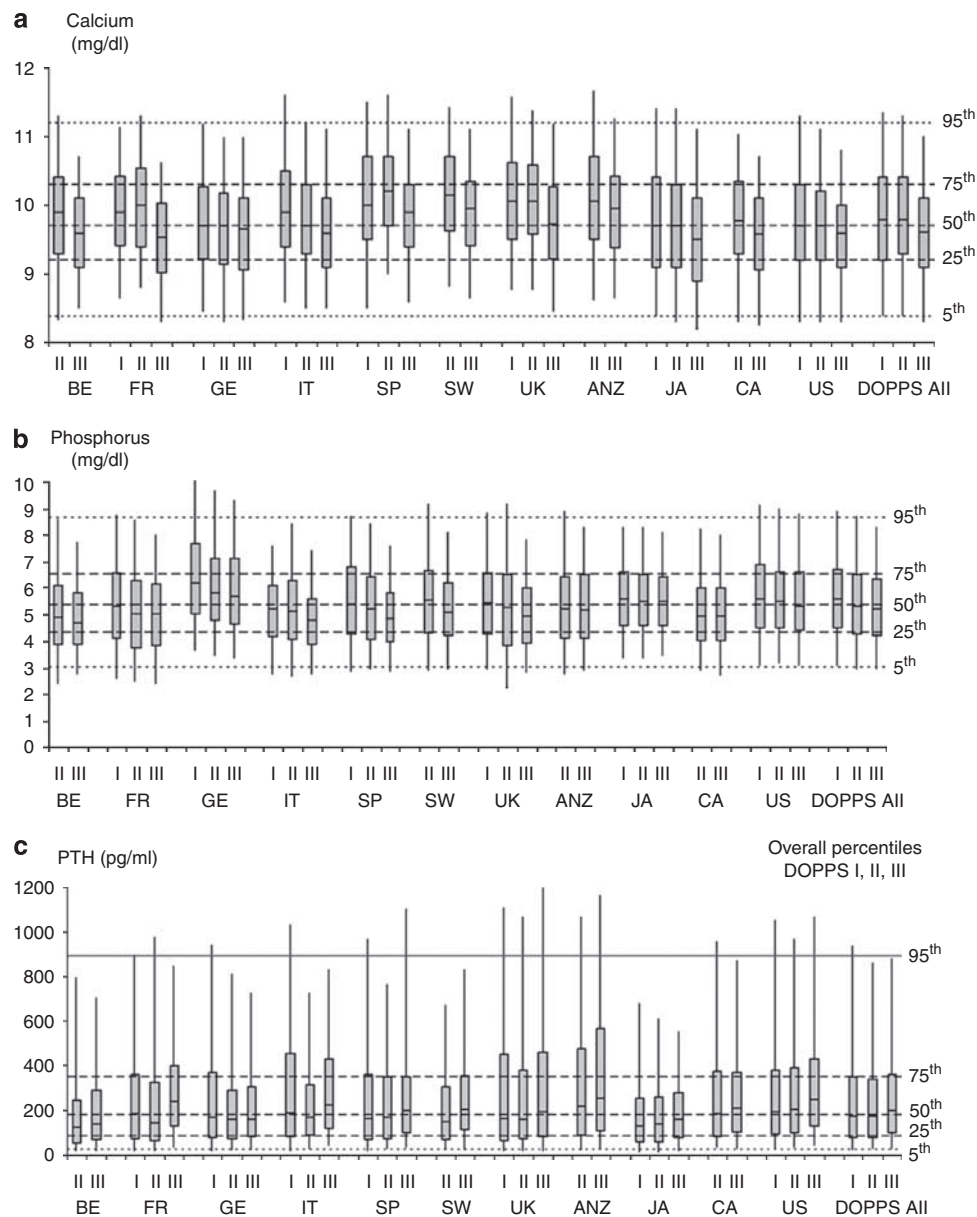


Figure 5 | Changes in serum calcium, phosphorus, and iPTH with time in hemodialysis patients of DOPPS countries. Distribution of baseline serum calcium (a), phosphorus (b), and PTH (c) by country and the DOPPS phase. See text for details. DOPPS, Dialysis Outcomes and Practice Pattern Study; PTH, parathyroid hormone. Reprinted with permission from Tentori *et al.*³³

among prevalent HD populations, in addition to U- or J-shaped curves for calcium, phosphorus, and PTH, further underscoring the complexity of the relationships of these laboratory abnormalities with outcomes. High levels of ALPs are associated with mortality, but there is no evidence that reducing these levels leads to improved outcomes. The use of ALPs to interpret other abnormalities of measured minerals within an individual (for example, as an indicator of bone turnover or as an indicator of other conditions such as liver disease, and so on) may be useful as detailed in Chapter 3.2.

Children. In children, one study showed that elevations in PTH occur as early as CKD stage 2, especially in children with slowly progressive kidney disease.³⁴ Given the significant associations of biochemical abnormalities of CKD-MBD with

growth and cardiac dysfunction³⁵ in children, the Work Group felt it was reasonable to assess children for the biochemical abnormalities of CKD-MBD initially at CKD stage 2.

3.1.2 In patients with CKD stages 3–5D, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (not graded).

Reasonable monitoring intervals would be:

- In CKD stage 3: for serum calcium and phosphorus, every 6–12 months; and for PTH, based on baseline level and CKD progression.

- In CKD stage 4: for serum calcium and phosphorus, every 3–6 months; and for PTH, every 6–12 months.
- In CKD stages 5, including 5D: for serum calcium and phosphorus, every 1–3 months; and for PTH, every 3–6 months.
- In CKD stages 4–5D: for alkaline phosphatase activity, every 12 months, or more frequently in the presence of elevated PTH (see Chapter 3.2).

In CKD patients receiving treatments for CKD–MBD, or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for trends and treatment efficacy and side-effects (not graded).

There are no data showing that routine measurement improves patient-level outcomes. Nevertheless, suggestions can be made as to a reasonable frequency of measurement of these laboratory parameters of CKD–MBD. The clinician should adjust the frequency on the basis of the presence and magnitude of abnormalities, and on the rate of progression of kidney disease. The frequency of measurement needs to be individualized for those receiving treatments for CKD–MBD to monitor for treatment effects and adverse effects.

Table 12 provides reasonable guidance as to the frequency of monitoring, given the numerous caveats outlined above; clinical situations (stability and treatment strategies) and other factors will influence the frequency of testing, and this must be individualized. As with any long-term condition, longitudinal trends are important and some forms of systematic (for example, fixed interval) monitoring is likely to be of greater value than random monitoring.

3.1.3 In patients with CKD stages 3–5D, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and therapeutic interventions (2C). We suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).

The Work Group acknowledged that there is emerging information on the potential role of vitamin D deficiency and insufficiency in the pathogenesis or worsening of multiple diseases. In addition, vitamin D deficiency and insufficiency may have a role in the pathogenesis of secondary hyperparathyroidism (HPT) as detailed in Chapter 4.2. The potential risks of vitamin D repletion are minimal, and thus, despite uncertain benefit, the Work Group felt that measurement might be beneficial.

The prevalence of vitamin D insufficiency or deficiency varies by the definition used. Most studies define deficiency as serum 25(OH)D (calcidiol) values <10 ng/ml (25 nmol/l), and insufficiency as values ≥ 10 but <20 – 32 ng/ml (50–80 nmol/l).^{36,37} However, there is no consensus on what defines ‘adequate’ vitamin D levels or toxic vitamin D levels,³⁸ although some believe a normal level is that which is associated with a normal serum PTH level in the general population, whereas others define it as the level above which there is no further reciprocal reduction in serum PTH upon vitamin D supplementation.^{39,40} Numerous publications have found associations of vitamin D deficiency, usually defined as serum 25(OH)D values <10 or 15 ng/ml (<25 or 37 nmol/l), to be associated with various diseases.^{41,42} In the general population^{43,44} and in patients with CKD,⁴⁵ there is an association of low 25(OH)D levels with mortality. There is one prospective randomized controlled trial (RCT) in the general population that shows that vitamin D supplementation reduces the risk of cancer.⁴⁶ However, there are no data showing that the repletion of vitamin D to a specific 25(OH)D level reduces mortality.

Defining specific target or threshold levels in the current era is likely to be premature (see Recommendation 3.1.4),^{37,42} and, in particular, using the criteria of a normal serum PTH level as vitamin D adequacy in CKD is problematic because of the multiple factors that affect PTH synthesis, secretion, target tissue response, and elimination in CKD. Studies in CKD patients and in the general population show widespread vitamin D deficiency; according to some definitions, almost 50% of those studied have suboptimal levels. In patients with CKD stages 3–4, some studies report lower 25(OH)D levels with more advanced stages of CKD.^{28,47,48} However, the Study To Evaluate Early Kidney Disease detailed above found no relationship between the stage of CKD and calcidiol levels. In the Study To Evaluate Early Kidney Disease, black individuals had lower levels of calcidiol and higher levels of PTH than did white individuals, despite higher levels of calcium and phosphorus.⁴⁹

Although position statements defining vitamin D deficiency exist, the definition of what level of vitamin D represents sufficiency is the subject of an ongoing debate. There are no data that the presence or absence of CKD would alter recommended levels. From a practical perspective, clinicians should also appreciate that—in the absence of knowing the optimum level, and with all the issues related to the measurement of serum levels of vitamin D sterols—the decision of whether to measure, when to measure, how often, and to what target level needs to be individualized. Furthermore, considerations as to how the information

Table 12 | Suggested frequencies of serum calcium, phosphorus, and PTH measurements according to CKD stage

	Progressive CKD stage 3	CKD stage 4	CKD stages 5 and 5D
Calcium and phosphorus	6–12 months	3–6 months	1–3 months
PTH and alkaline phosphatases	Baseline	6–12 months	3–6 months
Calcidiol	Baseline	Baseline	Baseline

CKD, chronic kidney disease; PTH, parathyroid hormone.

would impact management and treatment decisions should be considered on an individual patient basis, as well as by considering the impact on health-care resources/costs, where applicable. As detailed in Chapter 4.2, in patients with CKD stages 3 and 4, vitamin D deficiency may be an underlying cause of elevated PTH, and thus there is a rationale for measuring and supplementing in this population, although this approach has not been tested in a prospective RCT.

3.1.4 In patients with CKD stages 3–5D, we recommend that therapeutic decisions be based on trends rather than on a single laboratory value, taking into account all available CKD–MBD assessments (1C).

The interpretation of biochemical and hormonal values in the diagnosis of CKD–MBD requires an understanding of assay type and precision, interassay variability, blood sample handling, and normal postprandial, diurnal, and seasonal variations. Owing to these assay and biological variation issues, the Work Group felt that trends in laboratory values should be preferentially used over single values for determining when to initiate and/or adjust treatments.

Table 13 describes the sources and magnitude of variation in the measurement of serum calcium, phosphorus, PTH, and vitamin D sterols. This table serves as a guide for clinicians and forms the basis for the recommendation that laboratory tests should be measured using the same assays, and at similar times of the day/week for a given patient. Health-care providers should be familiar with assay problems and limitations (discussed below). Furthermore, an appreciation of this variability further underscores the importance of utilizing trends, rather than single absolute values, when making diagnostic or treatment decisions.

3.1.5 In patients with CKD stages 3–5D, we suggest that individual values of serum calcium and phosphorus, evaluated together, be used to guide clinical practice rather than the mathematical construct of calcium–phosphorus product ($\text{Ca} \times \text{P}$) (2D).

The mathematical construct of the calcium \times phosphorus product ($\text{Ca} \times \text{P}$) is of limited use in clinical practice, as it is largely driven by serum phosphorus and generally does not

provide any additional information beyond that which is provided by individual measures.^{50,51} The measurement of phosphorus is generally valid and reproducible, but is affected by diurnal and postprandial variation. Values may differ substantially (for example, up to 0.08 mg/dl; 0.026 mmol/l) in dialysis patients, depending on which shift or which interdialytic interval is chosen.³³ Furthermore, there are multiple situations in which a normal product is associated with poor outcomes, and the converse is similarly true. Thus, the Work Group advised against a reliance on this combined measurement in clinical practice.

3.1.6 In reports of laboratory tests for patients with CKD stages 3–5D, we recommend that clinical laboratories inform clinicians of the actual assay method in use and report any change in methods, sample source (plasma or serum), and handling specifications to facilitate an appropriate interpretation of biochemistry data (1B).

The use of biochemical assays for the diagnosis and management of CKD–MBD requires some understanding of assay characteristics and limitations, discussed by each assay below. The understanding of these sources of variability should allow clinicians and health-care providers to optimize the performance and interpretation of laboratory tests in CKD patients (for example, timing, location, laboratory used, and so on). Clinical laboratories should assist clinicians in the interpretation of data by reporting assay characteristics and kits used.

Calcium

Serum calcium levels are routinely measured in clinical laboratories using colorimetric methods in automated machines. There are quality control standards utilized by clinical laboratories. Thus, the assay is generally precise and reproducible. In healthy individuals, serum calcium is tightly controlled within a narrow range, usually 8.5–10.0 or 10.5 mg/dl (2.1–2.5 or 2.6 mmol/l), with some, albeit minimal, diurnal variation.⁵² However, the normal range may vary slightly from laboratory to laboratory, depending on the type of measurement used. In patients with CKD, serum calcium levels fluctuate more, because of altered homeostasis and concomitant therapies. In those with CKD stage 5D, there are additional fluctuations in association with dialysis-induced changes, hemoconcentration, and subsequent hemodilution. Moreover, predialysis samples collected from HD patients after the longer interdialytic interval during the weekend, as compared with predialysis samples drawn after the shorter interdialytic intervals during the week, often contain higher serum calcium levels. In the international Dialysis Outcomes and Practice Pattern Study, the mean serum calcium measured immediately before the Monday or Tuesday sessions was higher by 0.01 mg/dl (0.0025 mmol/l) than that measured before the Wednesday or Thursday sessions.³³

Table 13 | Sources and magnitude of the variation in the measurement of serum calcium, phosphorus, PTH, and vitamin D sterols

Variable	Calcium	Phosphorus	PTH	Vitamin D sterols
Coefficient of variation	+	+	++	++
Diurnal variation	+	++	++	–
Seasonal variation				++
Variation with meals	+	+	+	–
Variation with dialysis time	+	+		
Assay validity	+++	+++	+	+

NS, no shading; PTH, parathyroid hormone; S, shading. +, minimal or low; ++, moderate; + + +, high or good; –, no variability; blank space, not tested.

The serum calcium level is a poor reflection of overall total body calcium. Only 1% of total body calcium is measurable in the extracellular compartment. The remainder is stored in bone. Serum ionized calcium, generally 40–50% of total serum calcium, is physiologically active, whereas non-ionized calcium is bound to albumin or anions such as citrate, bicarbonate, and phosphate, and is therefore not physiologically active. In the presence of hypoalbuminemia, there is an increase in ionized calcium relative to total calcium; thus, total serum calcium may underestimate the physiologically active (ionized) serum calcium. A commonly used formula for estimating ionized calcium from total calcium is the addition of 0.8 mg/dl (0.2 mmol/l) for every 1 g decrease in serum albumin below 4 g/dl (40 g/l). This ‘corrected calcium’ formula is routinely used by many dialysis laboratories and in most clinical trials. Unfortunately, recent data have shown that it offers no superiority over total calcium alone and is less specific than ionized calcium measurements.⁵³ In addition, the assay used for albumin may affect the corrected calcium measurement.⁵⁴ However, ionized calcium measurement is not routinely available and, in some instances, may require additional costs for measuring and reporting. Presently, most databases are already using the corrected calcium formula and there is an absence of data showing differences in treatment approach or clinical outcomes when using corrected vs total or ionized calcium. The Work Group did not recommend that corrected calcium measurements be abandoned at present. Furthermore, the use of ionized calcium measurements is currently not considered to be practical or cost effective.

Phosphorus

Inorganic phosphorus is critical for numerous normal physiological functions, including skeletal development, mineral metabolism, cell-membrane phospholipid content and function, cell signaling, platelet aggregation, and energy transfer through mitochondrial metabolism. Owing to its importance, normal homeostasis maintains serum concentrations between 2.5–4.5 mg/dl (0.81–1.45 mmol/l). The terms, phosphorus and phosphate, are often used interchangeably, but strictly speaking, the term phosphate means the sum of the two physiologically occurring inorganic ions in the serum, and in other body fluids, hydrogenphosphate (HPO_4^{2-}) and dihydrogenphosphate (H_2PO_4^-). However, most laboratories report this measurable, inorganic component as phosphorus. Unlike calcium, a major component of phosphorus is intracellular, and factors such as pH and glucose can cause shifts of phosphate ions into or out of cells, thereby altering the serum concentration without changing the total body phosphorus.

Phosphorus is routinely measured in clinical laboratories with colorimetric methods in automated machines. There are quality control standards used by clinical laboratories. Thus, the assay is generally precise and reproducible. Levels will be falsely elevated with hemolysis during sample collection. In healthy individuals, there is a diurnal variation in both serum

phosphorus levels and urinary phosphorus excretion. Serum phosphorus levels reach a nadir in the early hours of the morning, increasing to a plateau at 1600 hours, and further increasing to a peak from 0100 to 0300 hours.^{55,56} Similar results were found in patients with hypercalcuria and nephrolithiasis.⁵⁷ However, another study found no diurnal variation in patients on dialysis when studied on a non-dialysis day.⁵⁸ There are usually higher levels after a longer period of dialysis. In the international Dialysis Outcomes and Practice Pattern Study, samples collected from HD patients immediately before a Monday or Tuesday session vs a Wednesday or Thursday session were higher by 0.08 mg/dl (0.025 mmol/l).³³

Thus, the measurement of phosphorus is generally valid and reproducible, but may be affected by normal diurnal and postprandial variation. Again, trends of progressive increase or decrease may be more accurate than small variations in individual values.

Parathyroid hormone

PTH is cleaved to an 84-amino-acid protein in the parathyroid gland, where it is stored with fragments in secretory granules for release. Once released, the circulating 1–84-amino-acid protein has a half-life of 2–4 min. The hormone is cleaved both within the parathyroid gland and after secretion into the N-terminal, C-terminal, and mid-region fragments of PTH, which are metabolized in the liver and in the kidneys. Enhanced PTH synthesis/secretion occurs in response to hypocalcemia, hyperphosphatemia, and/or a decrease in serum 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}$), whereas high serum levels of calcium or calcitriol—and, as recently shown, of FGF-23⁵⁹—suppress PTH synthesis/secretion. The extracellular concentration of ionized calcium is the most important determinant of the minute-to-minute secretion of PTH, which is normally oscillatory. In patients with CKD, this normal oscillation is somewhat blunted.⁶⁰

There has been a progression of increasingly sensitive assays developed to measure PTH over the past few decades (Figure 6). Initial measurements of PTH using C-terminal

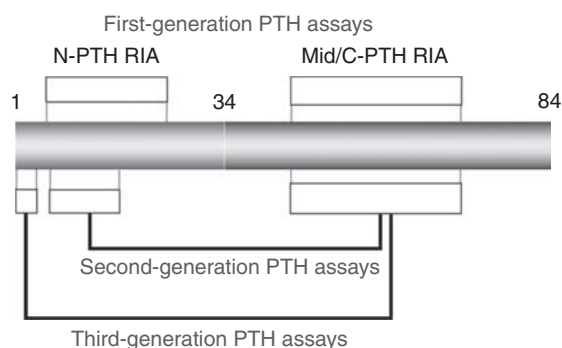


Figure 6 | PTH assays. The figure shows the entire parathyroid hormone molecule, composed of 84 amino acids. Mid/C-PTH, mid/carboxyl-terminus of parathyroid hormone; N-PTH, amino-terminus of parathyroid hormone; PTH, parathyroid hormone; RIA, radioimmunoassay. Reprinted with permission from Moe and Sprague.⁷⁰

assays were inaccurate in patients with CKD because of the impaired renal excretion of C-terminal fragments (and thus retention) and the measurement of these probably inactive fragments. The development of the N-terminal assay was initially thought to be more accurate but it also detected inactive metabolites.

The development of a second generation of PTH assays (Figure 6), the two-site immunoradiometric assay—commonly called an ‘intact PTH’ assay—improved the detection of full-length (active) PTH molecules. In this assay, a captured antibody binds within the amino terminus and a second antibody binds within the carboxy terminus.⁶¹ Unfortunately, recent data indicate that this ‘intact’ PTH assay also detects accumulated large C-terminal fragments, commonly referred to as ‘7–84’ fragments; these are a mixture of four PTH fragments that include, and are similar in size to, 7–84 PTH.⁶² In parathyroidectomized rats, the injection of a truly whole 1- to 84-amino-acid PTH was able to induce bone resorption, whereas the 7- to 84-amino-acid fragment was antagonistic, explaining why patients with CKD may have high levels of ‘intact’ PTH but relative hypoparathyroidism at the bone-tissue level.^{63–65} Thus, the major difficulty in accurately measuring PTH with this assay is the presence of circulating fragments, particularly in the presence of CKD. Unfortunately, the different assays measure different types and amounts of these circulating fragments, leading to inconsistent results.⁶⁶

More recently, a third generation of assays has become available that truly detect only the 1- to 84-amino-acid, full-length molecule: ‘whole’ or ‘bioactive’ PTH assays (Figure 6). However, they are not yet widely available and have not been shown convincingly to improve the predictive value for the diagnosis of underlying bone disease⁶⁷ or other serum markers of bone turnover,⁶⁸ in contrast to at least one report that suggested that levels of 1–84 PTH or the 1–84 PTH/large C-PTH fragment ratio may be a better predictor of mortality in CKD stage 5 than standard ‘intact’ PTH values.⁶⁹ Therefore, the Work Group felt that the widely available second-generation PTH assays should continue to be used in routine clinical practice at present.

There are a number of commercially available kits that measure so-called ‘intact’ PTH with second-generation assays. Much of the literature and recommendations from KDOQI Bone and Mineral guidelines⁵ were based on the second-generation Allegro assay from Nichols, which is not currently available. A study evaluated these other assays in comparison with the Allegro kit, using pooled human serum, and found intermethod variability in results because of standardization and antibody specificity. The different assays measured different quantities of both 7–84 and 1–84 PTH (when added to uremic serum).⁶⁶ In addition, there are differences in PTH results when samples are measured in plasma, serum, or citrate, and depending on whether the samples are on ice, or are allowed to sit at room temperature.^{71,72}

Thus, these data—which describe problems with sample collection and assay variability—raise significant concerns

with regard to the validity of absolute levels of PTH and their strict use as a clinically relevant biomarker for targeting specific values. Nevertheless, the clinical consequences of not measuring PTH and treating secondary HPT are of equal concern. In an attempt to balance the methodological issues of PTH measurement with the known risks and benefits of excess PTH and treatment strategies, the Work Group felt that PTH should be measured, with standardization within clinics and dialysis units in the methods of sample collection, processing, and assay used. In addition, the Work Group felt that trends in serum PTH, rather than single values, should be used in the diagnosis of CKD-MBD and in the treatment of elevated or low levels of PTH. However, ‘systematic’ unidirectional trends observed in the majority of patients in a single center should prompt suspicion that the central laboratory may have changed the assay. The Work Group also felt that using narrow ranges of PTH defining an ‘optimal’ or ‘target’ range was neither possible nor desirable.

Vitamin D₂ and D₃ and their derivatives

To ensure that the reader of this guideline is clear on the difference between these compounds, and to ensure the use of consistent nomenclature in clinical practice, **Table 14** is provided. Following the table is an in-depth discussion relating to the assays and measurement of these compounds.

Assays of serum vitamin D metabolites

25(OH)D. The parent compounds of vitamin D—D₃ (cholecalciferol) or D₂ (ergocalciferol)—are highly lipophilic. They are difficult to quantify in the serum or plasma. They also have a short half-life in circulation of about 24 h. These parent compounds are metabolized in the liver to 25(OH)D₃ (calcidiol) or 25(OH)D₂ (ercalcidiol). Collectively, they are called 25(OH)D or 25-hydroxyvitamin D. The measurement of serum 25(OH)D is regarded as the best measure of vitamin D status, because of its long half-life of approximately 3 weeks. In addition, it is an assessment of the multiple sources of vitamin D, including both nutritional intake and skin synthesis of vitamin D. There is a seasonal variation in calcidiol levels because of an increased production of cholecalciferol by the action of sunlight on skin during summer months.

There are three types of assays for measuring calcidiol. Fortunately, unlike PTH, the specimen collection process is well standardized and the sample is stable over time. However, there are real differences in measurement methods. The gold standard of calcidiol measurement is high-performance liquid chromatography (HPLC), but this is not widely available clinically. This is because HPLC is time consuming, requires expertise and special instrumentation, and is expensive. In early 1985, Hollis and Napoli⁷³ developed the first radioimmunoassay (RIA) for total 25(OH)D, which was co-specific for 25(OH)D₂ and 25(OH)D₃. The values correlated with those obtained from HPLC analysis, and DiaSorin RIA became the first test to be approved by the Food and Drug Administration for use in

Table 14 | Vitamin D₂ and D₃ and their derivatives

	D ₂ and derivatives	D ₃ and derivatives	Collective terminology
Parent compound			
Abbreviation	D ₂	D ₃	D
Full term	Vitamin D ₂	Vitamin D ₃	Vitamin D
Synonym	Ergocalciferol	Cholecalciferol	
Product of first hydroxylation			
Abbreviation	25(OH)D ₂	25(OH)D ₃	25(OH)D
Full term	25-Hydroxyvitamin D ₂	25-Hydroxyvitamin D ₃	25-Hydroxyvitamin D
Synonym	Ergocalcidiol	Calcidiol	
Product of second hydroxylation			
Abbreviation	1,25(OH) ₂ D ₂	1,25(OH) ₂ D ₃	1,25(OH) ₂ D
Full term	1,25-Dihydroxyvitamin D ₂	1,25-Dihydroxyvitamin D ₃	1,25 Dihydroxyvitamin D
Synonym	Ergocalcitril	Calcitriol	

clinical settings.⁷³ Subsequent developments led to the automation of the test. Nichols developed a fully automated chemiluminescence assay in 2001, allowing clinical laboratories the ability of rapid and large-volume detection. However, this assay was removed from the market in 2006. In 2004, DiaSorin (Stillwater, MN, USA) introduced its fully automated chemiluminescence assay, which, similar to its RIA, is co-specific for 25(OH)D₂ and 25(OH)D₃, reporting 'total' 25(OH)D concentration. This assay has recently been updated as a 'second-generation' assay with an improved assay precision.^{37,74} Additional manufacturers, IDS (Fountain Hills, AZ, USA) and Roche Diagnostics (Burgess Hill, West Sussex, UK) also make automated RIAs and/or enzyme-linked immunosorbent assay tests, but there are only limited publications thus far. In the majority of reports in this field, the DiaSorin assay was used.

Another method now carried out is liquid chromatography-tandem mass spectrometry (LC-MS/MS). Similar to HPLC, the LC-MS/MS method also has the ability to quantify 25(OH)D₂ and 25(OH)D₃ separately, which distinguishes it from RIA and enzyme-linked immunosorbent assay technologies. This method is very accurate and has been shown to correlate well with DiaSorin RIA.^{75,76} Next to DiaSorin assays, LC-MS/MS is the most frequently used procedure for the clinical assessment of circulating 25(OH)D.³⁷ However, most clinical laboratories do not use this technique because of the substantial cost and need for highly trained operators. Only HPLC and LC-MS/MS can differentiate 25(OH)D₂ and 25(OH)D₃, whereas RIA and automated chemiluminescence technologies only measure total 25(OH)D—the sum of 25(OH)D₂ and 25(OH)D₃. There is controversy as to whether the ability to differentiate these metabolites is important, as they have similar biological effects.^{77,78}

A recent study by Binkley *et al.*⁷⁹ analyzed blood obtained from 15 healthy adults for 25(OH)D. Aliquots of serum from all volunteers and a calibrator (known to contain 30 ng/ml (75 nmol/l) 25(OH)D by HPLC) were sent to four laboratories. The methods used for 25(OH)D measurement included HPLC, LC-MS/MS in two laboratories, and RIA (DiaSorin). A good correlation was observed for 25(OH)D measurement among the laboratory using HPLC, the two

laboratories using LC-MS/MS, and the laboratory using RIA ($R^2 = 0.99, 0.81, \text{ and } 0.95$, respectively). The classification of clinical vitamin D status as optimal or low was identical for 80% of the 15 individuals in all four laboratories. However, 20% would be variably classified depending on the laboratory used. A modest interlaboratory variability was noted, with a mean bias of the laboratories using LC-MS/MS and RIA being from +2.9 to +51 ng/ml (+7.2 to +127 nmol/l) when compared with the laboratory using HPLC. They found that a systematic bias led to 89% of values being higher in the non-HPLC laboratories, and that a correction of the 25(OH)D value using a single calibrator at all sites for all assays reduced the mean interlaboratory bias. This suggests that the use of a standard calibrator may increase agreement among laboratories.

Thus, the Work Group advises that clinicians should be aware of the assay methods when assessing vitamin D status. Currently, the assays for 25(OH)D are not well standardized, and the definition of deficiency is not yet well validated. At best, clinicians should ensure that patients use the same laboratory for measurements of these levels, if carried out. The most appropriate vitamin D assays presently available seem to be those that measure both 25(OH)D₂ and 25(OH)D₃. Presently, approximately 20–50% of the general population has low vitamin D levels, irrespective of CKD status. However, the benefits from replacing vitamin D have not been documented in patients with CKD, particularly if they are taking calcitriol or a vitamin D analog. Therefore, the utility of measurement is unclear, outside of clinical trial or research situations. Furthermore, there are no data indicating that the measurement is helpful in guiding therapy or in predicting outcomes in CKD, although vitamin D deficiency may be a treatable cause of secondary HPT, especially early in the course of CKD. The risk, benefit, and costs of testing in patients should be balanced with practical issues related to treatment trials.

1,25(OH)₂D. 1,25(OH)₂D is used to describe both hydroxylated D₂ (ergocalcitril) and D₃ (calcitriol) compounds, both of which have a short half-life of 4–6 h. Commercially available assays do not distinguish between 1,25(OH)₂D₂ and 1,25(OH)₂D₃, and there are insufficient data to support the

different biological effects of these compounds. The gold standard for assessment of $1,25(\text{OH})_2\text{D}$ is HPLC, and only a small number of kits are available for routine measurement. Circulating levels of $1,25(\text{OH})_2\text{D}$ are approximately 1/1000th that of $25(\text{OH})\text{D}$. The measurement of $1,25(\text{OH})_2\text{D}$ will be affected by both the stores of $25(\text{OH})\text{D}$ and the multiple factors that convert $25(\text{OH})\text{D}$ to $1,25(\text{OH})_2\text{D}$ by the $25(\text{OH})\text{D}$ - 1α -hydroxylase enzyme (CYP27B1), as well as its inactivation by the $24(\text{OH})\text{D}$ hydroxylase enzyme (CYP24A1) to $1,24,25(\text{OH})_3\text{D}$ and other inactivation steps. The renal CYP27B1 is regulated by nearly every hormone involved in calcium homeostasis. Its activity is stimulated by PTH, estrogen, calcitonin, prolactin, growth hormone, low calcium, and low phosphorus, and is inhibited by its product $1,25(\text{OH})_2\text{D}$, FGF-23, and metabolic acidosis. Recent data show that multiple other tissues and cells also have CYP27B1 activity, which is believed to have autocrine/paracrine functions.⁸⁰ This extrarenal 1α -hydroxylase does not seem to be regulated by factors related to calcium homeostasis, suggesting a role for the extrarenal production of $1,25(\text{OH})_2\text{D}$ other than that involved in mineral metabolism.

Furthermore, in patients with earlier stages of CKD and in the general population, mild-to-moderate vitamin D deficiency, or partly treated vitamin D deficiency, is frequently associated with increased levels of $1,25(\text{OH})_2\text{D}$. Thus, even accurate levels can be misleading. The serum levels of $1,25(\text{OH})_2\text{D}$ are uniformly low in late stages of CKD-MBD, at least in patients not treated with vitamin D derivatives.

Thus, the Work Group did not recommend a routine measurement of $1,25(\text{OH})_2\text{D}$ levels, as the assays are not well standardized, the half-life is short, the measurement will be artificially altered by the exogenous administration of calcitriol and vitamin D analogs, and there are no data indicating that the measurement is helpful in guiding therapy or predicting outcomes.

Alkaline phosphatases

Alkaline phosphatases are enzymes that remove phosphate from proteins and nucleotides, functioning optimally at alkaline pH. Measurement of the level of t-ALP is a colorimetric assay that is routinely used in clinical laboratories in automated machines, with quality control standards routinely used. The enzyme is found throughout the body in the form of isoenzymes that are unique to the tissue of origin. Highest concentrations are found in the liver and bone, but the enzyme is also present in the intestines, placenta, kidneys, and leukocytes. Specific ALP isoenzymes to identify the tissue source can be determined after fractionation and heat inactivation, but these procedures are not widely available in clinical laboratories. Bone-specific ALP (b-ALP) is measured with an immunoradiometric assay. Elevated levels of t-ALP are generally due to an abnormal liver function (in which case, other tests are also abnormal), an increased bone activity, or bone metastases. Levels are normally higher in children with growing bones than in adults, and often are increased after

fracture. In addition, t-ALP and b-ALP can be elevated in both primary and secondary HPT, osteomalacia, and in the presence of bone metastasis and Paget's disease.

The Work Group recommended that the measurement of t-ALP in the diagnosis and assessment of CKD-MBD may be used as an adjunct test, but if values are high, then liver function tests should be checked. t-ALP could reasonably be used as a routine test to follow response to therapy. The more expensive testing for b-ALP can be used when the clinical situation is more ambiguous. Relationships between b-ALP and bone turnover are discussed in the following chapter. However, testing for t-ALP is inexpensive and therefore may be helpful for following patients' response to therapy or determining bone turnover status when the interpretation of PTH is unclear. The use of b-ALP, an indicator of bone source, may provide additional and more specific information, although it is not readily available. Clinicians should consider the adjunct value of these tests in treating individual patients in the context of the caveats described above.

RESEARCH RECOMMENDATIONS

It is important to emphasize that CKD-MBD is a complex disorder affecting those at all stages of CKD. An understanding of the complex biology in combination with the complexity of measurement issues is of tantamount importance, if eventually the appropriate RCTs of treatment are to be conducted. Many different kinds of studies are required to further our knowledge. As it pertains to the recommendations and suggestions described in this chapter of diagnosis and monitoring, the key areas for research to address in the area of measurement and assay variability are listed below:

- To increase the understanding of inter- and intraindividual variations in the laboratory parameters of CKD-MBD, registries (for those in stages 3–4, on dialysis, and those with kidney transplants) should endeavor to collect serial data on CKD-MBD laboratory information.
- To ensure comparability between and within cohorts/facilities and countries and thus ensure the transferability of knowledge, there is a need to establish standards for all relevant laboratory parameters, including assays, handling, and timing of specimen collection.
- To conduct international trials (cohort, observational, or treatment), and to facilitate the appropriate uptake of study information, there is a need for the creation of an international registry to oversee and review the standardization of measurement methods. This group would necessarily work with pathology/laboratory medicine organizations to facilitate the implementation of these standards.
- To establish CKD cohort-specific ranges of normal and pathological values, there is a need to ensure the systematic collection of longitudinal prospective observational data and outcomes. Specific cohorts, about whom little is known about initial and serial 'expected' or acceptable values, include those initiating dialysis (with and without earlier CKD care), those receiving kidney transplants, and those on home-based therapies.

Chapter 3.2: Diagnosis of CKD–MBD: bone

Grade for strength of recommendation ^a	Strength	Wording	Grade for quality of evidence	Quality of evidence
Level 1	Strong	'We recommend...should'	A	High
			B	Moderate
Level 2	Weak	'We suggest...might'	C	Low
			D	Very low

^aIn addition the Work Group could also make ungraded statements (see Chapter 2 section on ungraded statements).

INTRODUCTION

The bone-disease component of CKD–MBD may result in fractures (including asymptomatic fractures seen on vertebral radiographs), bone pain, deformities in growing children, reduced growth velocity, and abnormal height. Complications of hip fractures include bleeding, infection, loss of independence, and increased mortality. Vertebral fractures lead to height loss, reduced pulmonary function, gastrointestinal reflux, and chronic disability. In children, growth retardation and skeletal deformities reduce quality of life. In clinical studies of bone disease, surrogate outcomes are bone density and findings on bone biopsies. Potential surrogate outcomes are serum biochemical markers of bone resorption and bone formation.

It is important to recognize that most patients with postmenopausal or age-related osteoporosis also have early stages of CKD (stages 1 through, perhaps, to early stage 3). Patients with more advanced stages of CKD (stages 3–5D), in whom the biochemical abnormalities of mineral metabolism that define CKD–MBD are present, have renal osteodystrophy. Both idiopathic osteoporosis and renal osteodystrophy can lead to increased bone fragility and fractures, but these diseases have different pathophysiological backgrounds. Bone fragility is due to varying combinations of low bone mineral content and abnormal bone quality. CKD–MBD can lead to an abnormal bone quality even in the setting of a normal or high bone-mineral content, and the gold standard diagnosis for the bone component of CKD–MBD is bone biopsy-based histologic analysis. Osteoporosis is traditionally diagnosed as low BMD. Given these pathophysiological and diagnostic differences, the definition of 'osteoporosis' in adults is most appropriate only for those with CKD stages 1–3; in later CKD stages, those with low BMD should be designated as having 'CKD–MBD with low BMD.'

RECOMMENDATIONS

3.2.1 In patients with CKD stages 3–5D, it is reasonable to perform a bone biopsy in various settings including, but not limited to: unexplained fractures, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and

prior to therapy with bisphosphonates in patients with CKD–MBD (not graded).

3.2.2 In patients with CKD stages 3–5D, with evidence of CKD–MBD, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B).

3.2.3 In patients with CKD stages 3–5D, we suggest that measurements of serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover (2B).

3.2.4 In patients with CKD stages 3–5D, we suggest not to routinely measure bone-derived turnover markers of collagen synthesis (such as procollagen type I C-terminal propeptide) and breakdown (such as type I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline) (2C).

3.2.5 We recommend that infants with CKD stages 2–5D have their length measured at least quarterly, while children with CKD stages 2–5D should be assessed for linear growth at least annually (1B).

Summary of rationale for recommendations

- Patients with CKD stages 3–5, 5D, and 1–5T have an increased risk of fracture compared with the general population. These fractures are associated with increased morbidity and mortality.
- Fracture risk relates to bone mineral density and bone quality, together with risk for falling and trauma.
- Bone biopsies provide measurements of bone turnover, mineralization, and volume. These help to assess bone quality and the underlying physiology. The histology is variable and influenced by many factors, including stage of CKD, serum biochemistries, age, and treatments. The different types of renal osteodystrophy have only modest relationships with clinical outcomes.
- In patients with CKD stages 4–5D, BMD of the hip and radius is generally lower than that in the general

population; lumbar spine BMD is similar to that in the general population.

- In the general population, a low BMD predicts fracture and mortality. The ability of BMD to predict fractures or other clinical outcomes in patients with CKD stages 4–5D is weak and inconsistent. BMD in patients with CKD stages 3–5D does not distinguish among types of renal osteodystrophy, as seen with bone histology.
- There are no longitudinal studies of changes in BMD in patients with CKD stages 4–5.
- PTH is one important factor that affects bone physiology. ALP may reflect osteoblast activity. Serum measurements of PTH and ALP are related to clinical outcomes, including relative risk of mortality. They also correlate with some of the histomorphometric measurements.
- Serum biochemical markers of bone turnover show correlations with findings on bone biopsies, but their diagnostic utility is limited and these serum tests have not been directly related to clinical outcomes, except ALPs and extreme values of PTH.
- An alteration in growth in infants and children is a sensitive indicator of the presence of CKD-MBD.

BACKGROUND: FRACTURES IN CKD PATIENTS

Prevalence

Abnormal bone quality and quantity can lead to increased bone fragility, resulting in fracture. In 1966, Pendras and Erickson⁸¹ reported their experience with the first 22 patients to receive long-term HD. Bone and mineral disorders emerged as one of the most troublesome complications; fractures occurred in 47% of the patients. Since then, several studies of fracture prevalence and incidence have been reported, with a prevalence from 10 to 40% in general dialysis populations and in approximately half of patients older than 50 years (*Supplementary Table 4*). The incidence rate of hip fractures in all patients who started dialysis in the United States from 1989 to 1996 was 4.4 times higher than that in the residents of Olmstead County.⁸² Fractures occur more commonly in elderly patients, in women, in diabetic patients, in those using glucocorticoids, and in those with a longer exposure to dialysis. Fractures are also common in elderly patients with CKD stages 3–4 (*Supplementary Table 5*). Hip fractures were seen two to three times more often than in persons without CKD.

Increased risk of another fracture

In the general population, previous fractures as an adult are strongly associated with the risk of a subsequent fracture. This is independent of age, bone density, or other identified risk factors.^{83–85} Among US women older than 65 years, those who had a vertebral fracture as seen on a spine radiograph were 5.4 times more likely to experience a new vertebral fracture in the next 3.7 years compared with women without a prevalent fracture. Even when adjusted for age and bone density, the risk was 4.1 times higher.⁸⁶ Similar findings are reported in several cohort studies and in the placebo

groups of clinical trials.⁸⁵ The World Health Organization fracture assessment tool includes earlier fracture after 50 years of age as one of the clinical risk factors, with a risk ratio for hip fracture of 1.85 without BMD, and 1.62 including BMD in the model.⁸⁷ The risk of a new vertebral fracture increases with the higher number and severity of fractures seen on spine radiographs, but even a mild asymptomatic fracture of one vertebra is associated with a significantly increased risk.⁸³ However, it is important for clinicians to appreciate that these vertebral fractures do not cause increased back pain in about 60% of cases, and that a severe loss of vertebral height can be asymptomatic.⁸⁸

In patients with CKD stage 5D, one study⁸⁹ found that a vertebral fracture identified on a radiograph increased the risk of a new fracture by over sevenfold.

Mortality

Mortality in patients with CKD stage 5 who have had a hip fracture is about twice as high as that in patients of similar age and gender who have not had a fracture (*Supplementary Table 7*). Coco *et al.* followed up 1272 HD patients over 10 years and observed that the mortality for CKD stage 5 patients with a hip fracture was 2.7 times higher than that in fracture-free HD patients and 2.4 times higher than that in patients without CKD who had a fractured hip.⁹⁰ Three studies used data from the US Renal Data System. Mittalhenkle *et al.*⁹¹ recorded hip fracture cases over 5.5 years, and the mortality incidence was 2.15 times higher in cases than in controls matched for age, duration of dialysis, and cardiovascular risk scores. Adjusting for multiple risk factors resulted in an RR of 1.99 for mortality associated with hip fracture. Danese *et al.*⁸⁹ evaluated 9007 patients and found that a history of hip, vertebral, or pelvic fracture was associated with an age- and sex-adjusted mortality rate that was 2.7 times higher than that for the other dialysis patients. Kaneko *et al.*⁹² found that the adjusted hazard ratio for mortality was 1.95 in patients with long bone fractures, using data from 7159 individuals in the Dialysis Morbidity and Mortality Study.

This topic represents a comprehensive review of the literature of selected topics by the Work Group with assistance from the evidence review team to formulate the rationale for clinical recommendations. Thus, this should not be considered to be a systematic review.

RATIONALE

3.2.1 In patients with CKD stages 3–5D, it is reasonable to perform a bone biopsy in various settings, including, but not limited to: unexplained fractures, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and prior to therapy with bisphosphonates in patients with CKD-MBD (not graded).

Abnormal bone histology, diagnosed by bone biopsy with histomorphometry, has been the primary tool used to diagnose

and classify renal osteodystrophy. Although bone biopsy is invasive and thus cannot be performed easily in all patients, it is the gold standard for the diagnosis of renal osteodystrophy. As detailed below, renal osteodystrophy is a complex disorder and biochemical assays do not adequately predict the underlying bone histology. Thus, bone biopsy should be considered in patients in whom the etiology of clinical symptoms and biochemical abnormalities is not certain. Aluminum bone disease, although less common in the current era, also requires a bone biopsy for diagnosis in many individuals, as detailed in the KDOQI Bone and Mineral guidelines.⁵ A bone biopsy should be considered in patients before treatment with bisphosphonates, because bone biopsy is the most accurate test for the diagnosis of adynamic bone disease, and the presence of adynamic bone disease is a contraindication to bisphosphonates. Thus, the Work Group encourages the continued training of nephrologists in the performance and interpretation of bone biopsies.

Classification of renal osteodystrophy by bone biopsy

Bone biopsies are performed to understand the pathophysiology and course of bone disease, to relate histological findings to clinical symptoms of pain and fracture, and to determine whether treatments are effective. The traditional types of renal osteodystrophy have been defined on the basis of turnover and mineralization as follows: mild, slight increase in turnover and normal mineralization; osteitis fibrosa, increased turnover and normal mineralization; osteomalacia, decreased turnover and abnormal mineralization; adynamic, decreased turnover and acellularity; mixed, increased turnover with abnormal mineralization.

A recent Kidney Disease: Improving Global Outcomes report² has suggested that bone biopsies in patients with CKD should be characterized by determining bone turnover, mineralization, and volume (TMV). Thus, in this guideline document, we have endeavored to examine data from published literature and report it using this TMV system.

Turnover. Patients with CKD display a spectrum of bone-formation rates from abnormally low to very high. Other measurements that help to define a low or high turnover (such as eroded surfaces, number of osteoclasts, fibrosis, or woven bone) tend to be associated with the bone-formation rate as measured by tetracycline labeling. This is the most definite dynamic measurement, hence it was chosen to represent bone turnover. It should be noted that an improvement of a bone biopsy cannot be determined on the basis of a simple change in the bone-formation rate, because the restoration of normal bone may require either an increase or a decrease in bone turnover, depending on the starting point.

Mineralization. The second parameter is mineralization, which reflects the amount of unmineralized osteoid. Mineralization is measured by the osteoid maturation time or by mineralization lag time, both of which depend heavily on the osteoid width as well as on the distance between tetracycline labels. The classic disease with an abnormality of minerali-

zation is osteomalacia, in which the bone-formation rate is low and the osteoid volume is high. Some patients have a modest increase in osteoid, which is a result of high bone-formation rates. They do not have osteomalacia because the mineralization lag time remains normal. The overall mineralization, however, is not normal because unmineralized osteoid is increased. Patients with low bone-formation rates and a normal osteoid have adynamic disease (they do not even form the osteoid matrix, hence they do not manifest a problem with mineralization).

Volume. The final parameter is bone volume, which has not traditionally been included in previous schemes for describing renal osteodystrophy. Bone volume contributes to bone fragility and is separate from the other parameters. The bone volume is the end result of changes in bone-formation and resorption rates: if the overall bone formation rate is higher than the overall bone resorption rate, the bone is in positive balance and the bone volume will increase. If mineralization remains constant, an increase in bone volume would also result in an increase in BMD and should be detectable by dual-energy X-ray absorptiometry (DXA). Although both cortical and cancellous bone volumes decrease in typical idiopathic osteoporosis, these compartments are frequently different in patients with CKD. For example, in dialysis patients with high PTH levels, the cortical bone volume is decreased but the cancellous volume is increased.⁹³

Prevalence of abnormalities on bone biopsies

A systematic literature review of the prevalence of types of bone disease in CKD is shown in Figure 7. The review analyzed studies carried out between 1983 and 2006. Differing prevalences of bone disease types observed between studies are due to differing classification methods, in addition to differences related to geographical areas, genetic background, and treatment modalities. One of the most problematic differences in classification relates to the bone-formation rate. This requires tetracycline labeling, and thus normal ranges cannot be determined on autopsy or surgical series. The reported normal bone-formation rates show inconsistencies and variations.²⁰

The prevalence of bone histology types in children with CKD-MBD is similar to that observed in adults. Figure 8 shows the results from 325 children who had CKD stages 5–5D.^{18,34,94–96}

Natural history of bone biopsy findings

The distribution of histological types in patients with CKD stage 5 was compared in studies before 1995 and after 1995 (Figure 9). The studies also revealed a decreased aluminum intoxication, from 40% of biopsies carried out before 1995 to 20% in patients biopsied after 1995.

The natural history of bone disease evaluated through bone histomorphometry is variable. The placebo groups from RCTs and from one longitudinal study are shown in **Table 15**. The overall trend is toward a worsening turnover (either getting too high or too low) and stable mineralization.

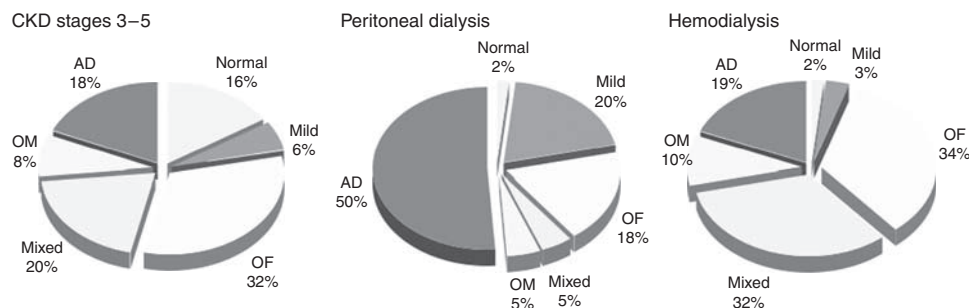


Figure 7 | Prevalence of types of bone disease as determined by bone biopsy in patients with CKD-MBD. Bone formation (turnover) is high in those with osteitis fibrosa and mild disease, and low in those with osteomalacia and adynamic bone disease. Mineralization is abnormal in those with osteomalacia and mixed disease. AD, adynamic bone; OF, osteitis fibrosa; OM, osteomalacia.

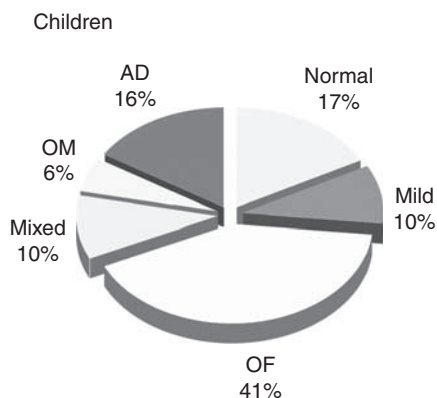


Figure 8 | Prevalence of histological types of renal osteodystrophy in children with CKD stages 5-5D. AD, adynamic bone; OF, osteitis fibrosa; OM, osteomalacia.

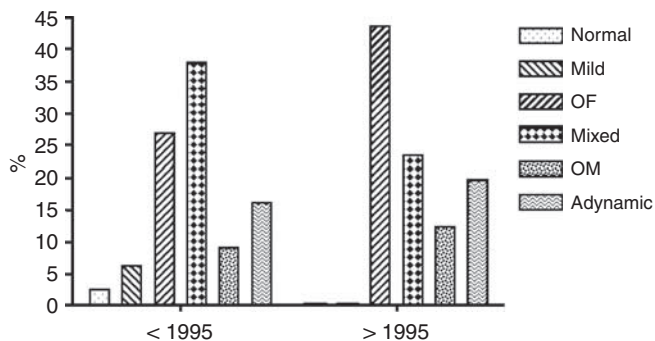


Figure 9 | Types of renal osteodystrophy before and after 1995. OF, osteitis fibrosa; OM, osteomalacia.

The wide variability in the natural history of bone histology reflects the complex pathophysiology of CKD-MBD (Supplementary Table 6). Another way to evaluate the natural history of bone disease in CKD is to compare bone volume by bone biopsy in predialysis patients with that in dialysis patients. Studies dating from 1969 to 2007 show that bone volume/trabecular volume (BV/TV) is generally lower in dialysis patients compared with that in non-dialysis CKD patients across all renal osteodystrophy categories.¹⁰⁵⁻¹¹²

Relationship between bone biopsy findings and clinical outcomes

Symptoms. A further analysis was carried out on 20 of the above studies conducted in HD patients to examine the relationship of bone biopsy histology findings to clinical symptoms and changing trends over time (Figure 10). Most of these patients had been referred for some clinical reason (6505 patients), whereas the remaining patients were apparently asymptomatic (863 patients). There did not seem to be differences in the prevalence of histological types between referred and asymptomatic patients.

Fractures. Most of the studies of bone histomorphometry have not been designed to fully evaluate the relationship between fractures and types of renal osteodystrophy. One study of 31 dialysis patients found that those with low-turnover osteodystrophy had fracture rates of 0.2 per year compared with 0.1 per year in those with osteitis fibrosa; this was because of a high number of rib fractures in the low-turnover patients.¹¹³ A review of 2340 biopsies carried out in Brazilian patients for clinical indications found that the frequency of fractures was significantly higher in those with osteomalacia compared with that in other forms. There were no differences in fracture history between those with adynamic bone disease, high bone turnover, or mixed bone disease.¹¹⁴ A study that followed up 62 patients for 5 years after bone biopsy found a higher rate of fractures in those with adynamic bone disease.¹¹⁵

Theoretically, we would expect that persons with a lower bone volume would be more likely to suffer fractures. However, we could locate no reports of prospective studies of patients with a low bone volume to determine the subsequent fracture rate.

Cardiovascular calcification. Several studies have examined this issue. London *et al.*¹¹⁶ found that aortic calcification was increased in HD patients with adynamic bone disease. They subsequently, with an expanded cohort, reported a significant interaction between the dosage of calcium-containing phosphate binders and bone activity, such that calcium load had a significantly greater influence on aortic calcifications and stiffening in the presence of adynamic bone disease.¹¹⁷ In contrast, Barreto *et al.*,¹¹⁸ in their series of 98 HD patients, did not observe an association between type of bone disease

Table 15 | Changes in bone histomorphometric measurements from patients in placebo groups of clinical trials or longitudinal studies

Author, year	Other Rx	CKD stages	N	Turnover				Mineralization			Volume change % of TV
				Worse		Better		Worse	Better	Change	
				Higher	Lower	Higher	Lower				
% of patients				% of patients							
Hamdy (1995) ^{97a}	Ca, binders	3–4	62	6.5	6.5	3.2	0	a	a	a	0.95
Spasovski (2006) ⁹⁸	Ca, vit D	5D, new	10	0	30	0	0	NR	NR	−4.3% [OV]	NR
Joffe (1994) ⁹⁹	None	5D, PD	10	10	0	10	10	10	0	−157 ^b [MLT]	−4.0
Sanchez (2004) ¹⁰⁰	Ca, Al, vit D	5D, PD	10	0	10	33 ^c	0	0	0	0.51 μm [Oth]	NR
Baker (1986) ¹⁰¹	Aluminum	5D	10	50	0	0	0	40	0	NR	NR
Freemont (2005) ¹³	Calcium	5D	30	10	20	13.5	6.5	0	3	−35 ^b [MLT]	NR
Nordal (1988) ¹⁰²	Aluminum	5	12		NR	NR	NR	0	0	1 ^b [MLT]	0
Malluche (2008) ¹⁰³	Standard	5D	32	29	16	3	0	0	0	−40 ^b [MLT]	−1.2
Ferreira (2008) ¹⁰⁴	Calcium	5D	35	2.8	17	17	8.6	3	0	14 ^b [MLT]	2.3

BFR, bone-formation rate; CKD, chronic kidney disease; MLT, mineralization lag time; N, number of subjects; NR, not reported; Oth, osteoid thickness; OV, osteoid volume; Rx, prescription; TV, trabecular volume.

^aInconsistencies in mineralization values; bone volume average of two groups.

^bMLT, mineralization lag time in days.

^cChange from adynamic to 'high turnover' but measurements were not above normal controls.

^dAs group, BFR increase from average of normals to above normal range.

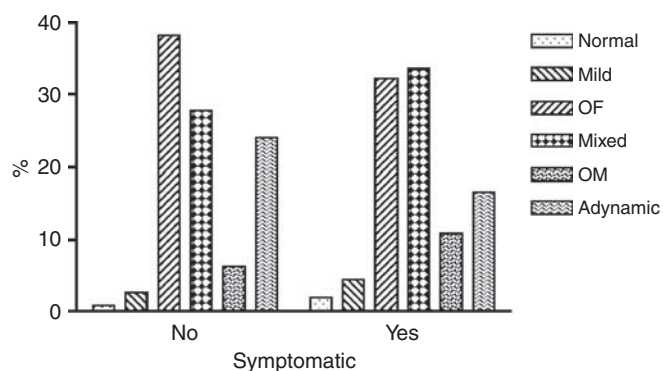


Figure 10 | Prevalence of bone histology types by symptoms in patients with CKD stage 5D receiving HD treatment.

CKD, chronic kidney disease; HD, hemodialysis; mixed, mixed renal osteodystrophy; OF, osteitis fibrosa; OM, osteomalacia.

and coronary artery calcification (CAC) on cross sectional analysis. A more recent prospective study in HD patients found that lower trabecular bone turnover was associated with CAC development, whereas an improvement in bone turnover was associated with lower CAC progression in patients with both high- and low-turnover bone disorders at baseline.¹¹⁹

3.2.2 In patients with CKD stages 3–5D with evidence of CKD–MBD, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B).

Bone density does not predict fractures very well in patients with CKD stages 4–5. In addition, no treatments have been shown to reduce fracture risk in those patients with CKD stages 3–5 who have low BMD and biochemical abnormalities of CKD–MBD (discussed in Chapter 4.3). Spine BMD

measurements can be misleading if there are anatomic abnormalities in the bone, if there is extensive osteophyte formation, or if there is aortic calcification; hip measurements also can have positioning errors. Although forearm measurements provide the least ability to predict fractures in older persons without CKD, the meta-analysis by Jamal *et al.*¹²⁰ found that the forearm was the most sensitive site in patients with CKD stage 5D. The Work Group acknowledges that having a low DXA or a decreasing DXA value is indicative of abnormal bones. However, as detailed below, the etiology of the abnormal bone in CKD–MBD is complex, and patients with CKD–MBD and osteoporosis should not be assumed to benefit from therapies such as bisphosphonates provided in the general population. Thus, the Work Group could not recommend the routine use of DXA in these patients.

BMD measurements

Noninvasive techniques for measuring BMD include DXA and quantitative computed tomography (CT). Other methods have been used in some studies, but they do not have the same extensive reference database or utility in clinical trials as does DXA.

The skeleton is composed of cortical and trabecular (cancellous) bone. The trabecular bone is very porous: about 20% of the tissue is bone and the rest is marrow or fat. DXA cannot differentiate between cortical and trabecular bone. Certain sites, however, contain higher percentages of trabecular bone (by weight). The forearm is almost all cortical bone, the vertebral body is 42% trabecular bone,¹²¹ the proximal femur is about 25% trabecular, and the total body about 80% cortical. These distinctions are important because bone remodeling in patients with CKD–MBD is different in trabecular bone compared with cortical bone. Quantitative CT can separately measure cortical and trabecular bone because it is a three-dimensional measurement.

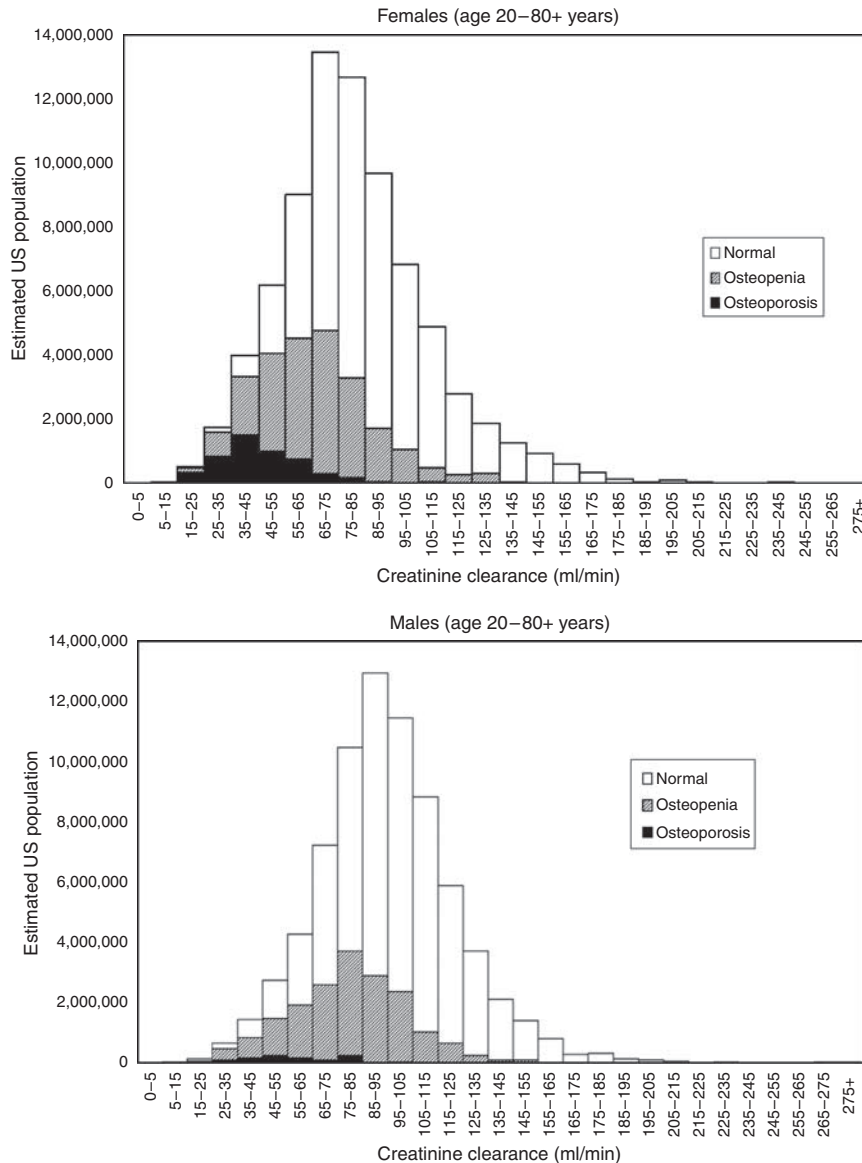


Figure 11 | Distribution of osteoporosis, osteopenia, and normal bone density by creatinine clearance in general US population. Reprinted with permission from Klawansky *et al.*¹²²

DXA measurements of the spine may also be inaccurate because of height. In children or short adults, DXA measurements seem lower than those in larger adults because the volume of bone increases at a faster rate than does the projected area of the bone. Thus, the interpretation of DXA results in children with growth delays must take into account the size of the bone.

BMD in patients with CKD stages 3-4

The Third National Health and Nutrition Examination Survey, 1988-1994, measured BMD and serum creatinine in 13,831 adults older than 20 years. On the basis of the Cockcroft-Gault equation, 23% of adult women with CKD stages 3-4 had osteoporosis (BMD at total hip <0.64 g/cm²).¹²² As seen in Figure 11, the percentage of people with low BMD was much greater in those with CKD than in those with normal kidney function.

Not only do patients with CKD stages 3-4 have a high prevalence of low bone density but elderly patients with osteoporosis usually have CKD stage 3 or 4 (Figure 12). In the US population, 61% of women with osteoporosis had CKD stage 3 and 23% had CKD stage 4. Most of this overlap is seen because both CKD and bone loss increase considerably with aging. In osteoporotic women younger than 60 years of age, the prevalence of CKD stage 4 was very low.¹²²

A cross-sectional and longitudinal study of 1713 older men and women found a significant linear association between estimated GFR and hip bone density. The bone loss over 4 years was associated with estimated GFR as measured by the Cockcroft-Gault equation, but not by the Modification of Diet in Renal Disease equation.¹²⁴

Clinical trials of postmenopausal osteoporosis therapy generally exclude patients with known kidney disease, hence

the proportion of patients with CKD in the trials is lower than that in the general population. Measurement of estimated GFR was lower than 45 ml/min per 1.73 m² in 3.8% of the individuals in the teriparatide trial,¹²⁵ in 52% of the individuals in the pooled risedronate trials,¹²⁶ and in 9% of the individuals in the alendronate Fracture Intervention Trial.¹²⁷

BMD in patients with CKD stage 5D

Figure 13 shows the average values of BMD in studies of patients with CKD stage 5D. These values are expressed as

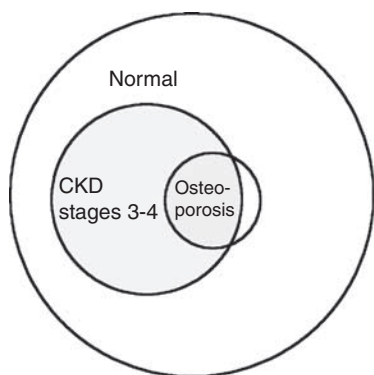


Figure 12 | Overlap between osteoporosis and CKD stages 3-4.

This graph shows the overlap between osteoporosis and CKD stages 3-4 in women from the United States, using data from the NHANES III survey. The kidney function was estimated using the Cockcroft-Gault equation, which results in a greater prevalence of CKD stage 3-4 than when other methods are used.¹²³ CKD, chronic kidney disease; NHANES III survey, The Third National Health and Nutrition Examination Survey.

Z-scores, which compare BMD in patients with BMD from the reference values of age- and gender-matched persons in the community. The prevalence of low BMD is influenced by the age of the cohort, the number of men, the proportion of non-Caucasians, the average duration of dialysis, and the skeletal sites used to define osteoporosis.

BMD and fractures in the general population

In 1994, the World Health Organization proposed guidelines for the diagnosis of osteoporosis on the basis of measurements of BMD.¹⁸³ Osteoporosis was defined as BMD lower than 2.5 s.d. from that of a young white female. In 2005, they reported a meta-analysis of data from 39,000 persons and found that BMD strongly predicted fractures. For example, at the age of 50 years, the RR of a hip fracture was 3.68 for each s.d. of hip BMD.¹⁸⁴ Although BMD is an important factor that predicts fracture, it does have limitations and it is not the only significant factor. In patients with osteoporosis, the degree of trauma and the quality of the bone also determine whether bones will fracture. The World Health Organization recently developed a method of assessing fracture risk on the basis of BMD and clinical risk factors: age, gender, race, weight, previous adult fracture, parental history of hip fracture, history of cigarette smoking, alcohol use, rheumatoid arthritis, and glucocorticosteroid use.¹⁸⁵ The equations used to calculate the risk score are derived from international studies of 46,340 persons and were validated in 230,486 persons, with a mean age of 63 years. The risk of a hip fracture was 4.2 times higher for every s.d. increase in the risk score.¹⁸⁶ These calculations of

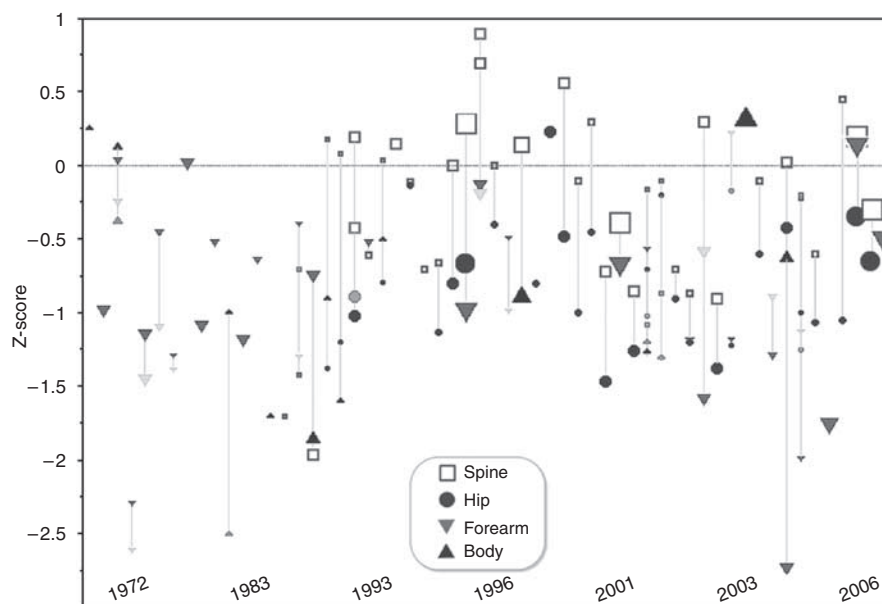


Figure 13 | Bone mineral density in patients with CKD stage 5D. The graph is a summary of studies arranged in chronological order; each point is the mean value for a study. When more than one skeletal site or gender was measured in a study, the points are connected by a vertical line. If data from men and women were reported separately, the points for women are in a lighter shade. The size of points is larger in studies with greater numbers of individuals. Data from studies that reported g/cm² were converted to Z-scores (hip and forearm) using the average age of the group of individuals and published normal reference ranges. Overall, the average cortical bone density for patients with CKD stage 5D was about 0.5–1 s.d. below that expected for age and gender, but at the spine, the bone density measurements were closer to the average in persons without known CKD.^{115,128–182} CKD, chronic kidney disease.

absolute fracture risk will apply to patients with CKD stages 1–3 but have not been studied in patients with CKD stages 4 and 5.

A definition of osteoporosis based on BMD does not distinguish among different etiologies. The ability of a BMD measurement to diagnose osteoporosis is similar to that of a hematocrit measurement to diagnose anemia. Just as there are different causes of anemia (such as iron deficiency or hemolytic anemia), there are different causes of low BMD (such as corticosteroid-induced osteoporosis, osteomalacia, myeloma, or renal osteodystrophy).

A relationship between BMD by DXA and fractures has also been recently shown in children without CKD. In over 7000 10-year-old children, a low BMD adjusted for size parameters was associated with an 89% increased risk of fractures in the subsequent 2 years.¹⁸⁷ In young adults and middle-aged men and women, there are no large studies relating fractures to DXA results.

BMD and fractures in CKD patients

In patients with CKD stage 5, the relationship between BMD and fractures is not as strong as that in the general population. We identified 13 cross-sectional studies that measured BMD and prevalent fractures; there were no prospective studies. The results were variable: five studies found no relationship between BMD and fracture rate,^{113,115,181,188,189} whereas eight studies found a relationship in at least one skeletal site.^{153,157,169,175,180,190–192} A meta-analysis by Jamal *et al.*¹²⁰ included six of these studies and found no increased risk of hip fracture related to BMD at the hip. The spine and distal radius BMD values, however, were significantly lower in patients who had a fracture than in those who did not. In a study of 187 men, Atsumi *et al.*¹⁵⁷ found that each s.d. lowering of spine bone density increased the odds ratio of a spine fracture by 2.0. Elder and Mackun¹⁸⁰ studied 242 patients and found a lower BMD at the hip in cases with fragility fractures, and a trend toward a lower spine BMD. Ersoy *et al.*¹⁸¹ studied 292 patients receiving peritoneal dialysis and found no relationship between BMD and fractures.

The reasons for the poor performance of DXA in patients with CKD are not defined. Partially, this is because the measurements may overestimate BMD due to arthritic conditions, scoliosis, and aortic calcifications, but those would apply mainly to the lumbar spine and not to the total hip. Another reason is that CKD patients have poor bone quality that cannot be measured by absorptiometry. Abnormal microarchitecture, mineralization density, crystal deposition in the bone matrix, or abnormalities in the matrix itself could all contribute to the loss of bone strength. Patients with CKD, especially those with a high serum PTH, have increased cancellous bone volume but decreased cortical thickness;⁹³ this can alter the relationship between the overall bone strength and BMD findings. Furthermore, patients with CKD may experience more trauma to the skeleton if they have more frequent falls.^{193–196}

BMD and relationship with bone biopsy findings in CKD

The relationship between BMD and bone biopsy is not well defined. In patients with postmenopausal osteoporosis, there is a significant but weak correlation between bone volume on biopsy and BMD measured by DXA. In patients with CKD, Lindergard⁹³ measured BV/TV on 71 biopsies from dialysis patients, and did not see a correlation with BMD at the radius. Similar results were seen by Gerakis *et al.*¹¹⁵ in a study of 62 patients. Torres *et al.*,¹⁹⁷ on the other hand, found a correlation coefficient of 0.82 between BV/TV and quantitative CT of the spine, and Van Eps *et al.*¹⁹⁸ found lower DXA values in patients with low BV on biopsy.

Is BMD different among the different types of renal osteodystrophy? Studies of 20–30 patients found similar BMD in all the types.^{146,167,199–201} Boling *et al.*²⁰¹ examined 27 patients; the types had similar values for BMD measured by DXA, but the spine quantitative CT was 5% above the normal mean in patients with a high bone turnover and 30% below the mean in those with a low turnover. In a study of 62 patients, Gerakis *et al.*¹¹⁵ found that BMD by DXA was lower in osteitis fibrosa than in adynamic bone, but there were wide ranges in both types. The BMD by DXA was lower in those with severe osteitis fibrosa in the study by Fletcher *et al.*²⁰² in 73 patients, particularly at the proximal forearm, in which the BMD Z-score was -1.94 in severe osteitis fibrosa compared with -0.17 in mild disease. The patients with adynamic disease also had a low forearm BMD with a Z-score of -1.85 . At the spine, those with mixed lesions were 2.85 s.d. higher than normal, compared with -0.77 s.d. lower in those with severe osteitis fibrosa.

BMD and mortality

In the general population, low BMD is associated with mortality. In CKD, low BMD was also associated with mortality, as shown in a single study by Taal *et al.*²⁰³ (*Supplementary Table 7*) in 88 HD patients. The risk was 4.3 times higher in those with hip BMD T-scores lower than -2.5 (the World Health Organization criteria for diagnosis of osteoporosis).

3.2.3 In patients with CKD stages 3–5D, we suggest that measurements of serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover (2B).

HPT is one of the most important causes of bone disease in patients with CKD. The circulating PTH is related to bone biopsy findings, but a prediction of the type of renal osteodystrophy may be inaccurate. Bone biopsy remains the gold standard for the assessment of bone turnover, and as detailed below, measurements of circulating PTH or b-ALP have limited sensitivity and specificity, especially in detecting adynamic bone. In addition, as detailed in Chapter 3.1, the availability of various assay kits for PTH is another problem. However, bone biopsy is not practical in the majority of clinical patients, and when these serum markers are above or

below thresholds, they can be used to estimate bone turnover. Large discrepancies between serum PTH and ALP measurements should prompt further investigation.

Serum PTH and ALPs and bone outcomes

Fractures. There have been several large prospective studies in CKD stage 5D patients relating serum PTH to fractures (Supplementary Table 8), with inconsistent results, as shown in Table 16.

Several other cross-sectional studies^{157,175,180,189,191,192,208} have also evaluated this relationship and, in general, were negative. However, a case-controlled cohort study did find a 31% (95% confidence interval 0.57–0.83, $P < 0.001$) reduction in global fracture risk after parathyroidectomy.²⁰⁹

An association between high serum t-ALP levels and the RR of fractures has been reported in dialysis patients by Blayney *et al.*³²

PTH and b-ALP relationship with bone histology. The classic findings of HPT in patients with CKD are high turnover with peritrabecular fibrosis, active osteoclasts and increased numbers of multi-nucleated osteoclasts, woven bone, blurry tetracycline labels, increased cancellous bone volume but decreased cortical thickness, and intratrabecular tunneling. The bone response to PTH, however, is not consistent, and there is evidence for skeletal resistance to PTH in patients with CKD-MBD.

The results of studies that reported correlations between PTH and bone-formation rates are shown in Figure 14, which shows the wide variabilities seen in different situations.^{69,99,108,111,146,210–224} The older studies tended to find better correlations between PTH and bone-formation rates, whereas more recent studies show poor correlations. This follows a trend for associating findings of adynamic bone disease with high PTH levels. The reasons for poor correlations between PTH and bone formation are not clear, but could involve differences in the assays for PTH, secular changes in the dialysis population with more diabetic and elderly patients, differences in therapies, and differences in the racial composition of the studies. This figure also shows correlations with several bone turnover markers. Osteocalcin is generally no better than intact PTH (iPTH), whereas b-ALP shows a higher correlation with tetracycline-based bone-

formation rates and has a better correlation to bone-formation rate than does PTH. b-ALP also has some predictive value for the diagnosis of high or low bone turnover (Table 17).

Even though there is usually a significant but weak correlation between serum PTH or other markers and bone formation rates, the ability to correctly classify an individual patient is limited. As with any diagnostic test, there is a trade-off between the sensitivity and the specificity of the test. The predictive value depends on the sensitivity and specificity, and on the overall prevalence of the condition. It also depends on which cutoff was used and how the diseases were defined. Some of the differences among studies could be caused by a different exposure to aluminum, which increases the skeletal resistance to PTH. The studies also used different PTH assays, which may confound interpretation as detailed in Chapter 3.1. Table 17 shows the results that were reported in studies that measured PTH and types of bone disease in patients with CKD stage 5D. The positive predictive value is the percentage of patients with a positive result on a test who actually have the disease (either high or low turnover), and the sensitivity is the percentage of patients with the disease who have a positive test result.

Much of the focus of renal osteodystrophy has been on bone turnover, but bone volume is another important factor in bone physiology. The correlations between BV/TV and PTH are not consistent among studies; four studies found no correlation,^{220,230–232} one reported a correlation coefficient of 0.51,²¹⁹ and another of 0.56.²¹³ b-ALP showed no relationship with bone volume in three studies;^{220,230,231} in another, the correlation was 0.54;²¹⁹ and in one, the correlation between b-ALP and BV/TV was not significant, but the b-ALP was lower in those who had histological signs of osteopenia.²³²

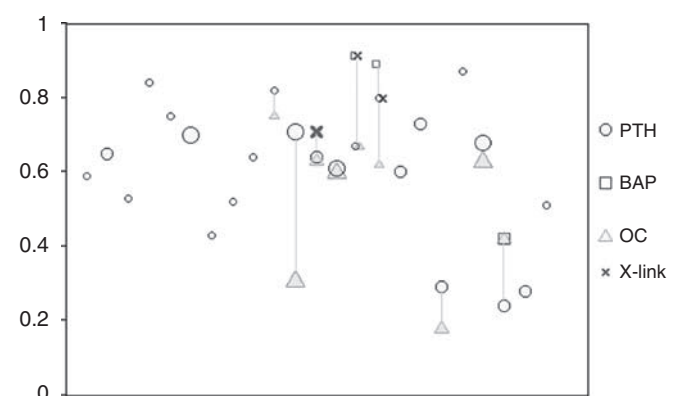


Figure 14 | Correlation coefficients between bone formation rate as seen on bone biopsies and serum markers of PTH, bone-specific ALP (BAP), osteocalcin (OC), and collagen cross-linking molecules (x-link) in patients with CKD stages 5-5D. Each point represents a study, and they are arranged in chronological order from 1981 to 2006 from left to right. Studies that measured more than one marker are joined by a vertical line. The small symbols are studies of 20–50 patients, medium symbols 51–100 patients, and large symbols > 100 patients. CKD, chronic kidney disease; PTH, parathyroid hormone.

Table 16 | Relationship between fractures and PTH in patients with CKD-MBD

Author, year	N	Relationship between fractures and PTH
Coco (2000) ⁹⁰	1272	High risk with low PTH
Stehman-Breen (2003) ²⁰⁴	4952	No relation
Block (2004) ²⁰⁵	40,538	Weak direct association, $P=0.035$
Danese (2006) ⁸⁹	9007	Higher risk with low or high PTH
Jadoul (2006) ²⁰⁶	12,782	RR=1.7 if PTH > 900
Mitterbauer (2007) ²⁰⁷	1774	No relation

CKD-MBD, chronic kidney disease-mineral and bone disorder; PTH, parathyroid hormone; RR, relative risk.

Table 17 | Positive predictive value for iPTH and b-ALP to predict bone turnover in patients with CKD stage 5

Author, year	N	High bone turnover			Low bone turnover		
		Cutoff	PPV	Sensitivity	Cutoff	PPV	Sensitivity
McCarthy (1989) ²²⁵	41	> 1200 ^a	79	92	< 490 ^a	76	93
Hutchison (1993) ¹⁴⁶	30	> 200	88	83	< 65	78	88
Torres (1995) ²¹⁵	119	> 450	100	43	< 120	89	48
Wang (1995) ^{216 b}	175	> 200	58	88	< 150	83	91
Qi (1995) ^{226 b}	79	> 250	80	89			
Couttenye (1996) ²²⁷	103				< 150	65	81
					b-ALP	75	78
Urena (1996) ²¹⁹	42	> 200	92	72	< 150	51	70
		b-ALP	90	84	b-ALP	58	70
Gerakis (1996) ²¹⁸	114	> 200	78	87	< 65	45	69
Fletcher (1997) ^{202 b}	73	> 100	89	81			
		b-ALP	97	70			
Carmen Sanchez (2000) ²²¹	57	> 250	92	57	< 150	97	92
Coen (2002) ¹⁰⁸	107				< 150	54	81
Bervoets (2003) ²²²	84				< 237	47	78
					b-ALP	57	83
Lehmann (2008) ²²⁸	132	> 161	89	75			
		b-ALP	91	71			
Barreto (2008) ²²⁹	97	> 300	62	69	< 150	83	50

b-ALP, bone-specific alkaline phosphatase; iPTH, intact parathyroid hormone; N, number of subjects; PPV, positive predictive value.

^aC-terminal assay.

^bCalculated from sensitivity, specificity, and prevalence.

Table 18 | Correlation between PTH or other serum markers and BMD

Author, year	N	Patients	% Male	Study design	PTH	Other markers
Rix (1999) ²³³	113	CKD 3-5	70	xs	Inverse	
Tsuchida (2005) ²³⁴	85	CKD 5	60	xs		OC, PINP, b-ALP: inverse; NTX, DPD, PYD: not related
Obatake (2007) ²³⁵	53	CKD 5	70	long		Higher OC had more bone loss; b-ALP, NTX, PINP not significant
Taal (1999) ¹⁵⁹	88	HD	88	xs	Inverse	
Atsumi (1999) ¹⁵⁷	187	HD	100	xs	Inverse (body, not spine)	
Gerakis (2000) ¹¹⁵	62	HD	66	xs	Inverse	OC: inverse
Kokado (2000) ¹⁶²	293	HD	60	xs	Inverse	
Barnas (2001) ¹⁶³	90	HD	60	xs	Not related	
Pecovnik (2002) ¹⁷⁰	50	HD		xs	Inverse	
Ueda (2002) ²³⁶	195	HD	100	long	Inverse to change in BMD	Radial BMD change inverse to PINP, b-ALP, OC, CTX, NTX, and DPD
Urena (2003) ¹⁷⁵	70	HD	60	xs	Inverse	CTX, b-ALP: inverse
Nakashima (2003) ¹⁷⁴	83	HD	53	xs	Inverse	
Negri (2004) ¹⁸⁹	65	PD		xs	Inverse	
Nakashima (2006) ¹⁸²	201	HD	60	long	Inverse to change in BMD	BMD change positive with OPG; b-ALP, NTX, OC, TRAP: inverse
Jamal (2006) ¹⁹²	52	HD	71	xs	Inverse	
Wittersheim (2006) ²³⁷	79	HD, PD	48	xs	Inverse	OPG, RANK-L not correlated; CTX: inverse
Ersoy (2006) ¹⁸¹	292	PD	56	xs	Not related	
Elder (2006) ¹⁸⁰	242	HD, PD	61	xs	Inverse	
Sit (2007) ²³⁸	70	HD	52	xs	Not related	
Doumouchtsis (2008) ²³⁹	54	HD	50	xs	Not related	OPG, ALP: inverse; OC, TRAP: not related

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; BMD, bone mineral density; CKD, chronic kidney disease; CTX, carboxyterminal cross-linking telopeptide of bone collagen; DPD, deoxypyridinoline; HD, hemodialysis; long, longitudinal; N, number of subjects; NTX, aminoterminal cross-linking telopeptide of bone collagen; OC, osteocalcin; OPG, osteoprotegerin; PD, peritoneal dialysis; PINP, procollagen type I N propeptide; PTH, parathyroid hormone; PYD, pyridinoline; RANK-L, Receptor Activator for Nuclear Factor κB Ligand; TRAP, tartrate-resistant acid phosphatase; xs, cross-sectional.

PTH relationship with BMD. Table 18 shows the results from studies that measured BMD and serum markers in at least 50 patients with CKD-MBD. None of the studies found a positive effect of PTH on BMD; either the relationship was not significant or there was a significant inverse correlation.

PTH and combinations of biochemistries in the prediction of bone histology. None of the studies published to date in

CKD patients have been adequately powered to assess if combinations of PTH and other bone-derived circulating biomarkers would be more predictive than individual markers. Kidney Disease: Improving Global Outcomes is coordinating an ongoing international collaborative effort to determine the predictive value of whole (1-84) PTH assays compared with currently used iPTH assays, with or without

other biomarkers, to predict underlying bone histology using the TMV classification system.

3.2.4 In patients with CKD stages 3–5D, we suggest not to routinely measure bone-derived turnover markers of collagen synthesis (such as procollagen type I C-terminal propeptide) and breakdown (such as type I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline) (2C).

Collagen-based markers of bone turnover, measured in the serum, have not been extensively evaluated in patients with CKD stages 4–5. The available studies show that these markers do not predict clinical outcomes or bone histology any better than does circulating PTH or b-ALP. Therefore, at this time, they are not recommended for diagnostic purposes in patients with later stages of CKD–MBD. In earlier stages of CKD, some of these markers seem promising for monitoring the treatment of osteoporosis, but they currently are not sufficiently validated to recommend their use.

Bone markers

Collagen based. Active osteoblasts secrete procollagen type I, and the propeptides at both C- and N-terminal ends are immediately cleaved and can be measured in the circulation (PICP and PINP). The collagen molecules are then covalently bonded through pyridinoline cross-linking. The fragments containing these pyridinoline links (at both the C- and N-terminal ends of the peptides) are released during bone resorption: carboxyterminal (CTX) and aminoterminal (NTX) cross-linking telopeptide of bone collagen, respectively. These collagen-based markers have been studied in normal populations, wherein there are significant but moderate correlations with bone-formation/resorption rates.²⁴⁰ The markers are increased after a fracture.²⁴¹

Other bone markers. Osteoblasts secrete other proteins that have been used to assess their function, including b-ALP (discussed in the previous section), osteocalcin, osteoprotegerin, and receptor activator for nuclear factor κ B ligand.²⁴² Osteoclasts secrete tartrate-resistant acid phosphatase. Osteocytes secrete FGF-23 in response to phosphate and calcitriol. High levels of FGF-23 are seen in patients with CKD, but this is a new measurement, and clinical significance remains to be determined. FGF-23 was recently shown to be associated with an increased RR of mortality in dialysis patients,²⁴³ but this may be related to phosphate or vitamin D metabolism and not to bone disease *per se*. Thus, although synthesized in bone, it seems premature to use FGF-23 as a bone biomarker.

Some of these markers are excreted by the kidneys, so in CKD, the serum concentrations may merely represent accumulation instead of bone turnover.

Markers of bone turnover and clinical outcomes. In cohorts of elderly women, most of whom have early stages of CKD, serum biochemical markers of bone turnover have been associated with fractures.^{244–246} The utility of these markers

in individual patients is uncertain, and they are currently not recommended in the routine evaluation of patients with postmenopausal osteoporosis. These markers, however, may be helpful in identifying those patients who respond to osteoporosis medications. In the fracture intervention trial of alendronate, the change in b-ALP and CTX was significantly related to the reduction in fracture incidence, and for hip fractures, the changes in markers predicted fractures better than did the BMD changes.²⁴⁷ Furthermore, in those women who had postmenopausal osteoporosis with low baseline PINP levels, alendronate did not reduce the risk of fractures.²⁴⁸ With raloxifene, the osteocalcin change predicted fracture incidence better than did the BMD change.²⁴⁹

In patients with CKD stages 4–5, there are limited data that relate serum markers to fractures. Urena *et al.*¹⁷⁵ found that cross-laps (C-terminal peptide) and b-ALP were not different between fracture and non-fracture cases in a survey of 70 dialysis patients.

A recent study evaluated patients with CKD stages 1–5 without known CVD and found that reduced tartrate-resistant acid phosphatase-5B and elevated b-ALP were both associated with an increase in the RR of cardiovascular mortality.²⁵⁰ These somewhat paradoxical findings suggest that much more work needs to be carried out to fully understand the clinical utility of such biomarkers.

Bone markers and bone histology

In CKD patients, a few studies show significant correlations between collagen cross-linking molecules and the bone formation rate (shown in Figure 14).

Bone volume was not related to these markers in two studies. Coen *et al.*²²⁰ measured a panel of circulating biomarkers (iPTH, osteocalcin, b-ALP, tartrate-resistant acid phosphatase, CTX, and deoxypyridinoline) in 41 patients with CKD stage 5, and none of them correlated with the BV/TV. Barreto *et al.*²³⁰ focused on factors that related to osteoporosis in 98 patients with CKD stage 5, half of whom had a BV/TV less than one s.d. from the normal mean. They found no relationship between the low BV/TV and serum iPTH, b-ALP, or deoxypyridinoline, but the tumor necrosis factor- α and the osteoprotegerin/receptor activator for nuclear factor κ B ligand ratio was higher in those with a low BV/TV. Thus, at this point in time, there is insufficient evidence for the use of these markers. More research is clearly needed.

Bone markers and BMD

Predicting BMD at a single point in time. In the general population, observational studies of elderly people show that circulating bone turnover markers are not related to BMD at one point in time.²⁵¹ In clinical trials of osteoporosis medications, the baseline biochemical markers do not consistently predict the change in BMD. (As noted above, however, the baseline biochemical measurements may predict fractures in some cases, and this is more important than predicting BMD results.) The data in patients with CKD stages 4–5 are limited and inconsistent, as shown in **Table 18**.

Predicting change in BMD. In studies on osteoporosis, the changes in measurements of bone formation and resorption may be related to the changes in BMD with some treatments.²⁴⁷ On an individual level, it is not certain how reliable these markers will be in predicting BMD change. At present, there is no consensus with regard to the clinical utility of markers in individual patients with osteoporosis, but many ongoing studies are examining this issue, especially as anabolic drugs are being developed.

On a theoretical basis, bone markers should be able to predict the change in bone volume, which is determined by bone balance. Unfortunately, none of the current serum or urine markers of bone turnover are sensitive enough to allow the calculation of bone balance, and the interpretation of the measurements depends on the clinical situation. For example, the highest serum levels of turnover markers are found in patients with metastatic cancer, Paget's disease, and in healthy adolescent boys.

When interpreting bone turnover markers, it is important to remember the distinction between bone volume, as measured on bone biopsies, and BMD, as measured with a radiographic technique. Density depends on both the bone volume and the mineralization of the bone. Newly formed bone is not as dense as older bone, and patients with a high turnover have a greater proportion of newly formed bone with a low BMD. When bone turnover is decreased, the bone becomes 'older' and accumulates more minerals, increasing the DXA value without necessarily increasing the bone volume. In patients with CKD, the relationships are even more complicated because the mineralization is frequently abnormally low, so that BMD can be low even when bone volume is normal. Rapid increases in BMD can be observed when osteomalacia is treated, even without any formation of new bone, because the osteoid fills with mineral. The markers of bone formation that depend on the secretion of new collagen would not be able to detect this improved mineralization.

3.2.5 We recommend that infants with CKD stages 2–5D should have their length measured at least quarterly, while children with CKD stages 2–5D should be assessed for linear growth at least annually (1B).

In children with CKD stages 2–5D, abnormalities in statural growth are commonly observed. Such abnormalities may include a height below the 3rd percentile of the growth curve for normal children of the same gender; a negative statural growth curve against the genetic potential based on mid-parental height formulas even when on the normal growth curve; or a negative growth velocity, based on gender-specific curves of normal children. Growth should be assessed at least monthly in infants, quarterly in children below 2 years of age, and at least annually in older children and adolescents, and plotted accurately on the appropriate growth chart for either height, velocity, or ideally, both. This allows for an optimal understanding of the defects in linear growth that may occur with CKD in children. Growth velocity as rates and absolute

changes in height is used as an end point in clinical trials of growth-hormone therapy in children and adolescents with CKD.

Linear height deficit (short stature) is one of the cardinal features of progressive CKD in pediatric patients. In normal children, the 50th percentile for height corresponds to a Z-score of 0. The 3rd percentile is a Z-score of -1.88 . In children with CKD, over one-third of patients have Z-scores lower than -1.88 .²⁵² Baseline kidney function, by height Z-score, shows that there are patients with severe height deficits, even though they have a moderate kidney function (>25 ml/min per 1.73 m²). In patients with a calculated clearance between 50 and 75 ml/min per 1.73 m², 18.2% (379 of 1720) had a height Z-score worse than -1.88 . The mechanisms of linear growth failure include the presence of chronic metabolic acidosis, renal osteodystrophy, nutrient wasting, chronic inflammation, functional hypogonadism in some adolescents, and dysregulation of the growth hormone–insulin-like growth factor 1 endocrine axis. The latter has led to the development and use of a recombinant human growth hormone, which has been licensed by the Food and Drug Administration in the United States since 1988 for the treatment of linear growth failure in children with CKD, one of the measures of bone in CKD–MBD. However, using data from the North American Pediatric Renal Transplant Cooperative Study 2006 data report,²⁵² only 6.5% of all patients at entry into the registry were using recombinant human growth hormone. By 24 months of follow-up, 15.9% of patients being followed up were receiving recombinant human growth hormone. This low usage prompted an examination of the benefit and harm of recombinant human growth hormone in children (see Chapter 4.3).

RESEARCH RECOMMENDATIONS

Additional research is called for:

- A prospective study of BMD to determine fracture risk thresholds in CKD stages 3–5, 5D, and 1–5T.
- A prospective study of circulating biochemical markers (PTH, b-ALP, PINP, PICP, NTX, CTX, tartrate-resistant acid phosphatase, and osteoprotegerin) to determine if they can predict fractures or other clinical outcomes in CKD stages 3–5, 5D, and 1–5T.
- The development of an international standard for the assessment of renal osteodystrophy, particularly for dynamic measurements.

SUPPLEMENTARY MATERIAL

Supplementary Table 4. Prevalence and incidence of fractures in patients with CKD 5D.

Supplementary Table 5. Fractures in patients with CKD stages 3–4.

Supplementary Table 6. Overview table of selected studies of the natural history of bone disorders.

Supplementary Table 7. Overview table of selected studies demonstrating the risk relationship between bone measurements and mortality in CKD stage 5D.

Supplementary Table 8. Overview table of selected studies demonstrating the risk relationship between hormonal parameter, PTH, and fractures in CKD stage 5D.

Supplementary material is linked to the online version of the paper at <http://www.nature.com/ki>

Chapter 3.3: Diagnosis of CKD–MBD: vascular calcification

Grade for strength of recommendation ^a	Strength	Wording	Grade for quality of evidence	Quality of evidence
Level 1	Strong	'We recommend...should'	A	High
Level 2	Weak	'We suggest...might'	B	Moderate
			C	Low
			D	Very low

^aIn addition the Work Group could also make ungraded statements (see Chapter 2 section on ungraded statements).

INTRODUCTION

The diagnosis of CKD–MBD includes the detection of extraosseous calcification, including arterial, valvular, and myocardial calcification. It is generally well recognized that the prevalence of calcification increases with progressively decreasing kidney function and is greater than that in the general population. Cardiovascular calcification is associated with, and predictive of, adverse clinical outcomes, including cardiovascular events and death. However, there are some uncertainties with regard to the sensitivity and specificity of the different imaging tests available for detecting cardiovascular calcification. Further, there is also uncertainty as to whether altering the progression of cardiovascular calcification will impact patient outcomes (cause–effect relationship) in different stages of CKD. Finally, there is no clear evidence-based protocol or algorithm for the diagnostic and therapeutic strategies that need to be followed after yielding a positive calcification test result.

RECOMMENDATIONS

3.3.1 In patients with CKD stages 3–5D, we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence or absence of valvular calcification, as reasonable alternatives to computed tomography-based imaging (2C).

3.3.2 We suggest that patients with CKD stages 3–5D with known vascular/valvular calcification be considered at highest cardiovascular risk (2A). It is reasonable to use this information to guide the management of CKD–MBD (not graded).

Summary of rationale for recommendations

- In the normal population, the magnitude of CAC as imaged by either electron beam CT (EBCT) or multislice CT (MSCT) is a strong predictor of cardiovascular event risk.
- In the CKD population, coronary artery and generalized vascular calcification is exceedingly more prevalent, more

severe, and follows an accelerated course compared with that in the normal population.

- The reference standard in the detection of cardiovascular calcifications in CKD and in the general population is the CT-based CAC score, but other, more easily available techniques—for example, lateral abdominal X-ray, pulse wave velocity (PWV) measurements, and echocardiography (valvular calcification)—may yield comparable information.
- The presence and the severity of cardiovascular calcification strongly predict cardiovascular morbidity and mortality in patients with CKD.
- However, there is limited evidence from RCTs in CKD that the reduction of arterial calcification progression impacts mortality.
- A majority of Work Group members felt that inconsistencies remained among RCT reports aimed at showing that intervention improved patient level outcomes, and hence, indiscriminate screening in every patient with CKD–MBD was not recommended.
- However, there was consensus that known vascular/valvular calcification and its magnitude identify patients at high cardiovascular risk. Therefore, the presence of vascular/valvular calcification should be regarded as a complementary component to be incorporated into the decision making of how to individualize treatment of CKD–MBD.

BACKGROUND

Tissue calcification is a complex and highly regulated process in bone and teeth, and also at extraosseous sites. The most threatening localization of unwanted calcification is at vascular sites, where it may manifest as both medial and intimal calcification of arteries. In the general population, autopsy and imaging studies have identified calcification in >95% of atherosclerotic plaques. Calcification seems to be a part of the natural history of atherosclerotic plaques, with extensive calcification associated with late-stage (American Heart Association Stage Va and VII) atherosclerosis. In the

general population, atherosclerotic plaque calcification is associated with cardiovascular events such as myocardial infarction, symptomatic angina pectoris, and stroke.^{253–255} Medial calcification causes arterial stiffness, resulting in an elevated pulse pressure and increased PWV, thereby contributing to left ventricular hypertrophy, dysfunction, and failure. Furthermore, an advanced calcification of the heart valves may lead to dysfunction contributing to heart failure and an increased risk of endocarditis. Cardiovascular calcifications are usually progressive, and their extent and severity are highest in patients with CKD. Recent reports suggest an increased prevalence of cardiovascular calcification in patients at early stages of CKD. Thus, a considerable percentage of CKD patients are at risk of cardiovascular events from vascular calcification.

As mentioned above, two patterns of vascular calcification have been described: predominantly intimal and predominantly medial calcification. There is, however, an ongoing debate with regard to the differential role of intimal (atherosclerotic) vs medial (arteriosclerotic) calcification in CVD in CKD patients.^{256,257} In the general population, an elevated coronary artery calcium score almost exclusively reflects the atherosclerotic disease burden. In two small autopsy studies, it became apparent that, in dialysis patients, CAC is also predominantly localized in the coronary intima, whereas the medial calcifications observed in a minority of such patients seemed to be adjacent to plaque areas just beneath the internal elastic lamina.^{258,259} Although the coronary vascular bed may differ considerably from other arteries with regard to the calcification process and its manifestations, the same group observed a 'pure' medial calcification in the coronary arteries during the early stages of CKD.²⁵⁷ A 'pure' medial calcification, in the absence of intimal disease, was also observed in epigastric arteries obtained from dialysis patients at the time of renal transplantation.²⁶⁰ An older study identified both intimal and medial calcifications in iliac arteries of such patients.²⁶¹ Thus, there is neither definitive evidence to suggest that isolated medial calcification is distinct from the calcification that occurs in the natural history of atherosclerosis nor is there definite proof against it.

Arterial calcification assessed by all the available imaging studies cannot accurately differentiate calcification that is localized to the intima from calcification in the media adjacent to the internal elastic lamina, or in the medial layer. Experimental and *ex vivo* studies suggest that the vascular smooth muscle cell may be critical in the development of calcification by transforming into an osteoblast-like phenotype.²⁶² In addition, the pericyte in the media and adventitia may have a role in the secretion of vascular calcification-inducing factors. The stimulus for such a transformation may depend on the location of calcification within the artery wall. For example, in intimal lesions, atherosclerosis may be the most important stimulus. However, in patients with CKD and medial calcification, there may be additional, or additive, factors potentially

explaining why medial calcification of the peripheral arteries can be seen without intimal changes and is more common in CKD than in the non-CKD population.²⁶⁰ Elevated phosphorus, elevated calcium, oxidized low-density lipoprotein cholesterol, cytokines, and elevated glucose, among others, stimulate this transformation of vascular smooth muscle cells into osteoblast-like cells *in vitro* using cell-culture techniques. These factors likely interact at the patient level to increase and/or accelerate calcification in CKD. Given the potential complexity of the pathogenesis and the inability of radiological techniques to differentiate the location of calcification, the approach to all patients with calcification should be to minimize atherosclerotic risk factors and control biochemical parameters of CKD-MBD. *In vivo* animal studies have shown less arterial calcification with non-calcium-based binders compared to that with calcium-based binders.^{263,264} Unfortunately, trials in dialysis patients evaluating such strategies to treat either atherosclerosis or CKD-MBD have not conclusively shown that such an intervention positively affects patient-level outcomes.^{265–267} Despite this, given the high cardiovascular burden in CKD, the majority of the Work Group felt that the treatment approaches to limit the calcium intake from phosphate binders in CKD patients with known vascular/valvular calcification were appropriate until definitive studies are conducted, as detailed in Chapter 4.1.

Extraosseous calcification in patients in advanced stages of CKD has been observed since the early days of dialysis,^{268,269} but was originally thought to result predominantly from a supersaturation of serum with calcium and phosphate ions, that is, passive precipitation. However, in recent years, it became evident that vascular calcification is also an active cellular process. As already pointed out above, the presence or upregulation of inducers of cellular osteogenic transformation and hydroxyapatite formation (among which high phosphate probably has a central role)²⁶² causes the differentiation of vascular smooth muscle cells into an osteoblast-like phenotype of vascular smooth muscle cells. Newly discovered calcium-regulatory factors, including fetuin-A, matrix Gla protein, osteoprotegerin, and pyrophosphates—all of which possess properties of systemic or local calcification inhibitors—may have a key role in fine-tuning protection against unwanted calcification, and some of these factors may be dysregulated in uremia.²⁷⁰ A seminal paper by Murshed *et al.*, however, showed that even complex pathological mineralization disorders can be prevented by modulating extracellular phosphate concentration.²⁷¹ Therefore, it is biologically plausible that the calcification process develops from unique stimuli and progresses in an accelerated manner in CKD patients. As epidemiological studies suggest a direct relationship between calcification and impaired clinical outcomes, cardiovascular calcification is thus regarded as a relevant clinical end point by most investigators mirroring cardiovascular event risk. However, it cannot yet be used as a reliable surrogate marker for interventions, as the link between intervention and

patient-level outcomes when calcification is ameliorated has not been shown conclusively.

Finally, a rare but very severe form of medial calcification of small (cutaneous) arteries is calciphylaxis, also called calcific uremic arteriopathy. This complication is strongly associated with CKD-related disturbances of mineral metabolism, including secondary HPT, in approximately one-third of cases. It is characterized by ischemic, painful skin ulcerations followed by superinfections, and is associated with high mortality. Relationships with dysregulated calcification inhibitors (fetuin-A and matrix Gla protein) have been implicated in the pathogenesis of calciphylaxis, but because of the relatively low incidence of the disease, no conclusive data are available to firmly comment on the nature of the disease process or to allow generalizable treatment options to be recommended.

This topic represents a comprehensive review of the literature of selected topics by the Work Group with assistance from the evidence review team to formulate a rationale for clinical recommendations. Thus, this should not be considered as a systematic review.

RATIONALE

3.3.1 In patients with CKD stages 3–5D, we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence or absence of valvular calcification, as reasonable alternatives to computed tomography-based imaging (2C).

Diagnostic tests

Most studies examining calcification in CKD reported on the use of CT-based techniques (EBCT and MSCT) in the detection of cardiovascular calcification in patients with CKD-MBD (*Supplementary Table 9*). EBCT and MSCT are currently regarded as the most sensitive methods for the detection and quantification of cardiovascular calcification. One study explicitly evaluated the sensitivity and specificity of several imaging tests and functional/hemodynamic measures for detecting CAC compared with EBCT.²⁷² This analysis focused on pulse pressure measurements, valvular calcification (by echocardiography), and abdominal aortic calcification (by lateral abdominal X-ray), respectively, according to the severity of CAC scores as assessed by EBCT scores of 30–99, 100–399, 400–999, and ≥ 1000 . No meaningful correlation was found between pulse pressure and CAC scores. In contrast, a strong correlation was detected between abdominal aortic calcification by plain radiograph and CAC scores. Valvular calcification, detected by echocardiography, was another good predictor of CAC.

We reviewed six additional studies which carried out correlation analyses comparing CT-based imaging techniques of assessing CAC with other measures of calcification. These latter measures included pulse pressure, abdominal aortic

calcification by lateral X-ray, PWV, echocardiography (valvular calcifications), intimal-media thickness (IMT) of the carotid arteries, and MSCT of the thoracic and abdominal aorta.^{273–278} PWV and abdominal aortic calcifications seemed to be reasonably good predictors of CAC scores, whereas the value of IMT, valvular calcification, and especially pulse pressure was limited. However, these studies were not designed to test sensitivity and specificity in this regard. The majority of the reported data referred to the CKD stage 5D population, whereas some studies included patients in different CKD stages.^{273,275} Only one study evaluated children (CKD stage ≥ 4).²⁷⁸ Thus, EBCT and MSCT remain the gold standard. However, a plain X-ray examination allows the detection of vascular calcification, and echocardiography allows the detection of valvular calcification, with reasonable sensitivity, as compared with the more expensive CT-based techniques. Thus, the Work Group felt that plain X-ray and echocardiography were reasonable alternatives to the gold standard of CT-based imaging.

3.3.2 We suggest that patients with CKD stages 3–5D with known vascular/valvular calcification be considered at highest cardiovascular risk (2A). It is reasonable to use this information to guide the management of CKD-MBD (not graded).

To recommend widespread global screening for the diagnosis of vascular calcification in all patients with CKD, the Work Group felt that the following was needed: (i) There should be an accurate and reliable diagnostic test (see above); (ii) vascular calcification should be prevalent enough to warrant screening; (iii) the tests should prompt a specific intervention; and (iv) the intervention should impact hard clinical end points. The Work Group felt that the data to support (i) and (ii) were strong, the data to support (iii) were somewhat inconsistent, and the data to support (iv) were limited. Thus, the Work Group did not recommend indiscriminate screening in all patients with CKD at this time, although this was a split decision. However, vascular calcification is an important component of CKD-MBD, and animal, epidemiological, and observational studies support that vascular/valvular calcification is a likely cause of cardiovascular morbidity and mortality in patients with CKD-MBD; thus, an assessment for vascular calcification is warranted in some patients. These may include, but are not limited to, patients with significant hyperphosphatemia requiring a differentiated high-dose phosphate-binder therapy, patients on a transplant waiting list, and any patient in whom the caring physician decides that a knowledge of the presence of vascular calcification may impact therapeutic decision making.

Prevalence

Twenty-five reports including information on the baseline prevalence of vascular or valvular calcification were evaluated (*Supplementary Table 10*). The studies included a total of

more than 4000 patients in different stages of CKD, the majority being in CKD stage 5D. In adult patients on dialysis, CAC has been detected in 51–93% of the study populations; prevalent dialysis patients had a higher likelihood of having detectable CAC scores than did incident ones. Valvular calcification was present in 20–47% of patients in CKD stage 5D. The prevalence of calcifications was variable at other vascular sites and was dependent on the sensitivity of the method used.

In CKD stages 3–5, published information related mostly to CAC scores showed that 47–83% of patients had cardiovascular calcification. In children with CKD stage 5D, the prevalence of a positive CAC was found to be 20% in one study.²⁷⁸ In young adults receiving dialysis treatment (age ranges: 20–30 years in one study, 19–39 years in a second study) with childhood-onset CKD, CAC prevalence was 87.5 and 92%, respectively.^{279,280} Valvular (aortal or mitral) calcifications were present in 20–25% of 653 patients with CKD stages 3–5 in the Multi-Ethnic Study of Atherosclerosis,²⁸¹ whereas the degree of renal dysfunction was only modestly associated with valvular calcification. In patients on dialysis, valvular calcification is more common, with one series reporting the presence of valvular calcification in 32% of patients.²⁸²

Eight studies investigating the natural history of calcification in a predefined prospective longitudinal approach in CKD were examined (*Supplementary Table 11*). Follow-up periods ranged from 1 to 3 years; detection methods were MSCT, EBCT, X-ray of pelvis and calves, and in one study, IMT. The major finding in this context is that once calcification is established, it follows a progressive course. In contrast, non-calcified patients with CKD have a high likelihood of remaining free of cardiovascular calcification over months to years. Compared with the non-CKD population, the progression of cardiovascular calcification is enhanced in patients with CKD. Furthermore, there is a strong relationship between the magnitude and severity of calcification and pre-existing coronary artery disease.

Risk relationships

We reviewed 10 reports on the risk relationships between cardiovascular calcification and mortality in patients with CKD (*Supplementary Tables 12 and 13*). Most of these studies were again conducted in dialysis patients, including one in peritoneal dialysis patients, but there is also information on renal transplant recipients and patients in CKD stages 4–5. EBCT, MSCT, ultrasound, echocardiography, and several X-ray techniques (pelvis, abdomen and hands) were used as diagnostic tests. In all but one study, cardiovascular calcification or progression of calcification were identified as independent risk predictors for cardiovascular and all-cause mortality. In only one study²⁸³ did valvular calcification lose its significance in predicting death after a multivariate adjustment.

In some of these studies (as well as in others that primarily addressed the natural history of calcification), risk associations were reported between the development and progres-

sion of calcification and epidemiological and biochemical parameters. Age was the most consistent risk factor for severe or progressive calcification, whereas diabetes, time on dialysis, male gender, high serum iPTH and/or ALP levels, inflammation (C-reactive protein levels), calcium intake, hyperphosphatemia, and increased $\text{Ca} \times \text{P}$ were identified in some studies, but the latter relationships could not be uniformly reproduced. No studies of adequate quality reported on the relationship between cardiovascular calcification and bone outcomes in CKD patients.

Management of patients with vascular/valvular calcification

Cardiovascular calcification development and progression can be influenced by treatment. Given that vascular calcification is associated with increased cardiovascular risk, and that the pathogenesis seems to be related to CKD-MBD (biochemical and bone) abnormalities and atherosclerosis, it is appropriate to evaluate and modify both.

CKD-MBD. Longitudinal studies have also shown that the progression of vascular calcification seems to be modifiable by the choice of phosphate binders. Five studies compared the effects of different phosphate-binder therapies on the progression of CAC scores in chronic HD patients^{284–288} (see Chapter 4.1). The Treat-to-Goal study ($n=200$) compared sevelamer-HCl to calcium-containing phosphate binders, analyzing the progression of coronary artery and aortic calcification (by EBCT) in prevalent HD patients over 1 year. Although calcification scores progressed with calcium-containing phosphate binders, treatment with sevelamer-HCl was associated with a lack of calcification progression. A similar design was used, and the results showed more calcification progression in patients treated with calcium-based binders compared with sevelamer-HCl in the Renegel in New Dialysis Patients study ($n=129$), which studied incident HD patients who were randomized within 90 days after starting dialysis treatment. The Calcium Acetate Renegel Evaluation-2 study ($n=203$) showed that the use of sevelamer-HCl and calcium acetate was associated with equal progression of CAC when statins were used to achieve a similar control of the serum low-density lipoprotein cholesterol in the two study arms.²⁸⁷ Interestingly, in Calcium Acetate Renegel Evaluation-2, the combination of sevelamer-HCl and atorvastatin was actually associated with a higher progression rate of CAC than that in Treat-to-Goal,²⁸⁴ instead of showing an amelioration of CAC progression with the combination of calcium acetate and statin. It is difficult to reconcile these differences, although one potential explanation is that the Calcium Acetate Renegel Evaluation-2 study patient population had a higher number of cardiovascular risk factors than did that of the Treat-to-Goal study.²⁸⁹ The Bone Relationship with Inflammation and Coronary Calcification study ($n=101$) investigated the effects of calcium acetate vs sevelamer-HCl on CAC progression and bone histomorphometry in HD patients. Although CAC progression rates did not differ between both phosphate-binder arms, this study was hampered by a much

smaller sample size and several significant confounders: imperfect matching of baseline CAC scores between the two study arms; the use of high dialysate calcium concentrations (1.75 mmol/l (3.5 mEq/l)) in most patients, resulting in a positive calcium balance; and multiple interventions during the course of the study aimed at improving adynamic bone disease.²⁸⁸ It is possible that these confounders 'neutralized' any potential advantage of sevelamer-HCl being a calcium-free phosphate binder. Finally, Russo *et al.* examined CAC score progression in patients with CKD stages 3–5 ($n = 90$). Patients were treated with either low-phosphate diet alone, low-phosphate diet plus calcium carbonate, or low-phosphate diet plus sevelamer-HCl. Calcification progression was lowest in the sevelamer-HCl-treated group compared with the calcium- and diet-only groups.²⁹⁰ These studies are discussed in more detail in Chapter 4.1.

There were no studies investigating the effect of parathyroidectomy on calcification progression or regression that met the inclusion criteria for review. There was one study addressing the issue of vascular calcification progression in renal transplant recipients (CKD stages 1–5T; $n = 55$) by measurements of IMT by high-resolution B-mode ultrasound at 3, 6, and 12 months after transplantation.²⁹¹ Regression of IMT was observed in association with a decline in serum iPTH levels. One question regarding this study is whether IMT indirectly reflects carotid artery calcification or other vascular remodeling processes induced by atherosclerosis or hypertension.

To date, there are no prospective studies in humans that have evaluated the impact of calcimimetics or calcitriol and vitamin D analogs on arterial calcification. However, a recent observational study showed a U-curve type of relationship between serum $1,25(\text{OH})_2\text{D}_3$ and arterial calcification in children and adolescents with CKD stage 5D.²⁹² No such association existed between serum $25(\text{OH})\text{D}$ and arterial calcification. In one study in adult patients with CKD stage 5, no independent association of serum $25(\text{OH})\text{D}$ or $1,25(\text{OH})_2\text{D}_3$ levels with arterial calcification was observed,²⁹³ although the authors of another report identified an association between $25(\text{OH})\text{D}$ deficiency and the magnitude of vascular calcification.²⁹⁴ It is noteworthy that, in the two latter studies, there was an association of arterial calcification with arterial PWV. Experimental studies showed differential effects of calcimimetics and calcitriol on extraosseous calcification, the former being neutral or protective, the latter being a dose-dependent risk factor for calcification.^{295–297} The experimental data supporting less toxicity of vitamin D analogs compared with calcitriol are not completely consistent across studies, but, in general, support the claim that there is reduced calcification with equivalent PTH lowering with different vitamin D analogs.^{295,298–300}

Atherosclerosis. CAC is a strong predictor of atherosclerotic disease in the general population. An evidence-based review of cardiovascular calcification in the general population was not carried out by the Work Group. However, it was recognized that most population studies measuring CAC did

not necessarily exclude individuals on the basis of kidney function and thus include variable numbers of CKD patients. These studies have been summarized in the American College of Cardiology/American Heart Association 2007 Clinical Expert Consensus Document on Coronary Artery Calcium Scoring by Computed Tomography.³⁰¹

In general, this literature evaluating the general population supports the view that CAC is part of the development of atherosclerosis and occurs almost exclusively in atherosclerotic human arteries. Calcification occurs early in the atherosclerotic process; however, the amount of calcification per lesion has a variable relationship with the associated severity of luminal stenosis. The relationship between the degree of calcification in an individual lesion and the probability of plaque rupture is unknown. In the general population, the overall coronary calcium score can be considered as a measure of the overall burden of coronary atherosclerosis. The American College of Cardiology/American Heart Association document indicates that the relationship between CAC and cardiovascular events in the CKD population is less clear than that in the non-CKD population because of a relative lack of informative studies and the possibility that medial calcification may not be indicative of atherosclerotic disease severity. In the non-CKD population, high-risk patients were not considered appropriate for this form of testing and so other approaches to clinical assessment and risk-reducing therapies were suggested. This latter suggestion may or may not be applicable to CKD patients, as the standard approaches for clinical assessment (Framingham risk-factor ranking) may be inappropriate for the kind of vascular disease in CKD patients. The almost exclusive relationship between magnitude of calcification and atherosclerosis burden is controversial in CKD patients,^{256,257} in contrast to the situation in the general population. For example, whereas $\geq 50\%$ of cardiovascular events are classical myocardial infarctions in the general population, this figure is below 20% in the CKD population, despite a higher absolute number of cardiovascular events.³⁰²

Antiatherosclerotic strategies using statin treatment have been shown to have a beneficial impact on the atherogenic profile, atheroma progression, and cardiovascular events in patients with no known CKD.^{303–305} However, at the same time, they do not seem to protect against the progression of arterial calcification when studied in the general population.^{306,307} In CKD patients, there are no data on the effects of statins on arterial calcification, as compared with those of placebo. Even worse, the 4D study failed to show a benefit of atorvastatin treatment on the outcome of diabetic dialysis patients. Studies in progress like SHARP (Study of Heart and Renal Protection) and AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) may help to gain a better understanding of the benefits of correcting atherosclerotic risk factors on cardiovascular events and mortality in patients with CKD stages 3–5 and 5D, respectively.^{308,309} (Note added in proof: In AURORA,

rosuvastatin failed to show a significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in chronic hemodialysis patients.) In the interim, we currently extrapolate the approach to atherosclerosis-related cardiovascular calcification from the general population, but there is some skepticism as to whether this approach may indeed apply to the CKD population, especially in CKD stage 5D.

RESEARCH RECOMMENDATIONS

- To determine the efficacy of different pharmacological agents for the prevention or delay of arterial calcification in patients with hyperphosphatemia, a prospective, randomized, placebo-controlled trial evaluating different phosphate-binder regimens in CKD stages 4–5D, should be conducted. The primary end point should be cardiovascular and all-cause mortality, with parallel assessments of cardiovascular and aortic calcification.
- Studies are needed to determine the role of screening for cardiovascular calcification and validate its usefulness for individual prognosis, risk reduction, and therapeutic decision making in patients with CKD. Such studies should address the question of whether a knowledge of vascular calcification may prospectively impact patient outcomes, and whether a broad approach of routine testing in patients with CKD should be considered for recommendation in the future.
- Studies are needed that compare patient outcomes of specified treatment strategies in response to the presence or absence of vascular calcification.
- To determine the efficacy of different pharmacological agents in the prevention or delay of arterial calcification in patients with secondary HPT, a prospective, randomized, placebo-controlled trial comparing calcitriol, vitamin D analogs, and calcimimetics in CKD stages 4–5D should be conducted. The primary end point should be cardiovascular and all-cause mortality, with parallel assessments of cardiovascular and aortic calcification.
- To determine the efficacy of different pharmacological agents for the prevention or delay of arterial calcification in patients with vitamin D deficiency, a prospective, randomized, placebo-controlled trial evaluating the administration of cholecalciferol or ergocalciferol in CKD

stages 4–5D should be conducted. The primary end point should be cardiovascular and all-cause mortality, with parallel assessments of cardiovascular and aortic calcification.

- To determine the efficacy of calcification inhibitors in the prevention or delay of arterial calcification, a prospective, randomized placebo-controlled trial evaluating the administration of vitamin K in CKD stages 4–5D should be conducted. The primary end point should be cardiovascular and all-cause mortality, with parallel assessments of cardiovascular and aortic calcification.
- To understand the pathophysiology of arterial calcification, additional case-control pathological studies should be conducted to evaluate the histological presence of intimal and medial calcification in the aorta and other non-coronary arteries in CKD patients compared with non-CKD patients.
- To understand the pathophysiology of calciphylaxis, epidemiological or registry studies should be conducted on individuals with calciphylaxis, either based on the clinical assessments (painful livedo and/or ulcerations and exclusion of differential diagnoses such as diabetic ulcers, vasculitis, or cholesterol emboli) or, preferably, based on biopsy results. The study should evaluate exposure to candidate risk factors (calcification inhibitor levels, CKD-MBD treatment, dialysis mode, vitamin K status, and mineral parameters such as PTH, calcium, phosphorus, and ALP) and the natural history of the disease on the basis of pathology and risk factors.

SUPPLEMENTARY MATERIAL

Supplementary Table 9. Overview table of selected studies of diagnostic tests: studies for vascular and valvular calcification techniques in CKD.

Supplementary Table 10. Overview table of selected studies presenting data on calcification prevalence.

Supplementary Table 11. Overview table of selected studies demonstrating the natural history of vascular and valvular calcifications in CKD.

Supplementary Table 12. Overview table of selected studies demonstrating the risk relationship between vascular calcification and mortality in CKD.

Supplementary Table 13. Overview table of selected studies demonstrating the risk relationship between valvular calcification and mortality in CKD stage 5D.

Supplementary material is linked to the online version of the paper at <http://www.nature.com/ki>

Chapter 4.1: Treatment of CKD–MBD targeted at lowering high serum phosphorus and maintaining serum calcium

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Grade for strength of recommendation ^a	Strength	Wording	Grade for quality of evidence	Quality of evidence
Level 1	Strong	'We recommend...should'	A	High
Level 2	Weak	'We suggest...might'	B	Moderate
			C	Low
			D	Very low

^aIn addition the Work Group could also make ungraded statements (see Chapter 2 section on ungraded statements).

INTRODUCTION

The overall phosphate balance is positive in patients with chronic kidney disease (CKD) stages 4–5D,³¹⁰ and therapeutic strategies are aimed at correcting this. Approaches include reducing phosphate intake by dietary modifications,³¹¹ reducing intestinal absorption using phosphate-binding agents,³¹² and in patients with CKD stage 5D, enhancing dialytic clearance with more dialysis.^{313,314}

RECOMMENDATIONS

- 4.1.1** In patients with CKD stages 3–5, we suggest maintaining serum phosphorus in the normal range (2C). In patients with CKD stage 5D, we suggest lowering elevated phosphorus levels toward the normal range (2C).
- 4.1.2** In patients with CKD stages 3–5D, we suggest maintaining serum calcium in the normal range (2D).
- 4.1.3** In patients with CKD stage 5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (2D).
- 4.1.4** In patients with CKD stages 3–5 (2D) and 5D (2B), we suggest using phosphate-binding agents in the treatment of hyperphosphatemia. It is reasonable that the choice of phosphate binder takes into account CKD stage, presence of other components of CKD–MBD, concomitant therapies, and side-effect profile (not graded).
- 4.1.5** In patients with CKD stages 3–5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia (1B).

In patients with CKD stages 3–5D and hyperphosphatemia, we suggest restricting the dose of calcium-based phosphate binders in the presence of arterial calcification (2C) and/or adynamic bone disease (2C) and/or if serum PTH levels are persistently low (2C).

- 4.1.6** In patients with CKD stages 3–5D, we recommend avoiding the long-term use of aluminum-containing phosphate binders and, in patients with CKD stage 5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication (1C).
- 4.1.7** In patients with CKD stages 3–5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (2D).
- 4.1.8** In patients with CKD stage 5D, we suggest increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia (2C).

Summary of rationale for recommendations

- Hyperphosphatemia has been associated with poor outcomes and mortality in CKD stage 5D, and high normal serum phosphorus levels have been associated with mortality in non-CKD patients and in CKD stage 3 patients.
- Many patients with CKD stages 4–5D have a high serum phosphorus level that is linked to the development of aspects of CKD–MBD, including secondary hyperparathyroidism (HPT), reduced serum calcitriol levels, abnormal bone remodeling, and soft-tissue calcification.
- Laboratory-based experimental data suggest that hyperphosphatemia may directly cause or exacerbate other aspects of CKD–MBD, specifically secondary HPT, a reduction in calcitriol levels, bone disease, and arterial calcification.

- There is no evidence that lowering serum phosphorus to a specific target range leads to improved clinical outcomes in patients with CKD. Recommended goals of therapy must therefore be based on observational data.
- Despite a lack of evidence from randomized controlled trials (RCTs) demonstrating that lowering phosphorus levels impact clinical outcomes, it is reasonable to lower phosphorus in CKD patients with hyperphosphatemia using phosphate binders. Additional options to lower phosphorus include limiting dietary phosphate intake (while ensuring adequate protein intake) and/or increasing the frequency or duration of dialysis (in those who require renal replacement therapy).
- There is insufficient evidence that any specific phosphate binder significantly impacts patient-level outcomes. Thus, the choice of phosphate binder should be individualized, and the guidance offered in this recommendation is based on the effects of available agents on a range of clinical parameters, rather than on phosphorus lowering alone.

BACKGROUND

Hyperphosphatemia is an important and inevitable clinical consequence of the advanced stages of CKD. The rationale for controlling serum phosphorus is based on epidemiological evidence suggesting that hyperphosphatemia is an important risk factor, not only for secondary HPT but also for cardiovascular disease (CVD).^{205,315} Long-standing hyperphosphatemia, together with an elevated serum $\text{Ca} \times \text{P}$, is associated with an increased risk of vascular, valvular, and other soft-tissue calcification in patients with CKD.²⁶² Large epidemiological studies have consistently shown the importance of hyperphosphatemia as a predictor of mortality in CKD stage 5 patients receiving dialysis.^{205,316–318} Taken together, these observational data suggest that there is a need to control serum phosphorus in patients with CKD. Experimental data suggest a direct causal relationship between phosphorus and several components of CKD-MBD, specifically secondary HPT,^{319,320} bone abnormalities,³²¹ calcitriol deficiency,³²² and extraskeletal calcification,³²³ providing biological plausibility to support these human observational studies.

The use of phosphate-restricted diets in combination with oral phosphate binders has become well established in the management of patients with CKD stages 3–5 (including CKD stage 5D), and this strategy has been endorsed by previous guidelines, with appropriate education and counseling to ensure adequate protein intake.⁵ Aluminum hydroxide is a potent phosphate binder, but concern about skeletal, hematological, and neurological toxicity led to a preferential use of calcium salts (carbonate and acetate) in the 1990s. The use of large doses of calcium-containing phosphate binders subsequently led to concerns about calcium overload because of a potential for generating a positive calcium balance. **Table 19** lists phosphate binders that are presently in use or that have been used in the recent past. Unfortunately, the true benefits of phosphate lowering with respect to hard clinical

end points have not been established, and most studies evaluate surrogate end points. In addition, because of ethical concerns regarding a prolonged lack of treatment, most studies evaluating these newer agents against placebo have been short term, with longer term studies using calcium salts as the comparator.

The following tables are found at the end of this chapter: **Table 20** summarizes the RCTs of phosphate binders in children with CKD. For CKD stages 3 and 4, only one sevelamer-HCl study met the inclusion criteria and is described in **Tables 21 and 22**. The evidence matrix, a table that describes the methodologic quality of all of the included studies for CKD stage 5D, and the evidence profile, a table that provides an overall assessment of the quality of the evidence and balance of potential benefits and harm are **Tables 23 and 24** for sevelamer-HCl compared to calcium containing phosphate binders, and **Tables 25 and 26** for lanthanum carbonate compared to other binders. A narrative review of the literature on the topic of alternate hemodialysis regimens can be found in **Tables 27–29**. These studies are discussed in the rationale for each recommendation. Additional detailed information about the studies of phosphate binders reviewed in this chapter are further described in detail in the *Supplementary Tables 14–23*.

RATIONALE

4.1.1 In patients with CKD stages 3–5, we suggest maintaining serum phosphorus in the normal range (2C). In patients with CKD stage 5D, we suggest lowering elevated phosphorus levels toward the normal range (2C).

No prospective studies have specifically examined the benefits of targeting different phosphorus levels to determine the effect on patient-level end points. Epidemiological data suggest that serum phosphorus levels above the normal range are associated with increased morbidity and mortality (*Supplementary Table 14*). Higher levels of serum phosphorus, even within the normal range, have been associated with increased risk of cardiovascular events and/or mortality (all-cause or cardiovascular mortality) in patients with a normal renal function who were free of CVD,³²⁴ in patients with coronary artery disease and normal renal function,³²⁵ and in patients with CKD stages 3–5.³¹⁶ Not all studies find these relationships. A subanalysis of the modification of diet in renal disease (MDRD) study failed to identify phosphorus as an independent risk factor for increased mortality in patients with CKD who were not on dialysis.³²⁶

In patients on dialysis, multiple studies from different parts of the world have shown that higher levels of serum phosphorus have been associated with an increased relative risk (RR) of mortality. In most of these studies, the observed risk associations were robust and ‘dose dependent’, with progressive increases in risk with higher levels of serum phosphorus. The inflection point or range at which phosphorus becomes significantly associated with increased

Table 19 | Phosphate-binding compounds

Binder source	Rx	Forms	Content (mineral/metal/element)	Potential advantages	Potential disadvantages
Aluminum hydroxide	No	Liquid, tablet, capsule	Aluminum content varies from 100 to >200 mg (per tablet)	Very effective phosphate-binding capacity; variety of forms	Potential for aluminum toxicity; altered bone mineralization, dementia; GI side effects
Calcium acetate	Yes/no	Capsule, tablet	Contains 25% elemental Ca ²⁺ (169 mg elemental Ca ²⁺ per 667 mg cap)	Effective phosphate-binding, potentially for enhanced phosphate-binding capability over CaCO ₃ potentially less calcium absorption	Potential for hypercalcemia-associated risks including extraskeletal calcification and PTH suppression; more costly than CaCO ₃ ; GI side effects
Calcium carbonate	No	Liquid, tablet, chewable, capsule, gum	Contains 40% elemental Ca ²⁺ (200 mg elemental Ca ²⁺ per 500 mg CaCO ₃)	Effective, inexpensive, readily available	Potential for hypercalcemia-associated risks including extraskeletal calcification and PTH suppression; GI side effects
Calcium citrate	No	Tablet, liquid, capsule	Contains 22% elemental Ca ²⁺	Not recommended in CKD	Enhancement of aluminum absorption; GI side effects
Calcium ketoglutarate					Similar to other calcium salts, costly, GI side effects, potentially less hypercalcemic than calcium carbonate or acetate, not well studied
Calcium gluconate		Tablet, powder			Similar to other calcium salts, not well studied
Ferric citrate					GI side effects, not well studied
Magnesium/calcium carbonate	No	Tablet	Approx 28% Mg ²⁺ (85 mg) per total mg carbonate and 25% elemental Ca ²⁺ (100 mg) per total CaCO ₃	Effective; potential for lower calcium load than pure calcium-based binders	GI side effects, potential for hypermagnesemia, not well studied
Magnesium carbonate/calcium acetate	Yes	Tablet			Lack of availability worldwide; assumed to have similar effects of its components
Sevelamer-HCl	Yes	Caplet	None	Effective; no calcium/metal; not absorbed; potential for reduced coronary/aortic calcification when compared with calcium-based binders in some studies; reduces plasma concentration of LDL-C	Cost; potential for decreased bicarbonate levels; may require calcium supplement in presence of hypocalcemia; GI side effects
Sevelamer carbonate	Yes	Caplet, powder	None	Effective; no calcium/metal; not absorbed; assumed to have similar advantages as sevelamer-HCl; potentially improved acid-base balance	Cost; may require calcium supplement in the presence of hypocalcemia; GI side effects
Lanthanum carbonate	Yes	Wafer, chewable	Contains 250, 500, or 1000 mg elemental lanthanum per wafer	Effective; no calcium; chewable	Cost; potential for accumulation of lanthanum due to GI absorption, although long-term clinical consequences unknown; GI side effects

CKD, chronic kidney disease; GI, gastrointestinal; LDL-C, low-density lipoprotein cholesterol; PTH, parathyroid hormone.

all-cause mortality varies among studies for the reasons cited above, 5.0–5.5 mg/dl (1.6–1.8 mmol/l),²⁰⁵ > 5.5 mg/dl (> 1.8 mmol/l),³²⁷ 6.0–7.0 mg/dl (1.9–2.3 mmol/l),³²⁸ and > 6.5 mg/dl (> 2.1 mmol/l).^{33,329,330} A recent Dialysis Outcomes and Practice Pattern Study (DOPPS) analysis shows that the relationship between elevations in serum phosphorus and the RR of mortality is consistent across all countries analyzed.³³ The study by Noordzij *et al.*³²⁷ also found similar relationships in peritoneal dialysis (PD) and hemodialysis (HD) patients. These observational data are consistent with animal and other experimental data, providing biological plausibility to the association, and leading the Work Group to recommend interventions that lower phosphorus toward the normal range. Hypophosphatemia may also be problematic. In the DOPPS series, there is an increased risk of mortality for CKD stage 5D patients with a phosphorus level less than 2.0 mg/dl (0.65 mmol/l). However, fewer than 5% of patients are in this risk category. Analyses of DOPPS data by a dialysis unit (which was randomly selected) showed that if a facility had 10% more patients with phosphorus levels between 6.1–7.0 and > 7.0 mg/dl (1.97–2.26 and > 2.26 mmol/l), the mortality risk was 5.3 and 4.3% higher, respectively.³³

In summary, although the benefits of lowering serum phosphorus on patient-level clinical outcomes (for example, hospitalization, bone fracture, cardiovascular events, and mortality) have not been studied, numerous epidemiological data show a positive association, although not a causal link, between higher serum phosphorus levels and RR of mortality, independent of CKD stage. Experimental data support the biological plausibility of a direct effect of phosphorus on PTH secretion and parathyroid cell proliferation,^{320,331,332} and on vascular calcification.³³³ However, the use of phosphate binders is associated with side effects, especially gastrointestinal, and with a high pill burden. Thus, in some patients, treatment to achieve a serum phosphorus level within the normal range may not be possible or may lead to a reduction in quality of life. Therefore, in the absence of a prospective RCT showing outcome benefits at any level of phosphate control, it seems reasonable that therapy is individualized. However, it is generally accepted and biologically plausible that elevated serum phosphorus levels should be lowered in patients with CKD stages 3–5D in an effort to control complications of CKD-MBD. The lack of data showing that patient-centered outcomes are improved by lowering serum phosphorus means that the strength of this recommendation is level 2 or ‘weak’, as it is based on observational and experimental data.

4.1.2 In patients with CKD stages 3–5D, we suggest maintaining serum calcium in the normal range (2D).

In patients with CKD stages 3–5, there are no data to support an increased risk of mortality or fracture with an increasing serum calcium concentration. The association in CKD stage 5D patients is generally similar to that of serum phosphorus. The

inflection point or range at which calcium becomes significantly associated with an increased RR of all-cause mortality varies among studies for the reasons cited above, from being > 9.5 mg/dl (> 2.38 mmol/l)²⁰⁵ to > 10.1 mg/dl (> 2.53 mmol/l),³³ > 10.4 mg/dl (> 2.60 mmol/l),³³⁰ > 10.5 mg/dl (> 2.63 mmol/l),³²⁸ and to > 11.4 mg/dl (> 2.85 mmol/l).³²⁹ Globally, 50% of CKD stage 5D patients have serum calcium levels above 9.4 mg/dl (> 2.35 mmol/l) and, of these, 25% have serum calcium levels above 10.0 mg/dl (> 2.50 mmol/l).³³ At the low end, there is little evidence of an increase in RR until serum levels fall below 8.4 mg/dl (< 2.10 mmol/l).³³ In another study from the United States, the increased RR of mortality with a low serum calcium was reversed when adjusted for covariates.²⁰⁵ It is therefore unclear at what level of low serum calcium is there an increased risk. It is also important to realize that none of these studies evaluated patients receiving cinacalcet, which lowers calcium by its effects on the calcium-sensing receptor (CaR) while also increasing the receptor’s sensitivity to the cation. Treatment leads to an expected decrease in the total serum calcium concentration. Thus, we do not know whether patients with low serum calcium levels due to cinacalcet have a similar risk as those with identical calcium levels who are not on the drug. Overall, the interpretation of serum calcium, similar to other biochemical values, should be evaluated on the basis of trends, which may be related to specific medications that raise (calcium-based phosphate binders, vitamin D sterols) or lower (cinacalcet) serum calcium values.

4.1.3 In patients with CKD stage 5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (2D).

There was a discussion among the Work Group members as to whether the optimal dialysate calcium concentration should be adapted to each patient’s individual needs, whenever possible. The final vote on this recommendation was 16 in favor and 1 vote against. The vote against was to argue that a 1.0 mmol/l (2.0 mEq/l) of calcium dialysate was also helpful in some patients to reduce their positive calcium balance.

Calcium balance during HD is important in determining short-term cardiovascular function, as it influences the hemodynamic tolerability of dialysis. In the longer term, calcium flux during HD is an important determinant of overall calcium balance. The calcium concentration of the dialysate therefore should be adjusted to optimize the total body calcium load.³³⁴ Theoretically, this strategy should help to improve bone health by reducing calcium flux during dialysis in patients with adynamic bone disease and extraskeletal calcification, and by inducing positive calcium flux during dialysis in patients with hypocalcemia. However, these possibilities have not been tested prospectively. The percentage of total body calcium that is dialyzable is very small, and studies that evaluate calcium balance are limited. The total amount of calcium removed with each dialysis treatment will depend not only on calcium concentration but also on the patient’s serum-ionized calcium

level, the intradialytic interval, and the rate of ultrafiltration.³³⁵ Studies that have measured spent dialysate for calcium to determine net flux have found near-neutral calcium flux in patients with a dialysis concentration of 1.25 mmol/l (2.5 mEq/l).^{336,337} A more recent study used more frequent assessments of spent dialysate and found a mean calcium flux with each dialysis session of -187 ± 232 mg (-46 ± 58 mmol) on a 1.25 mmol/l (2.5 mEq/l) of calcium dialysate. However, six of the 52 patients had positive calcium balance, supporting the fact that calcium flux with dialysis is not uniform in all patients.³³⁸ Thus, the Work Group felt that, in general, a dialysate calcium concentration of 1.25 mmol/l (2.5 mEq/l) would be a near-neutral calcium balance for most patients. However, it is important to point out that a low dialysate calcium concentration may also predispose to cardiac arrhythmias and hemodynamic instability during dialysis sessions, with intradialytic hypotension.^{339,340} At present, it is probably wise to maintain flexibility with dialysate calcium concentrations, which should be individualized, whenever possible, to meet specific patient requirements.

Similar considerations apply to PD, in which dialysate calcium concentration should be tailored to the individual patient's needs, if possible. Compared with patients receiving HD, patients receiving PD are exposed to a given dialysate calcium concentration for longer periods of time. Therefore, peritoneal dialysate calcium concentrations as high as 3.5 mEq/l (1.75 mmol/l) are generally avoided to prevent calcium overload and the induction of adynamic bone disease. Concentrations between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) are recommended.

4.1.4 In patients with CKD stages 3–5 (2D) and 5D (2B), we suggest using phosphate-binding agents in the treatment of hyperphosphatemia. It is reasonable that the choice of phosphate binder takes into account CKD stage, the presence of other components of CKD-MBD, concomitant therapies, and side-effect profile (not graded).

A systematic review of all RCTs examining phosphate binders was undertaken and considered in the context of the review of calcium-based binders published in the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines.⁵ These studies showed that all medications currently used as phosphate binders (calcium salts, aluminum salts, magnesium salts, sevelamer-HCl, and lanthanum carbonate) are effective in lowering serum phosphorus levels. The non-phosphorus-lowering effects are discussed in detail in the remainder of the chapter. The use of sevelamer, compared with the use of calcium-based salts, has been shown to attenuate progression of arterial calcification in one RCT involving patients with CKD stages 3–5²⁸⁶ and two RCTs involving patients with CKD stage 5D.^{284,285} However, two more recent RCTs have not reproduced these results and have found high and similar rates of progression of vascular calcification in patients receiving sevelamer-HCl as compared with those receiving calcium acetate.^{287,288} The effect of other

binders on progression of vascular calcification has not been systematically studied. Most importantly, it is not clear whether slowing vascular calcification translates into improvements in clinical outcomes or whether other non-calcium-containing binders (for example, lanthanum carbonate) have similar effects. The use of lanthanum carbonate and sevelamer-HCl does not adversely affect bone histology in short-term studies and, when compared with calcium-based binders, may be less likely to lead to adynamic bone disease. Comparative studies of phosphate binders have shown differences in effects on the biochemical parameters of CKD-MBD. For example, the use of calcium salts is generally associated with higher serum calcium (and more frequent episodes of hypercalcemia) and lower serum PTH levels when compared with the use of sevelamer-HCl or lanthanum carbonate. The effects of different binders on biochemical end points, on surrogate markers of bone and vascular calcification, or on mortality, are described in the rationale following Recommendation 4.1.5. Overall, there is insufficient comparative efficacy data on clinical outcomes to make a recommendation for the use of a specific binder for all patients.

4.1.5 In patients with CKD stages 3–5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia (1B).

In patients with CKD stages 3–5D and hyperphosphatemia, we suggest restricting the dose of calcium-based phosphate binders in the presence of arterial calcification (2C) and/or adynamic bone disease (2C) and/or if serum PTH levels are persistently low (2C).

The Work Group asked if there were differences between the various phosphate binders in terms of their effects on biochemical indices of CKD-MBD, bone, vascular calcification, or clinical end points. The group felt that there were inconclusive data to indicate that any one binder has beneficial effects on mortality or other patient-centered outcomes when compared with any other binder, and thus the strength of this recommendation is graded as level 2. The specific recommendations regarding limiting calcium intake from phosphate binders were extensively discussed. As detailed below, there are consistent data regarding the risk of inducing hypercalcemia and calcium overload in patients on calcium-based phosphate binders, necessitating dose reduction. The Work Group also felt that the available bone biopsy data suggested that patients receiving calcium-based binders were more likely to develop adynamic bone disease. There was extensive discussion with respect to the role of calcium- vs non-calcium-based binders in the pathogenesis of vascular calcification. The Work Group acknowledged that the evidence was not conclusive and that more research is needed. However, the majority of the Work Group felt that limiting

calcium intake in the form of phosphate binders was justified until further research is available on the basis of our knowledge of calcium balance in CKD patients. It was noted that at least some studies in humans showed a beneficial effect of sevelamer-HCl compared with calcium-based binders on progression of arterial calcification. The majority of the Work Group (16 of 17 members) felt that, given the high cardiovascular burden, recommending a limited calcium intake was likely to be more beneficial than harmful. A single member of the Work Group felt that this recommendation had the potential for too large an impact with too little data to support it, bringing the final vote to 16 in favor and 1 vote against.

Results of evidence review

The KDOQI guidelines⁵ extensively reviewed trials evaluating calcium carbonate and calcium acetate. No additional studies fulfilling our screening criteria were identified, with the exception of those comparing a calcium-containing phosphate binder with sevelamer-HCl or lanthanum carbonate. The KDOQI guidelines concluded that both calcium carbonate and calcium acetate were effective in lowering serum phosphorus when compared with placebo, but that both were associated with hypercalcemia and gastrointestinal side effects. A meta-analysis performed for the KDOQI guidelines indicated that calcium acetate is less hypercalcemic than is calcium carbonate.⁵ None of these studies assessed bone histology, vascular calcification, or hard clinical end points and thus will not be further reviewed. The KDOQI guidelines also evaluated aluminum hydroxide as a phosphate binder, but again no data on vascular calcification or hard clinical end points were identified. However, studies have shown that aluminum may induce osteomalacia, microcytic anemia, and central nervous system toxicity.^{341,342} Thus, in the absence of a clear benefit beyond phosphorus lowering, and because of known potential toxicity, the Work Group felt that the use of aluminum hydroxide should be restricted.

The remaining studies identified by our systematic search compared sevelamer-HCl or lanthanum with calcium-based binders, or lanthanum with a previously prescribed binder (a calcium salt or sevelamer). These studies are listed in tables by treatment comparisons and are reviewed below by end point.

a) *Patient-centered end points: Studies of phosphate binders comparing sevelamer-HCl and calcium-based binders that have mortality as the primary end point have been inconsistent.*

The largest of these studies, the Dialysis Clinical Outcomes Revisited (DCOR) study, randomized 2103 prevalent CKD stage 5D patients to either sevelamer-HCl or a calcium-based phosphate binder (70% calcium acetate or 30% calcium carbonate), (Table 24; Supplementary Tables 15–18).²⁶⁶ Patients were allowed to receive other medications according to current standards of care and were followed up for a mean of

approximately 20 months. The trial was designed to evaluate all-cause mortality as the primary end point and had 80% power to detect a 22% difference between the groups, assuming a mortality rate of 20 per 100 patient-years in the calcium-treated group and a two-sided alpha (α) of 0.05. The study had a high early discontinuation rate and collected only 90 days of follow-up data on discontinued patients, providing limited information on these individuals. The overall dropout rate was 47% in the sevelamer-HCl arm and 51% in the calcium-based binder arm. More patients discontinued because of adverse events (AEs) in the sevelamer-HCl arm (8 vs 5%), but types of events and event rates were not comprehensively reported. The study was extended because the mortality rate in the control group was lower than expected. No details of interventions, treatment targets, or dose-titration protocols were provided, neither were baseline biochemical parameters available. Only 1068 patients completed the study, and there were no differences in all-cause or cause-specific mortality rates when comparing sevelamer-HCl (mortality rate 15.0 per 100 patient-years) with calcium-treated patients (16.1 per 100 patient-years), hazard ratio (HR) 0.93, 95% confidence interval (CI) 0.79–1.10, log rank $P=0.40$. There were also no differences in cardiovascular mortality and hospitalization on the basis of data from case-report forms. Much attention has been focused on the analysis of subgroups, particularly patients over 65 years of age (a prespecified analysis) and those receiving treatment for more than 2 years in whom benefits associated with allocation to sevelamer-HCl therapy have been claimed. However, the Work Group took the view that, in light of the equivalence of the two therapies with respect to the primary end point in the overall cohort, such analyses could be, at best, considered hypothesis generating and should be interpreted with extreme caution. The ERT graded the quality of this study as C (low quality) with respect to all outcomes because of several factors, including the lack of an intention-to-treat analysis and possible bias resulting from the limited (90-day) follow-up of discontinued patients, as well as a lack of documentation of baseline biochemical parameters and AEs.

A secondary preplanned analysis of the DCOR study by St Peter *et al.*²⁶⁷ using Medicare claims data (rather than data collected at the study sites on case-report forms) showed no effect of phosphate-binder allocation on overall mortality (primary outcome), cause-specific mortality, morbidity, or first or cause-specific hospitalization (secondary outcomes).²⁶⁷ This study did show a beneficial effect of sevelamer-HCl on the secondary outcomes of multiple all-cause hospitalizations (1.7 vs 1.9 admissions per patient-year, $P=0.02$) and hospital days (12.3 vs 13.9 days per patient-year, $P=0.03$).²⁶⁷ This study was graded as ‘B’ (that is, moderate quality) for mortality outcome. The study ascertainment for mortality was complete and allowed a true intention-to-treat analysis, having included many patients lost to follow-up in the original publication; however, this could not overcome the high dropout rate.²⁶⁶ The quality of data for hospitalization was graded as low (or ‘C’). The

analysis by St Peter *et al.*²⁶⁷ using claims data described a higher rate of hospitalization in a smaller group of patients with a shorter duration of follow-up than that reported by Suki *et al.*,²⁶⁶ as a result of the fact that the denominator for hospitalization rates did not include days spent in the hospital. Thus, although both analyses showed a trend toward lower hospitalization rates, the fact that the difference between patients allocated to different binders was of statistical significance in the analysis by St Peter *et al.*²⁶⁷ was not considered to be robust. Furthermore, hospitalizations from CVD as ascertained from the administrative data did not differ, lending no support to the study's hypothesis that sevelamer-HCl reduces CVD morbidity.

The second study examining clinical outcomes data, RIND, randomized a smaller group of 148 incident HD patients (patients new to dialysis) to either sevelamer-HCl or calcium-based binder, but followed up these patients for a longer period. Only 127 patients received baseline electron-beam CT (EBCT) scans and the dropout rate was 26% in the sevelamer-HCl arm and 27% in the calcium-based phosphate-binder arm. At a median of 44 months, there was a difference in the unadjusted mortality rate for patients assigned to calcium-containing binders, which was 10.6 per 100 patient-years (CI 6.3–14.9), compared with 5.3 per 100 patient-years (CI 2.2–8.5) for patients assigned to sevelamer-HCl, with the HR for mortality in the univariate analysis for calcium vs sevelamer being 1.98 ($P=0.06$). However, in multivariate analysis, which included 10 variables (felt to be a large number considering that there had only been 34 deaths), the difference between the groups was significant (HR 3.1, $P=0.016$), suggesting an imbalance with respect to the covariates entered into the model and raising the possibility of an unsuccessful randomization. As a result of this concern, the Work Group downgraded the methodological quality of this study to B or 'moderate.'

No data on cardiovascular events other than death, fractures, or parathyroidectomy rates were available from either of these studies, making it impossible to draw conclusions on the impact of using sevelamer-HCl instead of a calcium-based phosphate binder on such outcomes. In addition, no studies have examined the effects of lanthanum carbonate or indeed any other phosphate binder (including calcium- and aluminum-based compounds) on patient-level outcomes.

b) Vascular calcification: The use of sevelamer-HCl attenuates the progression of arterial calcification in patients with CKD stages 3–5 and stage 5D when compared with the use of calcium-based salts in some, but not all, studies. The effect of other binders on progression of vascular calcification has not been systematically studied. Most important, it is not clear whether slowing vascular calcification translates into improvements in clinical outcomes.

Three of the five randomized trials (*Supplementary Tables 15, 16*), as reported in multiple publications, comparing

sevelamer-HCl with calcium-based binders^{284–286,288,343,344} studied the impact of phosphate-binder therapy on arterial calcification, assessed using computerized tomography imaging techniques. One examined the effect of these two oral phosphate-binder approaches on valvular calcification,³⁴⁵ and one compared the effect of sevelamer-HCl with calcium-based binders, adding atorvastatin treatment to both arms as required to reach a comparable low-density lipoprotein cholesterol target.²⁸⁷ Only one of these trials involved patients with CKD stages 3–4,²⁸⁶ whereas the remaining four recruited patients with CKD stage 5D.^{284,285,287,288,343–345}

In their study involving 90 binder-naïve Italian patients with CKD stages 3–5 who were not receiving dialysis, Russo *et al.*²⁸⁶ (**Tables 21, 22**) randomized patients (30 per group) into either a low-phosphate diet alone group, a low-phosphate diet in combination with fixed doses of calcium carbonate (2 g/d) group, or a low-phosphate diet in combination with sevelamer-HCl (1600 mg/d) group, and followed up these individuals for 2 years. The primary end point of the study was progression of coronary artery calcification (CAC), assessed as the total calcium score using multislice computed tomography. Among the 84 patients who completed the study, the final CAC scores were greater than the initial scores in those receiving diet alone ($P<0.001$) or diet in combination with calcium carbonate ($P<0.001$), whereas there was no progression of calcification in the diet-plus-sevelamer-HCl-treated group. In patients with CKD stage 5D, four studies have examined the effect of sevelamer-HCl compared with that of calcium-containing phosphate binders on the progression of CAC (*Supplementary Tables 15, 16*). One of the secondary aims of the 'Treat to Goal' study was to assess the progression of cardiovascular calcification in 200 prevalent HD patients randomized to receive either sevelamer-HCl or a calcium-based phosphate binder (107 calcium acetate in the United States and 93 calcium carbonate in Europe) in an open-label design.²⁸⁴ The study was conducted in the United States, Germany, and Austria, and was powered to achieve a serum $\text{Ca} \times \text{P}$ difference of $10 \text{ mg}^2/\text{dl}^2$ ($124 \text{ mmol}^2/\text{l}^2$). Patients were randomized after a 2-week 'washout' period and investigators were instructed to manage blood calcium, phosphorus, and PTH levels to achieve prespecified targets for the remaining 50 weeks (hence, the 'Treat to Goal' study). During this period, absolute calcium scores in the coronary arteries and aorta increased in the calcium-treated patients, but not in those receiving sevelamer-HCl. Many dropouts were reported, with 37% of the sevelamer-treated patients and 31% of the calcium-treated patients missing from the analysis at week 52. These data were partially duplicated in a publication that describes 93 patients from the European cohort³⁴³ (with 21 additional patients whose origin is unclear); in a third article that also reported valvular calcification, its progression did not differ when the two groups were compared at the start and end of a 52-week study period.³⁴⁵ Another report suggested that patients randomized to receive calcium salts, compared with those

randomized to sevelamer-HCl, experienced greater trabecular (but not cortical) bone loss on the basis of changes in thoracic bone mineral density (BMD) on EBCT scans in a subset of 132 patients in whom the necessary imaging was available.³⁴⁶ At the end of the 52-week study period, a European subgroup of 72 patients out of the initial ‘Treat to Goal’ cohort chose to remain under follow-up and attended for subsequent EBCT scans approximately 2 years after enrollment into the study (although no longer randomized to different phosphate binders beyond 52 weeks). This approach to subject retention may well have introduced biases. Data from this extended follow-up, during which 53% of the patients dropped out, were reported to endorse the observation that assignment to a calcium-based binder was associated with progressive arterial calcification and decreased trabecular bone density when compared with assignment to sevelamer-HCl treatment.³⁴⁴ Changes in bone density and vascular calcification did not correlate. As measurement of thoracic vertebral radiolucency by EBCT is not a valid measure of BMD or mass, and bearing in mind the high dropout rate, the Work Group was concerned with regard to the validity of these bone data and graded all these substudies of ‘Treat to Goal’ as being of low quality.

Assessment of changes in CAC at 12 months was the primary outcome of the RIND study²⁸⁵ (*Supplementary Tables 15, 16*). Of the 127 patients who underwent baseline EBCT, 26% did not receive follow-up EBCT scans. At 1 year, there was no statistically significant difference in calcification. The mean annual rates of progression of calcification were 13.4 and 25.3% for sevelamer-HCl and the calcium-based binder groups, respectively, $P=0.06$. The median increase in the calcification score at 18 months was 11-fold higher in the calcium-treated group compared with the sevelamer-HCl-treated group (an increase of 127 points from a baseline of 667 ± 1248 vs 11 points from a baseline of 648 ± 1499 , respectively, $P=0.01$). In a subgroup analysis, patients with a baseline CAC score of >30 Agatston units confirmed a trend for higher absolute and percentage increases in calcium-treated patients. In the RIND trial, the amount of calcium consumed in calcium-based binders was not associated with the rate of progression of calcification.

In the CARE 2 study, chronic HD patients from the United States were randomized to receive either calcium acetate or sevelamer-HCl.²⁸⁷ Patients in both groups received atorvastatin to achieve a low-density lipoprotein cholesterol goal of 70 mg/dl (1.81 mmol/l). The study was designed to assess non-inferiority, evaluating CAC using EBCT at 6 and 12 months after randomization. Before 1 year, 30% of the patients in the sevelamer arm and 43% in the calcium acetate arm dropped out. Although achieving comparable levels of serum cholesterol, no difference in the progression of arterial calcification was noted when comparing the two treatment arms (annual progression of coronary calcification was 29 and 30% in the calcium acetate and sevelamer-HCl groups, respectively, $P=0.90$). Although the study had a high percentage of loss of follow-up, several sensitivity analyses (including some that

imputed missing values under different assumptions) showed the findings to be robust. Furthermore, this is the only study that defined a metric for the primary calcification outcome up front. However, the study was downgraded from ‘high’ to ‘moderate’ quality, because the selection of the upper 95% confidence limit for outcome was not explained and, in the study design, it was not intuitive what the ‘upper bound for the non-inferiority margin of 1.8’ means in terms of clinically relevant differences in progression of calcification. It is noteworthy that CARE 2 showed that the combination of sevelamer-HCl and atorvastatin was associated with a much higher rate of progression of CAC than that in ‘Treat to Goal’,²⁸⁴ instead of showing a delay in CAC progression with the combination of calcium acetate and statin in accordance with the initial study hypothesis. One of the possible explanations for the equivalent progression of calcification in the two treatment arms of CARE 2, as opposed to less calcification in the sevelamer-HCl compared with the calcium arm in the ‘Treat to Goal’ study, is that the patient population was exposed to a greater number of cardiovascular risk factors in the CARE 2 study.²⁸⁹

The BRIC study investigated the effects of calcium acetate vs sevelamer-HCl on CAC progression and bone histomorphometry in chronic HD patients from Brazil. The authors randomized 49 patients to calcium acetate and 52 patients to sevelamer-HCl.²⁸⁸ The primary goal of the study was to test the hypothesis that treatment with calcium-containing phosphate binders has a negative impact on bone remodeling and this contributes to a more rapid progression of CAC compared with sevelamer-HCl treatment. The annual rates of progression of coronary calcification scores were 27 and 26% for sevelamer-HCl and calcium acetate, respectively, $P=NS$. The authors also found that neither CAC progression rates nor indices of bone remodeling differed between the two phosphate-binder arms. However, this study was hampered by several significant confounders, including small sample size, differences in baseline CAC scores between the two study arms (675 ± 1267 for calcium acetate and 507 ± 814 for sevelamer, $P=0.38$), the use of high dialysate calcium concentrations (1.75 mmol/l (3.5 mEq/l)) in most patients, resulting in a positive calcium balance, and multiple interventions during the course of the study based on bone biopsy results.

The inconsistencies between the results of the recent BRIC and CARE 2 studies on the one hand and those of the previous studies on the other hand cast some doubt on the hypothesis of a major role of calcium loading in the progression of arterial calcification, with the CARE 2 and BRIC study results not duplicating the beneficial effects observed with sevelamer-HCl in the other three trials. Taken together, the data on vascular calcification overall are only of low quality, bearing in mind that changes in the rate of calcium deposition have not been validated as a predictor of benefit in terms of clinical outcomes in CKD patients. Given the present uncertainty in this field, further trials comparing phosphate binders and examining hard clinical end points are needed.

- c) **Bone histology: Clinical trials comparing calcium carbonate with lanthanum carbonate or sevelamer-HCl do not show major differences among treatments. The changes in bone turnover with both calcium- and non-calcium-based binders are heterogeneous, with some patients showing worsening and others showing improvement. The results are also influenced by baseline turnover rates.**

Sevelamer-HCl. Two clinical trials compared sevelamer-HCl with calcium carbonate, yielding a moderately high quality for this outcome, and a smaller study compared these therapies in children (*Supplementary Table 17*).

In the first adult study comparing the effects of sevelamer-HCl and calcium carbonate on bone histology, Ferreira *et al.*¹⁰⁴ enrolled 119 HD patients in a 54-week randomized, open-label study. Of them, 100 patients underwent baseline and 68 underwent follow-up bone biopsies after 1 year. Serum calcium was lower and serum intact PTH (iPTH) was higher in those patients assigned to sevelamer-HCl. Neither overall bone volume nor mineralization changed after 1 year in an intention-to-treat analysis when compared with that at baseline in either of the two groups, but turnover increased in the sevelamer group compared with that in calcium-treated patients ($P=0.02$). The turnover worsened by becoming higher in 12% of sevelamer-HCl and 3% of calcium groups; on the other hand, it worsened by becoming lower (development of adynamic disease) in 17% of calcium patients and 9% of sevelamer-HCl patients. Turnover improved in 26% of calcium and 15% of sevelamer-HCl patients. Change in bone volume was almost the same in both groups (the volume increased by 0.9% in the calcium vs sevelamer-HCl group).

The second adult study, the BRIC study, also compared the effects of sevelamer-HCl and calcium acetate on bone histology.²⁸⁸ Among the 101 HD patients randomized, 27 in the calcium acetate arm and 37 in the sevelamer-HCl arm had an interpretable repeat bone biopsy after a 12-month treatment period. Overall, there were no significant changes in the main bone parameters. **Turnover:** The resulting 12-month bone-formation rates were not statistically different between groups. The mean bone-formation rate increased by 76% with calcium treatment, which was not statistically significant for the before and after within-arm comparison, and by 93% with sevelamer-HCl treatment, which was significant ($P<0.05$) for the before and after within-group comparison. The authors then separately analyzed those who initially had a high or low bone turnover. In those with a low bone turnover, there was a similar improvement with both treatments. In those with a high bone turnover, there was no mean change in bone formation with either treatment. **Mineralization:** There was no significant change in the mineralization lag time (MLT) with either treatment. In the low-turnover group, there was improvement with both treatments. It is noteworthy that bone aluminum surface was $21.1 \pm 28.7\%$ in the calcium-treated group and $27.6 \pm 27.4\%$ in the sevelamer-treated group, although the

number of patients who had positive aluminum staining was not provided. **Volume:** There was a significant ($P<0.05$) but slight improvement with calcium treatment and no change with sevelamer-HCl treatment.

A third study in children did not show differences between calcium and sevelamer-HCl for turnover or mineralization, and the same number developed adynamic disease.¹⁷

In all three of the studies, bone volume was slightly improved with calcium treatment compared with sevelamer-HCl treatment, but the results were not significant.

Lanthanum carbonate. Three studies compared the effects of lanthanum carbonate with those of calcium carbonate on bone histomorphometry (*Supplementary Table 22*). The larger studies^{13,103} were of moderate quality, with some inconsistencies in data reporting, and the third study⁹⁸ was limited by a small sample size.

In the first study by D'Haese *et al.*,¹² 98 HD patients underwent baseline bone biopsy, and paired iliac crest bone biopsies were measured after 1 year from 63 patients, 33 of whom received lanthanum carbonate and 30 of whom received calcium carbonate. These biopsy results were reported in three publications.^{12,13,21} The first report presented data in a categorical form. The second report presented changes in activation frequency (a marker of bone turnover), which were considered to have improved if they became closer to normal.¹³ Data were extracted from a figure that presented individual changes in the bone-formation rate per bone surface. The third report presented changes in activation frequency, and defined improvement in terms of 1 s.d.²¹ When all three reports of the same biopsy study were taken together, an improvement in turnover was seen in 36–45% of patients receiving lanthanum and in 20–23% of those receiving calcium. The turnover worsened in 30% with calcium treatment (20% developed adynamic disease) and in 12% with lanthanum treatment (6% developed adynamic disease). Mineralization changes were similar in both treatment groups. Volume was not reported. Overall, the results favored lanthanum carbonate treatment.

The second study by Malluche *et al.*¹⁰³ evaluated 2 years of treatment. Paired bone biopsy samples for histomorphometric analysis were available at baseline and at 1 year in 32 lanthanum carbonate-treated HD patients and in 33 HD patients receiving standard care, and at baseline and 2 years in 32 lanthanum carbonate-treated patients and in 24 patients receiving standard care. The majority of patients in the standard-care group (>80%) received calcium-containing phosphate binders.¹⁰³ **Turnover:** At 1 year, turnover worsened in 45% of the calcium group and in 42% of the lanthanum group, and improved in 3% of the calcium group and in 12% of the lanthanum group. At 2 years, the turnover had worsened in 72% of the calcium group (29% decreasing toward adynamic lesions) and in 40% of the lanthanum group (23% decreasing), with improvement being similar in both groups. Therefore, at 2 years, the results showed a better turnover with lanthanum carbonate treatment. Mineralization worsened in two patients receiving lanthanum carbonate

and in none receiving standard-care treatment. Volume was slightly better in the lanthanum carbonate group at 2 years.

The third study by Spasovski *et al.*⁹⁸ included 20 new HD patients randomly treated with lanthanum carbonate or calcium carbonate for 1 year, thereafter with calcium carbonate for an additional 2 years. Bone biopsies were performed at baseline, 1, and 3 years. *Turnover:* None of the patients in the lanthanum carbonate group developed low bone turnover at the 1-year biopsy in contrast to three patients developing adynamic bone disease in the calcium carbonate group. The bone-formation rate showed a non-significant increase in the first year and a return to baseline in year 3 in the lanthanum carbonate group, whereas it decreased slightly in the calcium group. Mineralization and volume were not reported.

In summary, there are only minor overall changes observed in response to non-calcium-containing phosphate binders, compared with calcium-containing phosphate binders, when patients are considered as a group. The changes in bone turnover are heterogeneous and influenced by initial bone turnover. None of the studies had enough power to provide adequate evidence for a change in volume. The studies did not identify consistent beneficial or adverse effects on bone with the administration of any of the phosphate binders in the doses used.

The Work Group felt it was important to acknowledge that existing adynamic bone or the development of a low-turnover disease may be related to the development of arterial calcification as described earlier. A cross-sectional study found that arterial calcification is higher in patients whose bone formation was below the median value. The mean calcium intake was higher in those with adynamic bone and in those with aortic calcification. Furthermore, in those with adynamic bone disease, calcium intake was directly related to the degree of aortic calcification.¹¹⁷ In the study by Barreto *et al.*,¹¹⁹ the relationship between bone histology and progression of arterial calcification was evaluated. In patients who began the 1-year study with a low-turnover disease, those who had coronary calcification progression were more likely to have a persistent low-turnover disease at the 12-month biopsy (58 vs 17%; $P=0.01$). Logistic regression analysis showed the diagnosis of a low-turnover bone state at the 12-month bone biopsy as being the only independent predictor for coronary artery progression ($P=0.04$; β -coefficient = 4.5; 95% CI 1.04–19.39). The mechanism for this effect may be that adynamic bone is an ineffective reservoir for excess calcium intake. A study showed that HD patients with biopsy-proven adynamic bone disease had minimal radio-labeled calcium influx into bone, whereas those with a high-turnover bone disease had a marked influx of calcium into the bone.³⁴⁷ The RCTs detailed above show that some patients develop adynamic bone disease with calcium-containing phosphate binders more often than do those with non-calcium-based binders in some,^{12,104} but not all, studies.^{103,118} This raises a concern with respect to excessive calcium intake and the risk of vascular calcification, but the amount of calcium intake that is safe

remains to be determined and is likely to not be a uniform amount across all patients. Despite these limitations, the Work Group recommended limiting calcium intake in the presence of low-turnover bone disease or adynamic bone disease, but acknowledged that this is a low-quality evidence and thus graded it as 2C. Formal balance research studies are needed.

d) *Biochemical end points:* Comparative studies of phosphate binders have shown differences in the biochemical parameters of CKD-MBD. For example, the use of calcium salts is generally associated with higher serum calcium (and more frequent episodes of hypercalcemia) and lower serum PTH levels when compared with sevelamer-HCl or lanthanum carbonate.

Sevelamer-HCl. All eight RCTs reported biochemical parameters reflecting a mineral-bone disorder (blood levels of calcium, phosphorus, and PTH) with broadly consistent results.^{104,266,267,284–288} In the context of these studies, sevelamer-HCl and calcium salts were equally effective as phosphate binders. In the population with CKD stages 3–5 studied by Russo *et al.*²⁸⁶ (Tables 21, 22), there were no differences in serum calcium, phosphorus, or PTH when comparing diet, diet plus calcium, or diet-plus-sevelamer-HCl-treated patients at the end of the 2-year study period. Compared with baseline, urinary phosphate excretion increased in the diet-only-treated patients but decreased in those receiving phosphate binders. Among-group comparisons of serum calcium, phosphorus, and PTH were not reported. Concerns with regard to this study included the imbalance between baseline levels of biochemical parameters, the lack of blinding, a high dropout rate (10% in the sevelamer-HCl arm), and the lack of a power analysis.

The DCOR investigators reported time-weighted biochemical parameters (but not baseline values). Patients receiving sevelamer-HCl had a lower serum calcium, but higher phosphorus and higher PTH serum levels than those receiving calcium-based binders. Serum calcium levels were also lower in the sevelamer-HCl-treated patients in the ‘Treat to Goal’ study²⁸⁴ and overt hypercalcemia was less common in such patients.²⁸⁴ These findings were broadly reflected in the RIND study results reported after 18 months of treatment,²⁸⁵ and in the CARE 2 study after 12 months.²⁸⁷ Ferreira *et al.*¹⁰⁴ reported similar results after 13.5 months of follow-up, although biochemical data were only included for those patients undergoing a second bone biopsy, potentially biasing the results. In BRIC, those patients randomized to sevelamer-HCl had both higher PTH and alkaline phosphatase (ALP) levels after 12 months of treatment, although there were no differences in serum calcium or in the frequency of hypercalcemic episodes.²⁸⁸ Thus, in all of these eight comparative studies, a randomization to sevelamer-HCl was associated with higher serum iPTH levels, and in all but one study (BRIC), with a lower serum calcium concentration. The Work Group considered these biochemical data to be of high quality, although the importance of laboratory

outcomes was considered to be low, the increase in PTH may or may not reflect a desirable change depending on the end point, and most importantly, the true relationship of biochemical measures with clinical end points has not been established.

Lanthanum carbonate. Of the three randomized studies comparing lanthanum carbonate with other binders (Supplementary Tables 20–22), only the study by Hutchison *et al.*³⁴⁸ reported biochemical parameters reflecting mineral bone disorder (serum phosphorus, calcium, $\text{Ca} \times \text{P}$, and PTH) as the primary end point. However, this study compared the ability of the binders to maintain phosphorus control only in those patients who achieved serum phosphorus levels ≤ 5.58 mg/dl (1.8 mmol/l) within the initial dose-titration phase. The ERT therefore considered these data to be of limited applicability and was concerned with regard to potential bias introduced by the exclusion of study participants after randomization. The results of the other two studies were broadly consistent in that lanthanum carbonate was as effective as calcium carbonate in controlling serum phosphorus, but neither of these studies were primarily designed to compare efficacy in phosphorus lowering or to examine other biochemical end points.^{13,349}

In a longer term study,³⁴⁹ 46% of patients in the lanthanum carbonate group (maximum daily dose of 3000 mg elemental lanthanum) achieved control of serum phosphorus levels to < 1.9 mmol/l (5.9 mg/dl) compared with 49% in the standard-therapy group ($P = 0.5$) after 2 years of treatment. However, there was a higher frequency of hypercalcemia reported as an AE in the calcium carbonate group (20.2%) compared with that in those receiving lanthanum carbonate therapy (0.4%). Serum PTH levels attained the range recommended by the KDOQI guidelines for patients with CKD stage 5 (150–300 pg/ml (15.9–31.8 pmol/l)) during titration in the lanthanum carbonate group, but remained below this range throughout the study period in the standard-therapy group. The Work Group considered these data on biochemical markers to be of low quality. First, the study was designed for safety analysis and not for efficacy. In addition, there was no option to switch treatments in the event of inefficacy in the lanthanum group. Patients in the lanthanum group were required to withdraw if they experienced AEs or if the investigator decided that additional therapy was required. However, patients randomized to the standard-therapy group were permitted to change to other phosphate binders or to receive additional binders. Furthermore, the lanthanum group was subjected to a dose-titration phase, whereas the standard-therapy group was placed on previously known and likely efficacious doses of phosphate binders. Overall, 38% of patients dropped out of the study. Dropouts due to AEs were higher in the lanthanum arm (14%) than in the ‘other binder’ arm (4%). The Work Group considered that these issues could bias efficacy results in favor of the standard-therapy group, who were more likely to complete the study.

In the smallest study involving 98 patients,¹³ serum calcium, phosphorus, $\text{Ca} \times \text{P}$, and calcitriol values were similar

in both groups and did not change from baseline throughout the study. The mean serum PTH also remained constant throughout treatment in the lanthanum carbonate group, but a reduction in levels was observed in calcium carbonate-treated patients. Overall, the Work Group considered these data on biochemical markers to be of moderate quality. However, in both studies,^{13,349} there was concern with regard to the directness of PTH data for the same reasons expressed above.

4.1.6 In patients with CKD stages 3–5D, we recommend avoiding the long-term use of aluminum-containing phosphate binders and, in patients with CKD stage 5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication (1C).

The use of aluminum-containing phosphate binders has been extensively evaluated in the KDOQI Bone and Mineral Metabolism Guidelines.⁵ The major toxicities are neurotoxicity and impairment of bone mineralization, both of which can be prevented by minimizing aluminum exposure. However, the Work Group acknowledged that the literature, as detailed in the KDOQI guidelines,⁵ supports that the most severe cases of aluminum toxicity occurred in patients whose dialysate was contaminated with aluminum, and that aluminum-based binders only played a secondary role. The quantity of aluminum-based phosphate binders that is safe is unknown. Moreover, several conditions may favor intestinal aluminum absorption, such as diabetes mellitus, secondary HPT, vitamin D status, and a high citrate intake.³⁵⁰ Therefore, the Work Group felt that as numerous alternative phosphate binders have become available, and there is no ability to predict a safe aluminum dose, the long-term use of aluminum-based phosphate binders should be avoided. This was a unanimous vote.

4.1.7 In patients with CKD stages 3–5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (2D).

Only one RCT, by Russo *et al.*,²⁸⁶ (Tables 21, 22) has specifically assessed the effect of dietary phosphate restriction on CAC. However, it was not designed to show a superiority or an equivalence of dietary phosphate modification when compared with oral phosphate binders. The investigators recruited 90 phosphate-binder-naïve patients with CKD stages 3–5 who were not on dialysis. Of these patients, 30 were randomized to a low-phosphate diet alone, with the remaining 60 patients receiving the diet in combination with fixed doses of calcium carbonate (2 g/d) or sevelamer-HCl (1600 mg/d) over a 2-year follow-up period. Final CAC scores were increased in the group receiving phosphate-restricted diet alone and in the group receiving diet in combination with calcium carbonate. There was no progression of calcification in the diet-plus-sevelamer-HCl-treated group (as discussed under Rationale 4.1.5). It is noteworthy that the

prescription of phosphate restriction alone did not lead to a decrease in urinary phosphate excretion. Thus, a low-phosphate diet alone did not prevent CKD-associated progression of CAC in patients not receiving dialysis.

In the absence of other RCTs, the Work Group then searched for studies that compared diet with an active or placebo control including more than 25 patients in each arm (or less for bone biopsy studies) with a follow-up of more than 6 months. The only two studies^{351,352} that met these extended criteria evaluated biochemical data, although one also assessed bone parameters and vascular calcification.³⁵² Zeller *et al.*³⁵¹ showed that the restriction of dietary protein and phosphate intake was feasible with the maintenance of nutritional parameters in a study of 35 type I diabetes patients with nephropathy. In relation to the biochemical markers of CKD-MBD, they found a significant reduction in urinary phosphate excretion in the group assigned a protein/phosphate restriction as compared with patients receiving a control diet. They did not examine markers of bone turnover. Using bone biopsy in 16 patients with CKD stages 4–5, Lafage-Proust *et al.*³⁵³ reported that after 5 years of a very-low-protein, low-phosphorus diet (supplemented with essential amino acids and their ketoanalogues), the bone-formation rate was normal or high in 10 patients, and low in the remaining six. They did not observe any low-protein-associated malnutrition in these patients.

Thus, there are insufficient data at present to strongly endorse dietary phosphate restriction as the primary intervention for the management of CKD-MBD, especially stage 5D. It is biologically plausible that such diets are helpful in early CKD and as an adjunct to phosphate binders and dialytic removal in dialysis patients. The limited safety data suggest that dietary phosphate restriction does not compromise nutrition in a monitored setting.

4.1.8 In patients with CKD stage 5D, we suggest increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia (2C).

A narrative review of the literature addressing this issue was carried out. Although research in this area is becoming more abundant, studies are typically small in sample size and lack the rigor required to direct practice. One prospective RCT has reported the impact of alternative dialysis therapies using biochemical markers of CKD-MBD as a secondary end point.³¹⁴ In this study, Culleton *et al.*³¹⁴ (Tables 27–29) compared the effect of a nocturnal prolonged-duration HD six times weekly (26 patients) with that of standard HD given thrice weekly for 4 h each session (25 patients) in a parallel design, reporting serum calcium, phosphorus, Ca × P, and iPTH. The authors found significant decreases in serum phosphorus and iPTH in patients allocated to frequent nocturnal HD, as compared with those on standard HD treatment. Serum calcium was comparable in the two groups. The amount of oral phosphate binder needed to control

hyperphosphatemia was also reduced. These data suggest that frequent nocturnal HD can lead to an improvement in mineral metabolism (see Tables 27–29). Thus, in efforts to control hyperphosphatemia, dialysis regimens that allow an increase in phosphate removal may be an alternative in patients who cannot tolerate phosphate binders or are not willing to take sufficient amounts of them.

SPECIAL CONSIDERATIONS IN CHILDREN

Of all the available binders, only sevelamer-HCl and calcium carbonate have been examined in children, with a total of 47 children studied in two RCTs to date (see Table 20). In one study, 29 children on maintenance dialysis were assigned to either sevelamer-HCl or calcium carbonate, as well as to either calcitriol or doxercalciferol in a factorial design.¹⁷ During sevelamer-HCl treatment, levels of serum phosphorus control were similar when compared with those with calcium treatment during the 8 months of study. Serum PTH was lower in the calcium arm compared with that in the sevelamer-HCl arm. There were more episodes of hypercalcemia in the calcium arms compared with that in the sevelamer-HCl arms. There was a 31% dropout rate in this study, but among those who attended for a second biopsy at the end of the study, bone histomorphometric data did not differ between the two groups. In the other study, which had a cross-over design and involved 18 children with CKD stages 3–5 not on dialysis, there was equivalent serum phosphorus control between the groups.³⁵⁴ Given the small number of children studied, the only conclusion that can be derived from these studies is that an avoidance of hypercalcemia may be easier to achieve with the use of sevelamer-HCl. There have been no studies on the use of lanthanum carbonate in children.

ADVERSE EVENTS

Sevelamer-HCl. (Supplementary Table 18) Compared with calcium-based phosphate binders, sevelamer-HCl seems to be well tolerated. Although European patients participating in the ‘Treat to Goal’ study reported more gastrointestinal side effects with sevelamer-HCl,³⁴³ this difference was not seen in the study cohort as a whole.²⁸⁴ As mentioned above, hypercalcemia was more commonly seen in patients treated with calcium-based binders participating in ‘Treat to Goal’ study,²⁸⁴ and accounted for several of the withdrawals in the calcium-treated arm of the DCOR study.²⁶⁶ In the two studies that reported total serious AEs,^{266,284} there was no difference between calcium-based phosphate binder and sevelamer-HCl treatment. This observation is consistent with the conclusion reached by Tonelli *et al.*³⁵⁵ in a recently published systematic review of the clinical efficacy and safety of sevelamer-HCl in dialysis patients.

Lanthanum carbonate. (Supplementary Table 23) Lanthanum carbonate was shown to be generally well tolerated. The most notable difference between lanthanum carbonate and calcium carbonate was the frequency of clinically significant hypercalcemia with the use of calcium carbonate reported as an AE, as

discussed earlier. The incidence of other AEs showed no clinically important differences between lanthanum carbonate and calcium carbonate groups.^{13,348,349}

Cognitive function was assessed in the substudy by Altmann *et al.*³⁵⁶ using the Cognitive Drug Research computerized assessment system. This showed that the use of lanthanum carbonate did not adversely affect cognitive function in HD patients compared with those undergoing standard therapy. Both groups showed a similar decline in cognitive function over a 2-year time period.

The plasma and bone lanthanum levels were assessed and compared as a primary end point in the study by Spasovski *et al.*⁹⁸ Plasma lanthanum levels reached a steady state of around 0.6 ng/ml after 36 weeks of treatment. Six weeks after the cessation of 1 year of lanthanum treatment, plasma lanthanum levels had declined to a value of 0.17 ± 0.12 ng/ml ($P < 0.05$) and after 2 years to 0.09 ± 0.03 ng/ml. The mean bone lanthanum concentration in patients receiving lanthanum carbonate increased from 0.05 ± 0.03 to 2.3 ± 1.6 $\mu\text{g/g}$ ($P < 0.05$) after 1 year and slightly decreased at the end of the study to 1.9 ± 1.6 $\mu\text{g/g}$ ($P < 0.05$). The mean bone lanthanum concentration in the calcium carbonate group was 0.1 ± 0.04 $\mu\text{g/g}$ at the 1-year biopsy and 0.15 ± 0.06 $\mu\text{g/g}$ at the end of 3 years. These data, together with the bone histomorphometry findings, suggested that bone lanthanum deposition was not associated with aluminum-like toxicity.

RESEARCH RECOMMENDATIONS

Advancing the evidence base for phosphorus-lowering therapies

The Work Group considered that robust studies of a large sample size addressing the following issues should be given priority.

- Does lowering serum phosphorus with any phosphate binder improve clinical outcomes, including mortality, cardiovascular events, bone pain, or fracture in patients with CKD stages 3–5 and 5D?
- Does the use of lanthanum carbonate improve cardiovascular calcification compared with the use of calcium-based phosphate binders in patients with CKD stage 5D?
- Is slower progression of arterial calcification (as observed in association with the use of non-calcium-based

phosphate binders, such as sevelamer, in comparison with calcium-containing phosphate binders) associated with better survival?

- Can aluminum hydroxide be used safely, at least in the short term, in selected CKD stage 5D patients, provided dialysis water is free of this metal?
- Do improvements in the biochemical parameters that have been associated with alternative dialysis regimens translate into an improvement in clinical outcomes of CKD-MBD?
- Studies are needed to evaluate the clinical benefits associated with the use of dietary intervention in patients with CKD stages 3–5D and stages 1–5T.
- Studies are needed to identify the presence and degree of phosphate additives in foods and their impact on phosphate metabolism.
- More studies in children with CKD-MBD are needed, especially to evaluate cardiovascular end points.

SUPPLEMENTARY MATERIAL

Supplementary Table 14. Overview table of selected studies demonstrating the risk relationships between biochemical parameters of Ca, P, Ca \times P, and mortality in CKD stages 3–5 and 5D.

Supplementary Table 15. Summary table of RCTs examining the treatment of CKD-MBD with sevelamer-HCl vs calcium-containing phosphate binders in CKD stage 5D—description of population at baseline.

Supplementary Table 16. Summary table of RCTs examining the treatment of CKD-MBD with sevelamer-HCl vs calcium-containing phosphate binders in CKD stage 5D—intervention and results.

Supplementary Table 17. Summary table of RCTs examining the treatment of CKD-MBD with sevelamer-HCl vs calcium-containing phosphate binders in CKD stage 5D—bone biopsy results.

Supplementary Table 18. Adverse events of sevelamer-HCl vs calcium-containing phosphate binders in CKD stages 3–5 and 5D.

Supplementary Table 19. Ongoing RCTs examining the effect of phosphate binders on CKD-MBD.

Supplementary Table 20. Summary table of the treatment of CKD-MBD with lanthanum carbonate vs other phosphate binders in CKD stage 5D—description of population at baseline.

Supplementary Table 21. Summary table of the treatment of CKD-MBD with lanthanum carbonate vs other phosphate binders in CKD stage 5D—intervention and results.

Supplementary Table 22. Summary table of the treatment of CKD-MBD with lanthanum carbonate vs other phosphate binders in CKD stage 5D—bone biopsy results.

Supplementary Table 23. Adverse events of lanthanum carbonate vs other phosphate binders in CKD stage 5D.

Supplementary material is linked to the online version of the paper at <http://www.nature.com/ki>

Table 20 | RCTs of phosphate binders in children with CKD

Author (year)	N	Population	F/U	Study design	Arm 1	Arm 2	Outcomes
Salusky (2005) ¹⁷	29	PD	8 months	RCT	Sevelamer	Ca carbonate	Bone Bx, P, Ca, Ca × P, PTH, hypercalcemic episodes
Pieper (2006) ³⁵⁴	18	HD, PD, CKD stages 3–4	8 weeks	RCT, cross-over	Sevelamer	Ca acetate	P, Ca, iPTH, lipids

Bx, biopsy; Ca × P, calcium–phosphorus product; CKD, chronic kidney disease; HD, hemodialysis; iPTH, intact parathyroid hormone; PD, peritoneal dialysis; PTH, parathyroid hormone; RCT, randomized controlled trial.

Table 21 | Summary table of RCTs examining the treatment of CKD–MBD with sevelamer-HCl vs calcium-containing phosphate binders in CKD stages 3–5—description of population at baseline

Author (year)	N	Age ^a	% Race	CKD stage	% DM ^a	Baseline MBD Labs ^a	Vascular/valvular calcification by EBCT ^a
	Country of study	% Male ^a			% Prior AI exposure ^a		
Russo (2007) ²⁸⁶	90	54 (55) [54]	ND	3–4	0%	Ca 2.30 (2.25) [2.30] mmol/l P 1.45 (1.49) [1.26] mmol/l PTH 14.5 (18.2) [14.9] pmol/l ALP 134.2 (148) [113.7] mg/dl Bioactive intact-PTH (Diagnostic Products) [ref: ND]	CAC by MSCT (TCS) 415 (340) [369] % with no CAC: 19% (18%) [17%]
	Italy	89 (82) [86]			0%		

ALP, alkaline phosphatase; CAC, coronary artery calcification; CKD, chronic kidney disease; CKD–MBD, chronic kidney disease–mineral and bone disorder; DM, diabetes mellitus; EBCT, electron-beam CT; MBD, mineral bone disease; MSCT, multislice computed tomography; N, number of subjects; ND, not documented; PTH, parathyroid hormone; TCS, total calcium score.

No study reported DXA or bone histology at baseline.

^aArm 1 (Arm 2) [Arm 3].

Table 22 | Summary table of RCTs examining the treatment of CKD–MBD with sevelamer-HCl vs calcium-containing phosphate binders in CKD stages 3–5—intervention and results

Author (year)	N	Arm		Cointerventions	Outcomes	Results	Quality
		Follow-up	Arm 2				
	CKD stage	[Arm 3]				Arm 1 vs Arm 2 vs Arm 3 (P-value)	
	90	Sevelamer 1600 mg/d			<i>Vascular calcification</i> ^a Mean CAC at 12 mo Δ Mean CAC	453 vs 473 vs 547 (NS) ^b 38 vs 133 vs 178 ^c	B B
Russo (2007) ²⁸⁶	Mean 24 months	Ca carbonate: 2000 mg/d Elemental Ca: 800 mg/d		Low P diet No vitamin D or statins	<i>Laboratory</i> Mean Ca (mmol/l) Mean P (mmol/l) Mean Ca × P (mmol ² /l ²) Mean PTH (pmol/l) Mean ALP (mg/dl) Mean total cholesterol (mmol/l)	2.25 vs 2.27 vs 2.32 (ND) 1.55 vs 1.52 vs 1.26 (ND) 3.48 vs 3.25 vs 2.91 (ND) 14.3 vs 18.7 vs 15.6 (ND) 103.4 vs 143.0 vs 85.1 (ND) 4.69 vs 4.76 vs 4.88 (ND)	B B B B B B
	3–4	[Control]			Mean LDL-C (mmol/l) Mean HDL-C (mmol/l) Mean triglycerides (mmol/l) CrCl (ml/min)	2.77 vs 2.61 vs 3.05 (ND) 1.3 vs 1.2 vs 1.3 (ND) 1.49 vs 1.57 vs 1.49 (ND) 24.1 vs 25.9 vs 33.6 (ND)	B B B B

ALP, alkaline phosphatase; CAC, coronary artery calcification; Ca × P, calcium–phosphorus product; CKD, chronic kidney disease; CKD–MBD, chronic kidney disease–mineral and bone disorder; CrCl, creatinine clearance; Δ, change; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N, number of subjects; ND, not documented; NS, not significant; PTH, parathyroid hormone; RCT, randomized controlled trial.

^aPrimary outcome.

^bNo two-arm statistical comparisons provided. Within-arm changes in CAC were NS for sevelamer-HCl arm and $P < 0.001$ for Ca carbonate and control arms.

^cCalculated from pre- and post-mean values.

Table 23 | Evidence matrix for sevelamer-HCl vs calcium-containing phosphate binders in CKD stage 5D

Outcome	Methodological quality									Adverse event reporting		
	Author	N (on agent)	F/U	Author	N (on agent)	F/U	Author	N (on agent)	F/U	Author	N (on agent)	F/U
Mortality	—	—	—	Block (2007) ²⁶⁵	127 (60)	44 months median	—	—	—	Chertow (2002) ²⁸⁴	200 (99)	12 months
	—	—	—	St Peter (2008) ^{267 a}	2102 (1051)	28 months	—	—	—	Braun (2004) ³⁴³	+ ≤21 (+ ≤11 ^b)	12 months
Clinical CVD	—	—	—	—	—	—	—	—	—	—	—	—
Hospitalization	—	—	—	—	—	—	Suki (2007) ^{266 c}	2103 (1053)	20 months	Chertow (2002) ²⁸⁴ Braun (2004) ³⁴³	200 (99) + ≤21 (+ ≤11 ^b)	12 months 12 months
QoL	—	—	—	—	—	—	—	—	—	—	—	—
Fractures	—	—	—	—	—	—	—	—	—	—	—	—
PTx	—	—	—	—	—	—	—	—	—	—	—	—
Bone density	—	—	—	—	—	—	Raggi (2005) ³⁴⁶ Asmus (2005) ³⁴⁴	111 (51) + ≤21 (+ ≤11 ^b)	12 months 21 months	—	—	—
Bone histology	Ferreira (2008) ¹⁰⁴	91 (44)	13.5 months	Salusky (2005) ¹⁷	29 (15)	8 months	—	—	—	—	—	—
	Barreto (2008) ²⁸⁸	101 (41)	12 months	—	—	—	—	—	—	—	—	—
Vascular/valvular calcification	—	—	—	Qunibi (2008) ²⁸⁷	203 (103)	12 months	Asmus (2005) ³⁴⁴	+ ≤21 (+ ≤11 ^b)	21 months	—	—	—
	—	—	—	Chertow (2002) ²⁸⁴	132 (62)	12 months	Barreto (2008) ²⁸⁸	101 (41)	12 months	—	—	—
	—	—	—	Block (2005) ²⁸⁵	148 (73)	18 months	—	—	—	—	—	—
Lab: Ca, P, PTH	—	—	—	Qunibi (2008) ²⁸⁷	203 (103)	12 months	Suki (2007) ²⁶⁶	2103 (1053)	20 months	—	—	—
	—	—	—	Chertow (2002) ²⁸⁴	200 (99)	12 months	Asmus (2005) ³⁴⁴	+ ≤21 (+ ≤11 ^b)	24 months	—	—	—
	—	—	—	Block (2005) ²⁸⁵	148 (73)	18 months	Barreto (2008) ²⁸⁸	101 (41)	12 months	—	—	—
	—	—	—	Ferreira (2008) ¹⁰⁴	91 (44)	13.5 months	—	—	—	—	—	—
Lab: ALP, b-ALP	—	—	—	Qunibi (2008) ²⁸⁷	203 (103)	12 months	Raggi (2005) ³⁴⁶	111 (51)	12 months	—	—	—
	—	—	—	Ferreira (2008) ¹⁰⁴	91 (44)	13.5 months	Barreto (2008) ²⁸⁸	101 (41)	12 months	—	—	—
	—	—	—	Qunibi (2008) ²⁸⁷	203 (103)	12 months	—	—	—	—	—	—
Lab: Bicarbonate	—	—	—	Chertow (2002) ²⁸⁴	200 (99)	12 months	—	—	—	—	—	—
	—	—	—	Ferreira (2008) ¹⁰⁴	91 (44)	13.5 months	—	—	—	—	—	—
Adverse events	—	—	—	—	—	—	—	—	—	Suki (2007) ²⁶⁶	2103 (1053)	20 months
	—	—	—	—	—	—	—	—	—	Qunibi (2008) ²⁸⁷	203 (103)	12 months
	—	—	—	—	—	—	—	—	—	Chertow (2002, 2003) ^{284,357}	200 (99)	12 months
	—	—	—	—	—	—	—	—	—	Braun (2004) ³⁴³	+ ≤21 (+ ≤11 ^b)	12 months
	—	—	—	—	—	—	—	—	—	Block (2005) ²⁸⁵ Ferreira (2008) ¹⁰⁴	148 (73) 91 (44)	18 months 13.5 months

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; CKD, chronic kidney disease; CVD, cardiovascular disease; F/U, follow-up; N, number of subjects; PTH, parathyroid hormone; PTx, parathyroidectomy; QOL, quality of life.

Number randomized may be higher than number analyzed; this evidence profile does not include studies of sevelamer-HCl vs calcium-containing phosphate binders in CKD stages 3-5 (refer to summary table entry for Russo (2007)²⁸⁶) or studies in pediatric population (refer to summary table entry for Salusky (2005)¹⁷).

^aSee also report by Suki (2007)²⁶⁶

^bUnclear reporting regarding the number of individuals who received study drug.

^cSee also report by St Peter (2008).²⁶⁷

Table 24 | Evidence profile^a for the treatment of CKD-MBD with sevelamer-HCl vs calcium-containing phosphate binders in CKD stage 5D

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies	Consistency across studies	Directness of the evidence (generalizability/ applicability)	Other considerations ^b	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	2 RCTs	2230 (1126)	Serious limitations (–1) ^c	Important inconsistencies ^d (–1)	Direct	—	Low	No difference in one moderate quality study in prevalent HD patients. Borderline statistically significant benefit for sevelamer-HCl in one moderate quality study in incident HD patients	Critical
	AE from 1+ RCTs ^e	221 (99+?)	Very serious limitations (–2)	—	—	—			
Clinical CVD and CeVD	—	—	—	—	—	—	—	—	Critical
All-cause hospitalization	1 RCT	2103 (1053)	Very serious limitations (–2) ^f	NA	Direct	—	Low	Trend to lower all-cause hospitalization in one low-quality study	High
	AE from 1+ RCTs ^e	221 (99+?)	Very serious limitations (–2)	—	—	—			
Quality of life	—	—	—	—	—	—	—	—	High
Fractures	—	—	—	—	—	—	—	—	High
PTx	—	—	—	—	—	—	—	—	High
X-ray bone assessment	1+ RCTs ^e	111+? (51+?)	Very serious limitation (–2) ^g	NA	Major uncertainty (–2) ^h	Sparse (–1)	Very Low	Unable to assess	Moderate
Bone histology	2 RCTs	192 (85)	No limitations	NA	Direct	Sparse (–1)	Moderate	Overall not much difference between groups	Moderate
Vascular/valvular calcification	4+ RCTs ^e	673 (316 +?)	Serious limitations (–1) ⁱ	Important inconsistencies ^j (–1)	Direct	—	Low	Trend toward less progression with sevelamer, but inconsistency regarding statistical significance and size of difference assessed with different metrics at different time points and at different sites	Moderate
<i>Laboratory measurements</i>									
Calcium	—	—	Serious limitations (–1) ^k	No important inconsistencies	Direct	—	Moderate	Higher with calcium	—
Phosphorus	—	—	Serious limitations (–1) ^k	No important inconsistencies	Direct	—	Moderate	No consistent difference	—
Ca × P	6+ RCTs ^e	2867 (1413+?)	Serious limitations (–1) ^k	No important inconsistencies	Direct	—	Moderate	No consistent difference	Moderate
PTH	—	—	Serious limitations (–1) ^k	No important inconsistencies	Direct ^l	—	Moderate	Lower with calcium	—
ALP, b-ALP	4 RCTs	595 (287)	Serious limitations (–1) ^m	NA	Direct	Sparse (–1)	Low	Unable to assess	—
Bicarbonate	3 RCTs	494 (246)	Serious limitations (–1) ^m	NA	Direct	Sparse (–1)	Low	Lower with sevelamer	—
Adverse events	6+ RCTs ^e	2867 (1413+?)	—	—	—	—	—	Inconsistent trend in GI and CVD events when using sevelamer-HCl vs Ca-containing P binders. More hypercalcemia with Ca-containing P binders	Depends on outcome

Balance of potential benefits and harm:

Sevelamer-HCl is as effective as calcium-based binders in terms of target-driven attainment of biochemical values. There is a trend towards slower progression of vascular calcification (sevelamer-HCl vs calcium-containing phosphate binders); there is no robust statistically significant difference for mortality or hospitalizations

Quality of overall evidence:

Moderate for biochemical outcomes
Low to very low for other surrogate outcomes
Low for patient-centered outcomes

Table 24 | Continued

AE, adverse event; ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; Ca × P, calcium-phosphorus product; CeVD, cerebrovascular disease; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; CVD, cardiovascular disease; GI, gastrointestinal, HD, hemodialysis; N, number of subjects; NA, not applicable; PTH, parathyroid hormone; PTx, parathyroidectomy; RCT, randomized controlled trial.

? Unclear number of patients studied for outcome.

^aThis evidence profile does not include studies of sevelamer-HCl vs calcium-containing phosphate binders in CKD stages 3-5 (refer to summary table entry for Russo (2007)²⁸⁶) or studies in pediatric population (refer to summary table entry for Salusky (2005)¹⁷).

^bOther considerations include imprecise or sparse data (-1), high probability of reporting bias (-1). For observational studies, other considerations include strong association (+1 or +2), dose-response gradient (+1), and all plausible confounders would have reduced the effect (+1).

^c2 grade B.

^dOne study showed a trend toward benefit in terms of all-cause mortality, whereas the other showed not statistically significant difference.

^eBraun (2004)³⁴³ and Asmus (2005)³⁴⁴ have considerable patient overlap (N=93 out of 114) with Chertow (2002)²⁸⁴ and Raggi (2005)³⁴⁶ respectively.

^fOne grade C, inconsistency for statistical significance for all-cause hospitalization between reports for same study (Suki (2007)²⁶⁶, St Peter (2008)²⁶⁷).

^gOne plus grade C.

^hNonvalidated method.

ⁱThree grade B, one grade C.

^jHeterogeneity in the study designs.

^kFour grade B, two grade C.

^lHowever, limited certainty about the directness of PTH due to bias in PTH assays, and biological variability of PTH values and effect of different PTH fragments.

^mTwo grade B, two grade C.

Table 25 | Evidence matrix for lanthanum carbonate vs other phosphate binders in CKD stage 5D

Outcome	Methodological quality									Adverse events (no grade)		
	A			B			C			Author	N	F/U
	Author	N (on agent)	F/U	Author	N (on agent)	F/U	Author	N (on agent)	F/U			
Mortality	—	—	—	—	—	—	—	—	—	Finn (2006) ³⁴⁹	1359 (682)	24 months
										Malluche (2008) ¹⁰³	211 (51)	24 months
										Spasovski (2006) ⁹⁸	24 (12)	12 months
Clinical CVD and CeVD	—	—	—	—	—	—	—	—	—	—	—	—
All-cause hospitalization	—	—	—	—	—	—	—	—	—	—	—	—
QoL	—	—	—	—	—	—	—	—	—	—	—	—
Fractures	—	—	—	—	—	—	—	—	—	—	—	—
PTx	—	—	—	—	—	—	—	—	—	—	—	—
Bone density	—	—	—	—	—	—	—	—	—	—	—	—
Bone histology	—	—	—	Malluche (2008) ¹⁰³	211 (51)	24 months	—	—	—	—	—	—
				Freemont (2005) ¹³	63 (30)	12 months	—	—	—	—	—	—
				Spasovski (2006) ⁹⁸	24 (12)	12 months	—	—	—	—	—	—
Vascular/valvular calcification	—	—	—	—	—	—	—	—	—	—	—	—
Lab: Ca, P, PTH	—	—	—	Freemont (2005) ¹³	98 (49)	12 months	Finn (2006) ³⁴⁹	1359 (682)	24 months	—	—	—
				Malluche (2008) ¹⁰³	211 (51)	24 months	—	—	—	—	—	—
Lab: ALP, b-ALP	—	—	—	Malluche (2008) ¹⁰³	211 (51)	24 months	Finn (2006) ³⁴⁹	1359 (682)	24 months	—	—	—
Lab: Bicarbonate	—	—	—	—	—	—	Finn (2006) ³⁴⁹	1359 (682)	24 months	—	—	—
Adverse events										Finn (2006) ³⁴⁹	1359 (682)	24 months
										Hutchison (2005) ³⁴⁸	800 (533)	6 months
										Malluche (2008) ¹⁰³	211 (51)	24 months
										Freemont (2005) ¹³	98 (49)	12 months
										Spasovski (2006) ⁹⁸	24 (12)	12 months

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; CeVD, cerebrovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; F/U, follow-up; N, number of subjects; PTH, parathyroid hormone; PTx, parathyroidectomy; QoL, quality of life.
N analyzed may be less than N randomized.

Table 26 | Evidence profile of lanthanum carbonate vs other phosphate binders in CKD stages 5D

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations ^a	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	— AE from 2 RCTs	— 1383 (694)	— Very serious limitations (−2)	—	—	—	Very low	Unable to assess	Critical
Clinical CVD and CeVD	—	—	—	—	—	—	—	—	Critical
All-cause hospitalization	—	—	—	—	—	—	—	—	High
Quality of life	—	—	—	—	—	—	—	—	High
Fractures	—	—	—	—	—	—	—	—	High
PTx	—	—	—	—	—	—	—	—	High
Bone density	—	—	—	—	—	—	—	—	Moderate
Bone histology	3 RCTs	333 (63)	Serious limitations (−1) ^b	No major inconsistencies	Direct	—	Moderate	Lanthanum biopsies showed overall better turnover with no differences in mineralization, and possible higher volume	Moderate
Vascular/valvular calcification	—	—	—	—	—	—	—	—	Moderate
<i>Laboratory measurements</i>									
Calcium	3 RCTs	1668 (782)	Very serious limitations (−2) ^c	No major inconsistencies	Direct	—	Low	Tendency toward lower Ca and lower rates for hypercalemic episodes	
Phosphorus	3 RCTs	1668 (782)	Very serious limitations (−2) ^c	No major inconsistencies	Direct	—	Low	Similar P control	
Ca × P	1 RCT	98 (49)	Very serious limitations (−2) ^d	NA	Direct	Sparse	Very low	Tendency toward higher Ca × P	Moderate
PTH	3 RCTs	1668 (782)	Very serious limitations (−2) ^c	No major inconsistencies	Direct ^e	—	Low	Tendency toward higher PTH	
ALP, b-ALP	2 RCT	1570 (733)	Very serious limitations (−2) ^f	NA	Direct	—	Low	Tendency toward higher b-ALP	
Bicarbonate	1 RCT	1359 (682)	Very serious limitations (−2) ^g	NA	Direct	—	Low	No difference in bicarbonate	
Adverse events	5 RCTs	2492 (1327)						One study showed no worse decline in cognitive function with lanthanum. Bone and plasma lanthanum levels were higher in lanthanum groups	Depends on outcome

Balance of potential benefits and harm:

No evidence of benefit or harm on clinical and calcification outcomes. Uncertain effect on bone laboratory outcomes. Bone histology was improved more often in lanthanum group but formal statistical comparisons were not done.

Quality of overall evidence:

Low for biochemical outcomes
Moderate for other surrogate outcomes
Very Low for patient-centered outcomes

AE, adverse event; ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; Ca × P, calcium-phosphorus product; CeVD, cerebrovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; N, number of subjects; NA, not applicable; PTH, parathyroid hormone; PTx, parathyroidectomy; RCT, randomized controlled trial.

^aOther considerations include imprecise or sparse data (−1), high probability of reporting bias (−1). For observational studies, other considerations include strong association (+1 or +2), dose-response gradient (+1), all plausible confounders would have reduced the effect (+1).

^bThree grade B.

^cTwo grade B and one grade C in studies not designed for comparative efficacy.

^dOne grade B in study not designed for comparative efficacy.

^eHowever, limited certainty about the directness of PTH due to bias in PTH assays, and biological variability of PTH values and effect of different PTH fragments.

^fOne grade B and one grade C.

^gOne grade C.

Table 27 | Summary table of RCT examining alternate HD regimens in CKD stage 5D—description of population at baseline

Author (year)	<u>N</u>	<u>Age^a</u>	% Race ^a	<u>Dialysis vintage^a</u>	<u>% DM^a</u>	Baseline MBD Labs ^a	Bone evaluation	Vascular/valvular calcification imaging
	Country of study	% Male ^a		Dialysate calcium ^a	% HD modality ^a			
Culleton (2007) ³¹⁴	52	55 (53)	White: 88 (84)	66 (58) months	38 (44)	Ca 2.37 mmol/l (2.27) P 1.78 mmol/l (1.58) Ca × P 4.18 mmol ² /l ² (3.62)	None	None
	Canada	69 (56)		Adjusted between 1.00 and 1.75 mmol/l	In-center: 69 (52) Home: 23 (28) Self-care: 8 (20)	Assay ND b-ALP ND		

b-ALP, bone-specific alkaline phosphatase; Ca × P, calcium-phosphorus product; CKD, chronic kidney disease; DM, diabetes mellitus; HD, hemodialysis; MBD, mineral bone disease; N, number of subjects; ND, not documented; PTH, parathyroid hormone; RCT, randomized controlled trial.

^aOverall or Arm 1 (Arm 2).

Table 28 | Summary table of RCT examining alternate HD regimens in CKD stage 5D—intervention and results

Author (year)	<u>N</u>	<u>Arm 1</u>	Cointerventions	Outcomes	Results Arm 1 vs Arm 2 (P-value)	Quality
	Follow-up	Arm 2				
Culleton (2007) ³¹⁴	52	Nocturnal HD 6 × /week	Dialysate calcium was adjusted between 1.00 and 1.75 mmol/l depending on serum Ca level	^a ΔLV mass	Not in the realm of the guideline	—
	6 months	Conventional HD 3 × /week		HRQOL	−8.9 vs +1.6 (0.05)	B
	HD			ΔiPTH	−0.02 vs −0.05 (NS)	A
				ΔCa	−0.36 vs +0.13 (<0.05)	A
				ΔP	−0.9 vs +0.19 (<0.05)	A
				ΔCa × P	73% vs 12% (<0.001)	B
				% Reduction or D/C of phosphate binders		

Ca × P, calcium-phosphorus product; CKD, chronic kidney disease; Δ, change; D/C, discontinued; HD, hemodialysis; HRQOL, health-related quality of life; iPTH, intact parathyroid hormone; LV, left ventricular; N, number of subjects; NS, not significant; RCT, randomized controlled trial.

^aPrimary outcome.

Table 29 | Adverse events of alternate HD regimens in CKD stage 5D

Author (year)	Follow-up	<u>Arm 1</u>	Hospitalizations Mean no. per Pt	D/C	Vascular access complications ^a % Pts	D/C	Other reported AE % Pts	Total D/C due to AE	Deaths	Modality change	
		Arm 2									
Culleton (2007) ³¹⁴	6 months	Nocturnal	0.62	0%	38	0%	None	—	0%	4%	8%
		Conventional	0.84	0%	32	0%	None	—	0%	0%	0%

AE, adverse event; CKD, chronic kidney disease; D/C, discontinued; HD, hemodialysis; N, number of subjects; pts, patients.

'—' indicates data not documented.

^aVascular access complications include bacteremia, insertion or replacement of tunneled dialysis catheter, vascular access angiogram, and vascular access surgical intervention (including percutaneous angioplasty or arterial or venous stenosis).

Chapter 4.2: Treatment of abnormal PTH levels in CKD–MBD

Grade for strength of recommendation ^a	Strength	Wording	Grade for quality of evidence	Quality of evidence
Level 1	Strong	'We recommend...should'	A	High
Level 2	Weak	'We suggest...might'	B	Moderate
			C	Low
			D	Very low

^aIn addition the Work Group could also make ungraded statements (see Chapter 2 section on ungraded statements).

INTRODUCTION

Patients with CKD and HPT may develop abnormalities of all components of CKD–MBD. Bone effects include an increased bone turnover that may be associated with marrow fibrosis and abnormal mineralization, described as osteitis fibrosa and mixed uremic osteodystrophy. Patient-level consequences may include increased bone and muscle pain, weakness, postural instability, and fracture, whereas marrow fibrosis may exacerbate the anemia of CKD. Severe HPT may lead to pruritus, worsening of residual kidney function caused by hypercalcemia, calciphylaxis, CVD, neuromuscular disturbances, and death. Over the years, approaches to the management of secondary HPT have included using oral calcium salts and increasing dialysate calcium levels to raise serum calcium levels, the prescription of vitamin D, calcitriol or its analogs, parathyroidectomy, and—more recently—the use of calcimimetics, alone or in combination with other drugs. However, some patients with CKD have PTH levels that are inappropriately suppressed, leading to a low bone turnover or adynamic bone disease, conditions that may be exacerbated by the measures listed above.

RECOMMENDATIONS

4.2.1 In patients with CKD stages 3–5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH (iPTH) above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency (2C).

It is reasonable to correct these abnormalities with any or all of the following: reducing dietary phosphate intake and administering phosphate binders, calcium supplements, and/or native vitamin D (not graded).

4.2.2 In patients with CKD stages 3–5 not on dialysis, in whom serum PTH is progressively rising and remains persistently above the upper limit of normal

for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs (2C).

4.2.3 In patients with CKD stage 5D, we suggest maintaining iPTH levels in the range of approximately two to nine times the upper normal limit for the assay (2C).

We suggest that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range (2C).

4.2.4 In patients with CKD stage 5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH (2B).

- It is reasonable that the initial drug selection for the treatment of elevated PTH be based on serum calcium and phosphorus levels and other aspects of CKD–MBD (not graded).
- It is reasonable that calcium or non-calcium-based phosphate binder dosage be adjusted so that treatments to control PTH do not compromise levels of phosphorus and calcium (not graded).
- We recommend that, in patients with hypercalcemia, calcitriol or another vitamin D sterol be reduced or stopped (1B).
- We suggest that, in patients with hyperphosphatemia, calcitriol or another vitamin D sterol be reduced or stopped (2D).
- We suggest that, in patients with hypocalcemia, calcimimetics be reduced or stopped depending on severity, concomitant medications, and clinical signs and symptoms (2D).
- We suggest that, if the intact PTH levels fall below two times the upper limit of normal for the assay, calcitriol, vitamin D analogs, and/or calcimimetics be reduced or stopped (2C).

4.2.5 In patients with CKD stages 3–5D with severe hyperparathyroidism (HPT) who fail to respond to medical/pharmacological therapy, we suggest parathyroidectomy (2B).

Summary of rationale for recommendations

- CKD may lead to a rise in the circulating PTH level, which is a component of CKD–MBD. Lowering serum PTH has been a primary focus of therapy for over 30 years.
- Severe HPT is associated with morbidity and mortality in patients with CKD stages 3–5D. Observational studies consistently report an increased RR of death in CKD stage 5D patients who have PTH values at the extremes (less than two or greater than nine times the upper normal limit of the assay).
- Once developed, severe HPT may be resistant to medical/pharmacological therapy and may persist after transplantation. Thus, progressive increases of PTH should be avoided.
- However, there is difficulty in establishing narrow target ranges for serum iPTH because of the following reasons:
 - Cross-sectional studies in the CKD population show that the median iPTH increases and the range widens with progressive CKD.
 - There are methodological problems with regard to the measurement of PTH, because assays differ in their measurement of accumulating PTH fragments and there is interassay variability (see Chapter 3.1).
 - With a progressive deterioration of kidney function, bone becomes increasingly resistant to the actions of PTH.
 - The predictive value of PTH for underlying bone histology is poor when PTH values are between approximately two and nine times the upper normal laboratory range.
- In RCTs of patients with CKD stages 3–4, calcitriol and vitamin D analogs each lower levels of serum PTH compared with placebo.
- In RCTs of patients with CKD stage 5D, calcitriol, vitamin D analogs, and calcimimetics each lower levels of serum PTH compared with placebo.
- In CKD stages 3–5D, calcitriol and vitamin D analogs may increase serum calcium and phosphorus levels compared with placebo.
- Laboratory-based experimental data show differences in the efficacy and adverse effects of calcitriol and vitamin D analogs, but an analysis of the limited comparative studies in humans fails to show consistent differences.
- In studies of patients with CKD stage 5D, calcimimetics may lower serum calcium and phosphorus levels compared with placebo.
- There are no comparative RCTs that evaluate the use of calcitriol or vitamin D analogs compared with calcimimetics alone.
- There is a lack of RCT data in patients with CKD stages 3–5D that directly shows that the change in PTH with vitamin D (cholecalciferol and ergocalciferol), calcidiol, calcitriol, vitamin D analogs, or cinacalcet leads to improved clinical outcomes or adequately describes potential harm.
- Therefore, these recommendations remain weak.

BACKGROUND

Secondary HPT is a common complication of CKD that, before currently available medical and surgical therapies, resulted in considerable morbidity and mortality, including crippling bone disease. Recently, many observational studies have reported associations between levels of serum PTH, calcium and/or phosphorus and the RR of cardiovascular and all-cause mortality. Experimental and clinical data support the hypothesis that abnormalities of mineral metabolism constitute important ‘nontraditional’ cardiovascular risk factors. Over the past few years, recommended target ranges have been promoted for serum calcium, phosphorus, and PTH, and an increasing number of therapies are available that assist in achieving these targets. Traditionally, these have included calcium salts, calcitriol, and alfacalcidol. More recently, active vitamin D analogs, cinacalcet hydrochloride, and non-calcium- or aluminum-based phosphate binders have become available. Surgical parathyroidectomy remains a definitive therapy.

Vitamin D

The nomenclature for vitamin D has become unnecessarily complicated over the last several years, although the terms are well defined in chemical and endocrinology literature. The term vitamin D represents both vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol). Ergocalciferol is synthesized in plants and yeasts after an ultraviolet radiation-catalyzed conversion of its precursor, ergosterol, and, together with some cholecalciferol from oily fish, is a dietary source of vitamin D in humans. However, over 90% of human vitamin D requirements come from exposure of the skin to ultraviolet-B solar radiation. Sunlight converts 7-dehydrocholesterol to previtamin D₃, which undergoes a rapid, temperature-dependent isomerization to vitamin D₃ or cholecalciferol. Both vitamin D₂ and D₃ are hydroxylated in the liver to metabolites specified as 25-hydroxyergocalciferol (ercalcidiol), 25-hydroxycholecalciferol (calcidiol), or commonly without specificity as 25-hydroxyvitamin D (25(OH)D). Further, 1- α -hydroxylation occurs mainly in the kidney and also at extrarenal sites. The most active, naturally occurring vitamin D derivative in man is calcitriol (1,25-dihydroxycholecalciferol; commonly abbreviated as 1,25(OH)₂D₃).

The therapeutic forms of vitamin D sterols available for use in patients with CKD include naturally occurring ergocalciferol, cholecalciferol, 25(OH)D, and calcitriol. Synthetic vitamin D₂ analogs include paricalcitol and

doxercalciferol, and synthetic vitamin D₃ analogs include alfalcidol, falecalcitriol, and 22-oxacalcitriol (maxacalcitol). Doxercalciferol and alfalcidol, which are 1- α vitamin D derivatives, require 25-hydroxylation by the liver for activity and are commonly referred to as 'prodrugs.'

VITAMIN D NOMENCLATURE: For the purposes of common nomenclature, the KDIGO Work Group recommended utilization of the following terms and abbreviations in this Guideline (see also Chapter 3.1):

Vitamin D to represent cholecalciferol and/or ergocalciferol.

25-Hydroxyvitamin D to represent the 25-hydroxylated metabolites of vitamin D, also known as ercalcidiol or calcidiol; abbreviated as 25(OH)D.

Calcitriol to represent 1,25-dihydroxycholecalciferol; abbreviated as 1,25(OH)₂D₃.

Vitamin D analogs to represent derivatives of vitamin D₂ and vitamin D₃, of which the clinically investigated synthetic derivatives include doxercalciferol, paricalcitol, alfalcidol, falecalcitriol, and 22-oxacalcitriol (maxacalcitol).

Vitamin D has an established role in mineral homeostasis and musculoskeletal function and is recognized to have pleiotropic extraskelatal effects, including modulation of endothelial and immune function, inflammatory responses, and cell cycle regulation. The rate of calcitriol production and inactivation is tightly regulated. In the setting of normal kidney function, a reduction in the levels of calcitriol is sensed by parathyroid gland vitamin D receptors, with a consequent increase in the production and release of PTH. Increased PTH levels increase the activity of renal 1- α -hydroxylase and the conversion of 25(OH)D to calcitriol, which suppresses PTH to its former level. In addition to a transient rise in levels of PTH, this feedback loop may result in a reduction in the levels of serum 25(OH)D. In the presence of CKD, most patients have reduced circulating levels of calcitriol. Initially, this is related to reduced phosphate excretion and a rise in the levels of serum phosphate and fibroblast growth factor-23, both of which suppress renal 1- α -hydroxylase activity. Lower calcitriol levels (and reduced intestinal calcium uptake) facilitate a rise in PTH production, and for a time, this restores levels of serum calcitriol, increases renal phosphate excretion, and improves renal calcium conservation. However, despite increasing circulating levels of PTH, these homeostatic mechanisms inevitably fail if CKD progresses and the number of functioning nephrons decline.

Vitamin D, calcitriol, and vitamin D analogs are used in CKD stages 3–5 and CKD stage 5D to improve abnormal mineral homeostasis and to reduce the risk of secondary HPT developing and progressing. An evaluation of this therapy has generally focused on maintaining levels of serum PTH and calcium within predetermined 'target' ranges, or gauged by bone histomorphometry. A number of preclinical (animal) studies have shown differences in PTH suppression, gastrointestinal calcium absorption, incidence of hypercalcemia and hyperphosphatemia, vascular calcification, and bone histology between calcitriol and some synthetic vitamin D

analogs.^{299,358–362} However, the evaluation of these drugs in patients with CKD has only rarely shown similar clear-cut differences. It is well known that, in humans, such a demonstration is inherently difficult, particularly when drugs such as calcium-based phosphate binders are used concomitantly.

The use of cholecalciferol and ergocalciferol has received relatively little attention because of an earlier, widely held view that the kidneys were the only sites of 1- α -hydroxylation of calcidiol and that, in the presence of kidney failure, serum 25(OH)D levels were of less significance. On the other hand, recent data suggest a potential role for 25(OH)D in a number of tissues, independent of renal conversion.^{363–366} In patients with CKD, levels of serum 25(OH)D are commonly insufficient or deficient.^{48,180} Thus, consideration may need to be given to both the management of endocrine (PTH lowering and calcium increasing) and autocrine (local inflammation and cell cycle regulation) effects of vitamin D and calcitriol and its analogs.

Calcimimetics

Physiological studies in animals and humans in the 1980s showed that there was a rapid release of PTH in response to small reductions in serum-ionized calcium,³⁶⁷ lending support to the existence of a calcium sensor in parathyroid glands. This CaR was cloned in 1993,³⁶⁸ leading to a revolutionary understanding of the mechanisms by which cells adjust to changes in extracellular calcium. It is now known that the CaR is expressed in many organs controlling calcium homeostasis, including parathyroids, thyroid C cells, intestine, kidneys, and other tissues. In parathyroids, an activation of CaR stimulates cell-signaling pathways to mobilize intracellular calcium and decreases PTH secretion, whereas an inactivation reduces intracellular calcium and increases PTH secretion.

Calcimimetics are a group of drugs that are allosteric modulators of CaR, augmenting the signal caused by the binding of extracellular ionized calcium to CaR to increase intracellular calcium and decrease PTH release.³⁶⁹ Thus, these drugs 'mimic' an increase in levels of extracellular calcium. Cinacalcet, the only clinically available calcimimetic agent, does not enhance intestinal calcium and phosphorus absorption, and this action differentiates it from vitamin D sterols and their analogs in that it can lower PTH without an increase in circulating levels of calcium and phosphate.

The following tables are found at the end of this chapter: **Table 30** summarizes the RCTs of calcitriol or vitamin D analogs in children with CKD. The evidence matrix, a table that describes the methodologic quality of the included studies, and the evidence profile, a table that provides an overall assessment of the quality of the evidence and balance of potential benefits and harm are **Tables 31, 32** (CKD stages 3–5) for calcitriol or vitamin D analogs compared to placebos; **Tables 33, 34** (CKD stage 5D) for calcitriol compared to vitamin D analogs; and **Tables 35, 36** (CKD stage 5D) for calcimimetics. Additional detailed information

about the studies of vitamin D, calcitriol and its analogs reviewed in this chapter are further described in detail in the *Supplementary Tables 24–38*.

RATIONALE

4.2.1 In patients with CKD stages 3–5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH (iPTH) above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency (2C).

It is reasonable to correct these abnormalities with any or all of the following: reducing dietary phosphate intake and administering phosphate binders, calcium supplements, and/or native vitamin D (not graded).

In patients with CKD stages 3–5, the optimal level of PTH is unknown. There are no strong associative data sets to link elevated PTH to patient-centered outcomes and, unfortunately, at this time, no RCTs have assessed the balance between therapeutic risk and benefit when modest PTH rises are suppressed in patients with CKD stages 3–5. Furthermore, in earlier stages of CKD, secondary HPT with modest increases in levels of PTH represents an appropriate adaptive response to declining kidney function that maintains phosphate, calcitriol, and calcium homeostasis. It is not yet clear how to differentiate an appropriate response from a maladaptive response, but it is likely that future studies evaluating urinary phosphate excretion or fibroblast growth factor-23 levels early in the course of CKD will clarify this issue. In addition, it is possible that a patient whose PTH level is always low is quite different from a patient who has a history of a sustained elevation in PTH and has the level lowered to the same value. Thus, prevention and treatment may not require similar approaches. When patients have very high PTH levels, it is more difficult to lower those levels because of marked parathyroid gland hyperplasia and possible clonal parathyroid cell proliferation, with a reduced or absent ability of the gland to involute.³⁷⁰

Given this lack of data, yet a desire for guidance in the management of patients with CKD stages 3–5, the Work Group felt that continuous increases in PTH over time likely represent a maladaptive response, and it is the persistent rise that should prompt therapy more than an absolute value. In addition, because modest increases in PTH may represent adaptations to a number of underlying factors in patients with CKD stages 3–5, it is appropriate to consider all modifiable factors that may have led to secondary HPT, in addition to the loss of GFR.

Calcium

Both historical use and experimental data support the efficacy of calcium supplementation in lowering PTH, but these findings are not supported by RCTs in patients with CKD stages 3–5 that fulfill our criteria for inclusion

into evidence tables. In the absence of such RCTs, it is unknown if benefits outweigh the possible harm associated with calcium overload and AEs of hypercalcemia. In a secondary analysis of one RCT designed to assess the effect of calcium supplementation or placebo on bone density and fracture in postmenopausal women without CKD, a trend was reported toward an increased risk for myocardial infarction and a composite end point of myocardial infarction, stroke, or sudden death in the calcium-treated group.³⁷¹ However, this finding is controversial; investigators in the much larger Women's Health Initiative did not detect an association between supplementation with calcium/vitamin D and myocardial infarction, coronary heart disease, or stroke.³⁷² Russo *et al.*²⁸⁶ examined the effects of calcium supplementation on serum iPTH in patients with CKD stages 3–5. The administered daily dose was 2 g of calcium carbonate over a time period of 2 years. Serum iPTH levels did not change in response to this treatment (172 vs 176 pg/ml or 18.2 vs 18.7 pmol/l), whereas the GFR remained remarkably stable over the same time period. However, there was an increase in coronary calcification scores (see Chapter 4.1).

Thus, although historically calcium is efficacious in lowering PTH in patients with CKD stages 3–5, it is important to realize that the potential harm has not been adequately evaluated.

Hyperphosphatemia

There are no RCTs in patients with CKD stages 3–5 that specifically evaluate the effect of phosphate binders and lowering of serum phosphorus on PTH that fulfilled our inclusion criteria. However, a recent 8-week RCT in patients with CKD stages 3–4 with hyperphosphatemia found a decrease in PTH in lanthanum-treated patients compared with those with placebo.³⁷³ In addition, secondary HPT is known to be a compensatory response to phosphate retention, hence this approach has theoretical efficacy.

Low serum 25(OH)D levels

Vitamin D insufficiency and deficiency occur commonly in the general population and in patients with CKD. A recent *post hoc* analysis of the Vitamin D, Calcium, Lyon Study II was conducted by Kooienga *et al.*³⁷⁴ (*Supplementary Tables 25–26*). This study assessed the impact of treatment with cholecalciferol 800 IU plus calcium 1200 mg daily vs placebo on biochemical parameters in 610 elderly French women, of whom 322 had estimated glomerular filtration rate (eGFR) values < 60 ml/min per 1.73 m², using the MDRD formula. Similar improvements in the proportion of individuals achieving 25(OH)D levels > 30 ng/ml (75 nmol/l) at 6 months were seen in all kidney function groups. The proportion of individuals with a ≥ 30% reduction in iPTH at 6 months was 50% in all eGFR groups receiving treatment with cholecalciferol plus calcium compared with 6–9% for those on placebo (*P* < 0.001 for all). However, this study was unable to distinguish between the effects of calcium and vitamin D, because the treatments were given in combination and the results may not be applicable to other demographic groups. In patients

with CKD stages 3 and 4 with 25(OH)D levels < 30 ng/ml (75 nmol/l) and elevated levels of PTH, an observational treatment study using ergocalciferol reported a normalization of the mean 25(OH)D levels in both CKD stages.³⁷⁵ A significant reduction in the median levels of PTH was seen in patients with CKD stage 3, with a trend toward reduced median PTH levels in CKD stage 4.³⁷⁵

4.2.2 In patients with CKD stages 3–5 not on dialysis, in whom serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs (2C).

Calcitriol or its analogs

Four RCTs were identified that assessed patients with CKD stages 3–5 and met inclusion criteria (Tables 31, 32; Supplementary Tables 25–26). These trials compared the use of doxercalciferol, paricalcitol, alfacalcidol, or calcitriol with placebo. The study evaluating doxercalciferol included 55 patients³⁷⁶ and the study evaluating paricalcitol included 220 patients.³⁷⁷ Both assessed laboratory biochemical end points. African-Americans contributed toward one-quarter to one-half of study participants, with the remainder predominantly Caucasians. The study using alfacalcidol included 176 patients⁹⁷ and the study using calcitriol included 30 patients.¹⁰² Both assessed laboratory values and bone histomorphometry. These latter studies were from 1995 and 1998, respectively, which creates problems of interpretation because of changing patient demographics and altered clinical practices. Many patients in these studies were treated with aluminum-based phosphate binders, and the racial distribution of participants in the European studies was not provided. These studies will be discussed with respect to their end points.

- a) **Patient-centered end points:** For CKD stages 3–5, data on mortality were available from safety analyses of two studies,^{97,377} on clinical CVD and cerebrovascular disease from one study,³⁷⁶ and on other clinical outcomes from three studies^{97,102,376} (see Evidence Profile for stages CKD 3–5, Table 32). However, because these data were based on safety and toxicity rather than on end points identified *a priori*, the information suffered from serious methodological limitations such that treatment effects could not be assessed for these outcomes. Data were absent for hospitalization, fracture, parathyroidectomy, quality-of-life measures, and for changes in BMD.
- b) **Vascular calcification:** No study has evaluated the role of calcitriol or its analogs or of cinacalcet on vascular calcification in CKD stages 3–5.
- c) **Bone histomorphometry:** Three studies evaluated the effect of calcitriol or its analogs on bone histology

in CKD stages 3–5: (Tables 31, 32 and Supplementary Table 27)

Nordal and Dahl¹⁰²: In this study published in 1988, 30 patients had bone biopsies at baseline and 28 patients had bone biopsies after 8 months of treatment with calcitriol or placebo. **Turnover:** The mean bone-formation rate decreased significantly in the calcitriol group and increased in the placebo group, with a significant difference between treatment groups. Approximately 25% of the calcitriol-treated patients had low bone formation (adynamic bone disease) at the end of the study. The eroded surfaces showed a similar pattern, so that calcitriol treatment decreased bone turnover. Fibrosis disappeared in all but four of the biopsies in the calcitriol group, but in none of those taking placebo. **Mineralization:** Median mineralization, assessed by MLT, was similar and normal in both groups and did not change with either therapy. **Volume:** Median bone volume was normal in both groups and there was no significant change with either therapy. Overall, calcitriol treatment was effective in treating osteitis fibrosa. The report was limited because adynamic bone disease was not discussed. Approximately 25% of calcitriol-treated patients developed low bone formation after therapy, but none of them had osteomalacia. However, the exact number was not reported.

Hamdy et al.⁹⁷: In this study published in 1995, bone biopsies were performed in 176 patients at baseline and in 134 patients after treatment with alfacalcidol or placebo. The biopsies were initially placed into diagnostic categories, but later some of the abnormalities were felt to be unimportant. The criteria for ‘important’ abnormalities were not specified. The measurements were analyzed separately in those patients with unimportant abnormalities at baseline; this was therefore a *post hoc* subgroup analysis. The paper did not report the changes in measurements according to the entire group of placebo vs the entire group of alfacalcidol-treated patients. There was also an apparent error in the mineralization lag-time calculation in the placebo group. Although detailed measurements were made in a large number of biopsies, the presentation does not allow a critical evaluation of the results. **Turnover:** The following percentages were deduced from the results section: for patients treated with alfacalcidol, biopsies improved in 32% (improved osteitis fibrosa) and worsened (developed adynamic disease) in 11%. Placebo biopsies improved in 3% and worsened in 13% (6% developed adynamic disease and the rest developed worsened osteitis fibrosis). **Mineralization:** MLT and osteoid width improved in the alfacalcidol group. There was an increase (worsening) in the osteoid width in some of the placebo-treated patients. **Volume:** The mean bone volume did not change significantly in any of the groups. Overall, the alfacalcidol treatment resulted in bone histological improvement (related to improvement in osteitis fibrosa and mineralization) more often than did the placebo treatment. However, adynamic bone disease developed more frequently.

Birkenhäger-Frenkel et al.³⁷⁸: This study examined the effect of 24,25(OH)₂D in subjects who were already taking

alfacalcidol. The study met our inclusion criteria, but 24,25(OH)₂D is not commercially available so we have not included this in our evidence tables. Interpretation of the biopsy data was limited because the final biopsies were taken close to the site of a biopsy performed 9 months earlier, which alters the results. Also, the treatment group had a significantly different prior response to alfacalcidol so the groups were not comparable at the beginning of the study.

d) Biochemical end points: For patients with CKD stages 3–5, studies using doxercalciferol,³⁷⁶ paricalcitol,³⁷⁷ and alfacalcidol⁹⁷ (as compared with placebo) assessed laboratory biochemical outcomes. The doxercalciferol study was a 24-week-duration, double-blind, intention-to-treat analysis with a <20% loss to follow-up. In the paricalcitol and alfacalcidol studies, premature patient withdrawal averaged 20–22%. Alfacalcidol doses were adjusted to maintain calcium levels at the upper limit of the laboratory reference range. Compared with placebo, PTH levels fell significantly with these active treatments. Only one study of patients with CKD stages 3–5 was included that compared calcitriol with placebo.¹⁰² Over 8 months, the levels of PTH fell significantly in the calcitriol arm compared with the baseline values and the end-of-study placebo values. However, this study enrolled only 15 individuals in each arm and, although it was included in this guideline because of the bone biopsy data, it did not achieve entry criteria for biochemical outcomes.

In studies of patients with CKD stages 3–4, calcium levels trended upward for paricalcitol and doxercalciferol,^{376,377} whereas calcium levels increased significantly for alfacalcidol.⁹⁷ Phosphate levels and the calcium phosphorus product significantly increased for doxercalciferol, with an upward trend for paricalcitol and alfacalcidol.

In CKD stages 3–4, levels of bone-specific ALP (b-ALP) were assessed in two studies,^{376,377} and fell significantly with doxercalciferol compared with placebo (28% for doxercalciferol with no outcome value provided for the placebo arm; $P < 0.05$) and with paricalcitol vs placebo ($P < 0.001$). Total ALP levels were assessed in the alfacalcidol study⁹⁷ and fell significantly in the active treatment arm ($P < 0.001$).

ADVERSE EVENTS (Supplementary Table 28)

For paricalcitol vs placebo, the percentage of patients reported with hypercalcemia (> 2.62 mmol/l) over two consecutive measurements was 2 vs 0%, respectively, and the incidence of hyperphosphatemia was reported to be similar between groups.³⁷⁷ Twelve percent of paricalcitol-treated patients and 6% of placebo-treated patients had two consecutive measurements of $\text{Ca} \times \text{P} > 4.44$ mmol²/l². For doxercalciferol vs placebo, neither hypercalcemia (defined as > 2.67 mmol/l and reported in 4% of both active- and

placebo-treated groups) nor hyperphosphatemia differed significantly between active and placebo arms.³⁷⁶ For doxercalciferol, serum phosphorus levels > 5.0 mg/dl (1.61 mmol/l) and > 6.0 mg/dl (1.94 mmol/l) occurred in 8.5 and 2.6% of patients, respectively, vs 6.5 and 0.5%, respectively, for those in the placebo-treated group, this difference being nonsignificant. Nevertheless, at 24 weeks, serum phosphorus levels were higher in the doxercalciferol group, as were levels of $\text{Ca} \times \text{P}$. Levels of serum calcium were not significantly different. One patient in the doxercalciferol arm had treatment suspended twice because of hypercalcemia; one had a suppression of serum iPTH to < 150 pg/ml (15.9 pmol/l) at week 24; and doxercalciferol treatment was reduced in three patients because of low levels of iPTH. In the alfacalcidol vs placebo study from 1995, hypercalcemia (> 10.5 mg/dl or 2.62 mmol/l) occurred in 14% of alfacalcidol-treated patients vs 3% of placebo-treated patients ($0.05 < P < 0.01$ between groups),⁹⁷ and in the calcitriol vs placebo study from 1998, eight calcitriol-treated patients developed hypercalcemia (undefined) vs zero placebo-treated patients.¹⁰² Study discontinuation due to AEs ranged from 0 to 12%, with no patient reported to have discontinued treatment because of abnormal laboratory results. When reported, the incidence of other AEs was high for both active treatment and placebo arms.

Calcimimetics

Only one RCT which assessed the effect of the calcimimetic cinacalcet treatment in patients with CKD not receiving dialysis met our inclusion criteria.³⁷⁹ This study assessed biochemical outcomes and AEs. It was not designed to assess effects on vascular calcification, bone histomorphometry, or other clinical outcomes. Patients meeting entry criteria with CKD stage 3 were enrolled, if iPTH levels were ≥ 100 pg/ml (10.6 pmol/l) and patients with CKD stage 4 were enrolled if iPTH levels were ≥ 160 pg/ml (16.8 pmol/l). The study, conducted over 32 weeks with a 16-week dose titration and a 16-week drug efficacy phase, allowed the concomitant use of vitamin D sterols and/or calcium supplementation. Compared with placebo, cinacalcet reduced plasma iPTH (43 vs 1%), but at the price of frequent, generally asymptomatic decreases in serum calcium (two consecutive values < 8.4 mg/dl (2.1 mmol/l) in 62% of participants taking cinacalcet) and increases in levels of serum phosphorus and 24-h urinary calcium excretion. More patients taking cinacalcet than placebo received vitamin D sterols (46 vs 25%). The proportion of participants receiving phosphate binders/calcium supplements increased from 19 to 58% for those taking cinacalcet and from 18 to 20% for those taking placebo. In CKD stages 3 and 4, the effect on bone turnover of this reduction in PTH is unknown, as is the change in urinary calcium. The long-term impact of increased levels of serum phosphorus combined with increased calcium supplementation is of concern, and thus the Work Group felt more data were needed before suggesting that calcimimetics could be used in CKD stages 3–5.

4.2.3 In patients with CKD stage 5D, we suggest maintaining iPTH levels in the range of approximately two to nine times the upper normal limit for the assay (2C).

We suggest that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range (2C).

The target PTH in the KDOQI guidelines for CKD stage 5D was based on the predictive ability of PTH, using a Nichols iPTH assay, to predict low- and high-turnover bone disease.⁵ Unfortunately, that assay is no longer available, and recent studies have shown that iPTH levels within a range of 150–300 pg/ml (15.9–31.8 pmol/l) are not predictive of underlying bone histology (see Chapter 3.2)²²⁹ or fractures (Figure 15).

Thus, additional evidence in the form of observational data determining associations between PTH and patient-level end points (mortality, cardiovascular death, and fractures) was evaluated by the Work Group (*Supplementary Table 24*). However, an important caveat is that conclusions based on these reports are limited, because of residual confounding and artificial constraints induced by statistical modeling. Some studies find a ‘U’-shaped association with increased risk at both ends,³²⁸ although more current international analyses (DOPPS) often find only an increased RR of all-cause but not cardiovascular mortality when the PTH is >600 pg/ml (63.6 pmol/l).³³ The inflection point or range at which PTH becomes significantly associated with

increased all-cause mortality varies among studies for the reasons cited above, and ranges from >400 pg/ml (42.4 pmol/l)³²⁸ to >480 pg/ml (50.9 pmol/l),³²⁹ >500 pg/ml (53 pmol/l),³³⁰ >511 pg/ml (54.2 pmol/l),³¹⁷ and >600 pg/ml (>63.6 pmol/l).²⁰⁵ All PTH analyses have been complicated by problems with assay methods and poor precision, as detailed in Chapter 3.1. Unfortunately, most of these analyses either do not indicate the assay type, or the data come from PTH measured with multiple assays. Another confounding factor for these analyses is that many studies feature single-baseline PTH values or infrequent (quarterly or less) measurements. One report has suggested that the 1–84 PTH ‘bio-intact’ or ‘whole’ assay is a better predictor of mortality than so-called iPTH assays.³⁰ However, this finding needs to be confirmed. Therefore, the Work Group does not recommend the routine use of 1–84 (‘bio-intact’ or ‘whole’) PTH assays at present. On the basis of these observational data, the Work Group considered that levels of iPTH less than two or greater than nine times the upper limit of normal for the PTH assay used represent extreme ranges of risk.

It is important to recognize that there are no RCTs showing that treatment to achieve a specific PTH level results in improved outcomes. In addition, there are no interventional RCTs that establish a ‘cause and effect’ relationship between the observed outcomes and the measured biochemical variables; the observational data cannot fully evaluate benefits and harm and are inherently biased. The analysis of such relationships is further complicated by the clinical ‘reality’ that these laboratory parameters do not move in isolation from one another, but rather change in often unpredictable ways depending on the levels of other parameters. This is best demonstrated by the work of Stevens *et al.*,³⁸⁰ which assessed various biochemical combinations in concert with dialysis vintage and found that specific risks varied significantly according to three-pronged constellations. Thus, the RR for mortality was greatest when levels of serum calcium and phosphorus were elevated in conjunction with low levels of iPTH, and was lowest with normal levels of serum calcium and phosphorus in combination with high levels of iPTH. In addition, duration of dialysis significantly affected the results. A DOPPS study also evaluated combinations of serum parameters of mineral metabolism and reached slightly different conclusions.³³ For example, in the setting of an elevated serum PTH (>300 pg/ml (31.8 pmol/l)), hypercalcemia (>10 mg/dl (2.5 mmol/l)) was associated with increased mortality risk even with normal serum phosphorus levels (Figure 16).

Thus, future studies aimed at risk-stratifying patients with CKD should look at combinations of various biochemical abnormalities, rather than isolated parameters. At present, the Work Group felt that clinicians should avoid extreme ranges of PTH, and interpret changes in PTH together with calcium and phosphorus levels to guide therapy. Serum PTH, calcium, and phosphorus are all expected to change with PTH-altering treatments. As extreme values of these

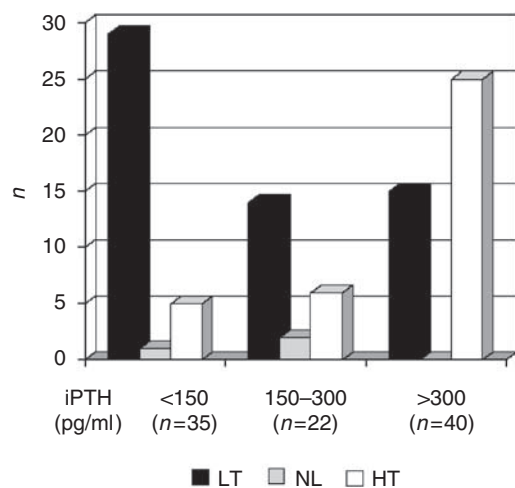


Figure 15 | Comparison of PTH levels to underlying bone histology in chronic hemodialysis patients. Intact PTH levels <150 pg/ml presented a 50% sensitivity, an 85% specificity, and an 83% positive predictive value for the diagnosis of low bone turnover (LT). In contrast, iPTH levels >300 pg/ml presented a 69% sensitivity, a 75% specificity, and a 62% positive predictive value for the diagnosis of high bone turnover (HT). iPTH, intact parathyroid hormone; n, number of patients; NL, normal bone turnover. Reprinted with permission from Barreto *et al.*²²⁹

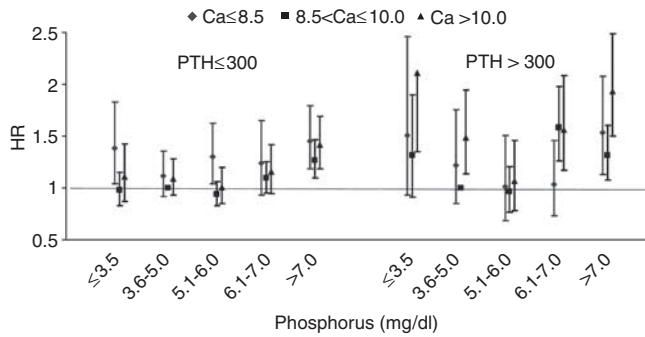


Figure 16 | Risk of all-cause mortality associated with combinations of baseline serum phosphorus and calcium categories by PTH level. HR, hazard ratio; PTH, parathyroid hormone. Reprinted with permission from Tentori *et al.*³³

biochemical parameters have been linked to adverse patient outcomes in large observational studies, it is important to monitor serum levels of calcium and phosphorus during PTH-altering treatments more frequently.

4.2.4 In patients with CKD stage 5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH (2B).

- It is reasonable that the initial drug selection for the treatment of elevated PTH be based on serum calcium and phosphorus levels and other aspects of CKD-MBD (not graded).
- It is reasonable that calcium or non-calcium-based phosphate binder dosage be adjusted so that treatments to control PTH do not compromise levels of phosphorus and calcium (not graded).
- We recommend that, in patients with hypercalcemia, calcitriol or another vitamin D sterol be reduced or stopped (1B).
- We suggest that, in patients with hyperphosphatemia, calcitriol or another vitamin D sterol be reduced or stopped (2D).
- We suggest that, in patients with hypocalcemia, calcimimetics be reduced or stopped depending on severity, concomitant medications, and clinical signs and symptoms (2D).
- We suggest that, if the intact PTH levels fall below two times the upper limit of normal for the assay, calcitriol, vitamin D analogs, and/or calcimimetics be reduced or stopped (2C).

The Work Group asked if there were differences between the various therapies used to lower PTH in their effects on biochemical indices of CKD-MBD, bone, vascular calcification, or clinical end points. A systematic search was undertaken to evaluate RCTs of vitamin D, calcitriol, or any vitamin D analog vs each other or with placebo in individuals with CKD stage 5D. The *a priori* criteria chosen

by the Work Group for inclusion of an RCT were duration of at least 6 months and a sample size of at least 50, except for bone biopsy studies and studies evaluating children, which were included with a sample size of 10. Importantly, our recommendations parallel recent Cochrane reviews, which were inclusive of all studies and found similar results for calcitriol and its analogs⁸ and for calcimimetics.³⁸¹ Studies evaluated with the KDIGO systematic review are reviewed below by end point (see Tables 33–36).

a) **Patient-centered end points:** No RCTs of patients with CKD have specifically evaluated the effect of vitamin D, calcitriol, or vitamin D analogs on patient-level outcomes (mortality, fracture, quality of life, hospital admission, and cardiovascular outcomes), and observational data are inconclusive.

There are no studies of either moderate or high quality that show a beneficial or harmful effect of calcimimetics on mortality, CVD, hospitalization, fractures, or quality of life.

Vitamin D, calcitriol, or its analogs. (Tables 34, 35) Patients with all stages of CKD, particularly those on dialysis, have greatly increased mortality and morbidity compared with the general population. Patient-level outcomes of vitamin D therapy that were considered to be of critical or high importance included mortality, cardiovascular events, rates of hospital admission, parathyroidectomy, fracture, musculoskeletal pain, and quality of life. No RCT evaluated mortality, cardiovascular events, hospitalizations, quality of life, or fracture as a primary or secondary end point.

Although the effects of vitamin D therapy on mortality have not been studied in prospective RCTs, recent retrospective observational studies have suggested that survival on dialysis may be improved by vitamin D therapy.^{45,328,382,383} Furthermore, in the large historical cohort study that compared treatment with the vitamin D₂ derivative, paricalcitol, with calcitriol, treatment with the former was reported to provide a survival advantage over the latter.³⁸⁴ However, this finding was not confirmed (after adjustment for laboratory values and clinical standardized mortality) in another report that also assessed the vitamin D₂ derivative, doxercalciferol,³⁸³ or in a more recent DOPPS analysis.³⁸⁵ In addition, in the latter analysis, no relationship was detected between the use of vitamin D and outcome using an instrumental-variable approach. However, using a patient-level approach, there was an apparent survival benefit for vitamin D usage, as previously reported, suggesting a significant degree of residual confounding. Therefore, evidence from these observational studies could not be used in the development of this guideline when applying the Grades of Recommendation Assessment, Development, and Evaluation approach (GRADE), which requires consistent evidence of an association with an RR > 2 (or an HR < 0.5) from two or more observational studies, with no plausible

confounders. None of these studies achieved an RR > 2 (or an HR < 0.5). Furthermore, authors of these studies pointed to a number of potential confounders and, importantly, there is inconsistency in findings among the published studies. Thus, RCTs are needed to confirm these findings.

Calcimimetics. All-cause hospitalization, quality of life, fractures, and parathyroidectomy were defined as outcomes of high importance and were evaluated in a secondary analysis³⁸⁶ of prospective RCTs^{387,388} that evaluated cinacalcet vs placebo (with the majority of both groups receiving calcitriol or an analog). This analysis reported no statistically significant differences in mortality or all-cause hospitalizations, but a reduction in cardiovascular hospitalization. No differences in quality of life were detected using the Cognitive Functioning scale from the Kidney Disease Quality of Life instrument, but improvements were seen in some domains using the Medical Outcomes Study Short Form 36 (SF-36). The number of fractures and parathyroidectomies in cinacalcet-treated patients was significantly reduced compared with that in those receiving placebo. However, data were sparse for fracture and, although the RR for parathyroidectomy was 0.07 (95% CI 0.01–0.55), there was no description of the indications or protocol for parathyroidectomy, hence the overall quality for both these outcomes was classified as very low.

For all of these clinical outcomes, there were serious methodological limitations, because they were not predefined as either primary or secondary outcomes for RCTs and were taken from the safety data of prospective trials, creating a probable reporting bias. Furthermore, the length of the follow-up varied among patients and, at most, 266 had a 1-year follow-up from the total of 1184, with some having only a 6-month follow-up. More of the control patients agreed to follow-up (138 placebo vs 128 cinacalcet), although a much higher number were randomized to cinacalcet. In addition, quality of life was measured at variable points during the study, but the results were evaluated together, and only 876 out of 1184 individuals had their quality of life data evaluated. In both the Block *et al.*³⁸⁷ and Lindberg *et al.*³⁸⁸ studies, the percentage of dropouts was high, and it was not clear whether those who dropped out when their PTH was < 250 pg/ml (26.5 pmol/l) were counted as successes or failures. The overall quality of evidence for mortality, hospitalization, and quality of life was thus deemed low.

b) Vascular calcification: There are no conclusions as to the effect of calcitriol or vitamin D analogs or calcimimetics on cardiovascular calcification, as these relationships have not been adequately evaluated in humans.

Only one RCT of calcitriol that met our inclusion criteria evaluated any measure of cardiovascular calcification.¹⁰¹ In that study of calcitriol vs placebo, plain X-rays of the hands, chest, pelvis, and feet were assessed. No differences were reported for the development or progression of CAC or for the calcification of the vessels of the hands, feet, or pelvis.

However, vascular calcification was only evaluated in patients without radiological evidence of bone disease, and this number was not provided, creating a potential bias. Furthermore, aluminum hydroxide was used for phosphate control, the dialysate calcium level was 1.65 mmol/l (3.3 mEq/l), and hypercalcemia was common. There are no studies evaluating the effect of cinacalcet on vascular calcification in humans. Thus, the Work Group felt these data were insufficient to reach any conclusions.

c) Bone histology: On the basis of bone biopsy studies, the use of calcitriol or vitamin D analogs is associated with an improvement of osteitis fibrosa and mineralization, and a reduction of bone turnover. The latter may increase the risk of developing adynamic bone disease.

There are insufficient data to determine the effect of cinacalcet on bone histomorphometry.

Calcitriol and its analogs. (Supplementary Table 32) Two studies evaluated patients with CKD stage 5D, one in adults and one in children.

Baker et al.¹⁰¹: Bone biopsies were taken from 54 patients at baseline and from 20 patients after 12–57 months of follow-up; the results were published in 1986. The bone biopsies were separated into categories of normal, osteomalacia, osteitis fibrosa, and mixed osteodystrophy on the basis of a visual assessment by the investigator. No tetracycline labels were given; therefore, some of the patients who were designated as normal could have had adynamic bone disease. The majority of the patients had positive aluminum staining. **Turnover:** None of the follow-up biopsies showed an improvement in turnover as indicated by a change to the normal category. Bone turnover became too high (normal to osteitis fibrosa or mixed) in 50% of patients taking placebo and in 10% of those taking calcitriol, and too low (normal to osteomalacia) in 30% of the calcitriol group. Thus, turnover worsened in 50% of the placebo and in 40% of the calcitriol-treated individuals. **Mineralization:** It worsened (normal to osteomalacia or mixed) in 40% of placebo-treated patients and in 30% of calcitriol-treated patients. **Volume:** No data were provided. Overall, calcitriol may have retarded the development of osteitis fibrosa, but it may have contributed to low bone turnover.

Salusky et al.¹⁸: This clinical trial included 46 children undergoing PD. They were randomly assigned to oral or intraperitoneal calcitriol for 12 months. The group receiving intraperitoneal dosing had lower PTH values, but the bone biopsy data were not significantly different between groups. **Turnover:** Improvement was seen in 23% of oral and in 36% of intraperitoneal treatment groups (all from improved osteitis fibrosa), but a worsening of turnover was seen in 41% of those receiving oral treatment and in 44% of those given intraperitoneal treatment (mostly development of adynamic bone disease). **Mineralization:** This parameter improved in 6% of the oral treatment group. **Volume:** No changes were reported. Overall, there were no significantly

different bone biopsy findings between these two different routes of administration.

Calcimimetics. (Supplementary Table 36) There is only one RCT on the effect of cinacalcet vs standard treatment on bone histomorphometry in patients with CKD stage 5D, using repeat bone biopsies at time zero and 12 months.³⁸⁹ Patients receiving HD who had HPT, defined by serum iPTH > 300 pg/ml (31.8 pmol/l), were randomly given cinacalcet or placebo for a year. Tetracycline-labeled bone biopsies were performed before and after therapy in 13 placebo and in 19 cinacalcet patients. Although all had a high serum PTH, five patients did not have an increased bone turnover at baseline. **Turnover:** In placebo biopsies, 45% showed an improved turnover (one patient increased from adynamic to normal and the rest decreased toward normal) and 23% showed an increased (worsened) turnover. In cinacalcet biopsies, 26% showed a decreasing (improved) turnover and 26% showed a worsened turnover (three patients developed adynamic bone disease and, in two patients, an abnormally high turnover became higher). **Mineralization:** None of the patients had overt osteomalacia, and the change in median MLT was the same in placebo and cinacalcet groups. Some of the biopsies had an abnormally high MLT, but details were not presented. **Bone volume:** It increased slightly but not significantly in the cinacalcet group, and did not change in the placebo group. Overall, there were no significant differences between groups on the basis of histomorphometry. The study was limited by a small sample size.

d) Biochemical end points: The use of calcitriol or vitamin D analogs is effective in decreasing serum PTH levels and ALP levels, but may increase calcium and phosphorus levels.

The use of cinacalcet lowers serum PTH, calcium, phosphorus, the calcium phosphorus product, and b-ALP in patients with CKD stage 5D.

Vitamin D. Despite potential theoretical benefits, data are lacking in CKD stage 5D patients to support treatment to increase levels of 25(OH)D in patients on dialysis. No RCTs of treatment with cholecalciferol or ergocalciferol were identified, but one uncontrolled study reported biochemical responses to 6 months of treatment with oral 25(OH)D₃ given to patients on HD.³⁹⁰ In that study, levels of b-ALP improved toward the normal range over 6 months and levels of PTH, calcium, and phosphorus improved toward the KDOQI target ranges in some patients. AEs, such as hyperphosphatemia, were infrequent.

Calcitriol and its analogs

PTH suppression: (Tables 34 and 35) In patients with CKD stage 5D, PTH levels were effectively suppressed by calcitriol compared with placebo in a study by Baker *et al.*¹⁰¹ conducted from 1977 to 1982.¹⁰¹ The placebo arm of that study had a higher median PTH level at baseline. (Supplementary Tables 30, 31) Levels of calcium increased for calcitriol

compared with placebo. In another study of calcitriol compared with maxacalcitol (available in Japan), within-arm PTH levels fell significantly in both groups.³⁹¹ In that study, doses of calcitriol and maxacalcitol were reduced or ceased if levels of calcium were >2.87 mmol/l or levels of iPTH were <15.9 pmol/l. Within-arm calcium levels rose significantly and there was a trend toward increased phosphate levels, which did not differ between the arms. An average of 20% of patients withdrew from this study, which was not powered adequately to show differences between the treatment groups. Sprague *et al.*³⁹² studied CKD stage 5D patients randomized in 1995–1996 to calcitriol and paricalcitol, using a 1:4 dosing ratio of calcitriol to paricalcitol. Doses were titrated at 4-week intervals to achieve a 50% or more reduction in levels of PTH, with doses modified when calcium levels exceeded 2.87 mmol/l, Ca × P exceeded 6.05 mmol²/l² for 2 weeks, or levels of PTH were <10.6 pmol/l. PTH levels fell significantly in both arms, and approximately 60% of patients in both groups achieved a ≥50% reduction in levels of PTH at the end of the study period. Hypercalcemia occurred at least once in 68% of calcitriol-treated patients and in 83% of paricalcitol-treated patients (a nonsignificant difference), and hyperphosphatemic episodes were reported to be comparable. In a secondary analysis of this study, patients treated with paricalcitol showed more rapid reductions of PTH with fewer sustained episodes of hypercalcemia and/or an elevation of Ca × P (18 vs 38%, *P* = 0.008). This composite outcome was defined as two consecutive measurements of corrected total calcium >11.5 mg/dl (2.87 mmol/l) and/or Ca × P > 75 mg²/dl² (6.05 mmol²/l²) for at least one period of four consecutive blood draws. The authors point out that lower doses of paricalcitol (using a 1:3 ratio) may have increased the time taken by paricalcitol to lower levels of PTH but decreased the incidence of hypercalcemia and hyperphosphatemia in paricalcitol-treated subjects.

Calcium: Support for the use of newer vitamin D analogs (22-oxacalcitriol, doxercalciferol, paricalcitol, and falecalcitriol) is based on experimental studies showing a similar or superior dose-equivalent suppression of PTH with less calcemic and/or phosphatemic activity.³⁹³ Therefore, the included RCTs were assessed for these end points. For calcitriol vs 22-oxacalcitriol (maxacalcitol),³⁹¹ there were no significant between-arm differences in any laboratory biochemical parameter, although initially, calcium levels rose more rapidly in response to therapy with maxacalcitol. Outcomes of the earlier (1995–1996) study of calcitriol vs paricalcitol have been described above.³⁹²

Alkaline phosphatases: For CKD stage 5D, median total ALP values were lower for calcitriol than for placebo,¹⁰¹ and b-ALP values did not differ between treatments with calcitriol and maxacalcitol.³⁹¹ Similar findings were reported in a recent meta-analysis that assessed responses to vitamin D compounds in CKD using more liberal inclusion criteria.⁸ This review also found no differences in levels of total ALP for intravenous (i.v.) vs oral vitamin D therapy (four studies) or for intermittent vs daily therapy (two studies).

Route of administration: Another question is the relative efficacy of the administration of i.v. compared with oral calcitriol or its analogs. Owing to a lack of comparative data in the included studies, no conclusions could be reached for preferred routes of administration or for dosing frequency. A meta-analysis of vitamin D therapy that included additional studies has reported that i.v. administration of vitamin D was superior to oral administration in reducing end-of-treatment PTH levels.⁸ However, there was significant heterogeneity in this analysis, and when one study that used higher i.v. doses of vitamin D was removed,³⁹⁴ there were no differences in the levels of PTH. Levels of serum phosphorus were marginally but significantly lower for the i.v. route (weighted mean difference -0.10 mmol; CI -0.19 to -0.01) with no differences in episodes of hypercalcemia or in levels of ALP. No differences were observed for daily compared with less-frequent intermittent administration.

Calcimimetics. A change in PTH was deemed as a moderately important outcome at the outset of the review (Tables 35, 36 and Supplementary Tables 34, 35). The primary outcome in the RCTs conducted by Block *et al.*³⁸⁷ and Lindberg *et al.*³⁸⁸ was the percentage of patients with iPTH ≤ 26.5 pmol/l. In both studies, significantly more patients achieved this outcome with cinacalcet (43% in Block's study and 39% in Lindberg's). The percentage of patients with a $\geq 30\%$ reduction in iPTH was also significantly higher for cinacalcet. The methodological quality of these studies was graded B because of the relatively short duration of follow-up (26 weeks), the relatively high percentage of patients who dropped out before the evaluation time point (26–32% in cinacalcet-treated subjects vs 22–24% in the control arm), and because of concerns with regard to the generalizability of the studies to patient care because the assay for PTH (the primary measured end point) suffers from methodological problems, including reproducibility (see Chapter 3.1). In addition, one study³⁹⁵ was not analyzed on an intention-to-treat basis, the outcome definitions were shifted compared with the parent protocol, and one of the three studies differed with respect to the inclusion criteria governing the percentage of individuals with very high baseline levels of PTH. Both Block's and Lindberg's studies^{387,388} showed that cinacalcet significantly reduced the mean percentage of serum calcium, phosphorus, and $\text{Ca} \times \text{P}$, which were secondary outcomes of both, with no major inconsistencies. The study by Moe *et al.*³⁹⁵ showed that significantly more patients achieved the KDOQI targets when given cinacalcet than when they underwent the optimal standard treatment. The methodological quality for these end points was graded B because of the dropout rate and the other outcomes reported in the paragraph on PTH above. The quality of evidence for these moderately important outcomes was moderate overall. The study by Block *et al.*³⁸⁷ reported a lowering of the circulating levels of b-ALP (a bone turnover marker) toward normal in the cinacalcet compared with the control arms. No ALP data (total or bone specific) were provided in other studies.

The ACHIEVE study assessed the use of cinacalcet plus paricalcitol/doxercalciferol vs flexible vitamin D analog

therapy,³⁹⁶ although this study did not fulfill our inclusion criteria in terms of duration. The proportion of patients reaching the KDOQI targets for PTH and $\text{Ca} \times \text{P}$ was higher with the combined therapy (21 vs 14%), although this did not reach significance. Of those using cinacalcet plus vitamin D analogs, 19% had iPTH levels < 150 pg/ml and only 8% achieved all KDOQI targets for calcium, phosphorus, PTH, and $\text{Ca} \times \text{P}$ compared with 0% using flexible vitamin D analog treatment. No other RCTs comparing calcitriol or vitamin D analogs with calcimimetics, nor comparing different combinations of therapy, are available. Thus, the Work Group could not recommend one therapy, or combination therapy, over another.

Integrating therapies that alter PTH and phosphorus levels. Therapeutic interventions to suppress PTH, but which may compromise levels of calcium and phosphorus, may not be beneficial. Therefore, the use of phosphate binders is an important component of any integrated approach to PTH control, because a dose modification of binders can ameliorate unwanted changes in levels of calcium and phosphorus caused by calcitriol, vitamin D analogs, and calcimimetics. In addition, phosphate binders affect levels of iPTH independently. Calcium-based binders increase serum calcium, which suppresses PTH through the CaR, whereas a reduction in serum phosphorus by calcium- or non-calcium-based binders reduces PTH production at the posttranscriptional level.

SPECIAL CONSIDERATIONS IN CHILDREN

Calcitriol has been studied in RCTs in 102 children with CKD stage 5D and in some children with earlier stages of CKD (Table 30). Only one study was placebo controlled (Greenbaum, $n = 42$),³⁹⁷ whereas the others compared varying dosages (daily vs twice weekly; oral vs i.v.). In 46 patients on PD studied for 1 year, equivalent calcitriol doses were given either i.v. or orally thrice weekly. The groups showed a similar improvement in histomorphometric changes of secondary HPT at follow-up bone biopsy and adynamic bone disease developed in both groups. Intravenously administered calcitriol reduced iPTH levels significantly and raised calcium levels, whereas orally administered calcitriol did not lead to a reduction in the levels of iPTH (values remaining above KDOQI suggested target levels), but increased serum phosphorus. In a 12-week study, calcitriol therapy led to a $> 30\%$ decrease in iPTH when compared with placebo, and in 24 patients studied for 1 year, daily calcitriol was superior to twice weekly calcitriol for the control of secondary HPT. Another study of paricalcitol compared with placebo in 29 children on maintenance HD showed a $> 30\%$ reduction in iPTH over a 12-week period. There are insufficient data to recommend one vitamin D sterol over another. In addition, there are no studies evaluating calcimimetics in children.

ADVERSE EVENTS

Calcitriol and its analogs. (Supplementary Table 28) For the study comparing calcitriol and placebo, 16% of patients

treated with calcitriol and 5% treated with placebo discontinued treatment because of hypercalcemia.¹⁰¹ Parathyroidectomy rates were 13% for calcitriol (five patients with parathyroid hyperplasia) and 5% for placebo (one patient with a parathyroid adenoma and one with hyperplasia). For maxacalcitol vs calcitriol, calcium levels >11.5 mg/dl (2.87 mmol/l) occurred in 5 vs 2%, respectively (two measurements in two patients vs two measurements in one patient), and phosphorus levels >6.1 mg/dl (1.94 mmol/l) occurred in 68 vs 64%,³⁹¹ but no patient discontinued treatment because of adverse effects of therapy. For paricalcitol vs calcitriol, calcium levels >11.5 mg/dl (2.87 mmol/l) and/or a $\text{Ca} \times \text{P} > 6.05$ mmol²/l² occurred in 68% of paricalcitol- and 64% of calcitriol-treated patients.³⁹²

Calcimimetics. (Supplementary Table 37) Nausea and vomiting are the most frequently reported AEs in studies by Block *et al.*,³⁸⁷ Lindberg *et al.*,³⁸⁸ and Moe *et al.*³⁹⁵ In the cinacalcet-treated group, nausea occurred consistently, approximately one-and-a-half times more frequently, and vomiting occurred about twice as often. Serious AEs that may or may not have been treatment related occurred in about a quarter of patients in both the treatment and placebo groups in Lindberg's study. Approximately twice as many patients in the cinacalcet group, in both Block's (15%) and Lindberg's (9%) studies, discontinued treatment because of side effects, principally nausea, vomiting, and other gastrointestinal events. In both Block's and Lindberg's studies, 5% of patients in the cinacalcet groups and less than 1% of those in the control groups had serum calcium values that fell below 7.5 mg/dl (1.9 mmol/l). Hypocalcemic episodes were transient and rarely associated with symptoms. In a safety and efficacy 26- to 52-week extension study reported by Sterrett *et al.*,¹⁵ treatment with cinacalcet was considered to be safe and effective. AEs (principally nausea and vomiting) caused the discontinuation of therapy in 10% of those treated with cinacalcet and in 0% of controls, whereas 3% of controls withdrew for parathyroidectomy but none treated with cinacalcet. At 12 months, there was no difference in the use of vitamin D (64 vs 63%: cinacalcet vs placebo) or phosphate binders (92 vs 96%), and elemental calcium ingested per meal did not differ between the groups (930 ± 641 vs 940 ± 625 mg).

4.2.5 In patients with CKD stages 3–5D with severe hyperparathyroidism (HPT) who fail to respond to medical/pharmacological therapy, we suggest parathyroidectomy (2B).

There are no studies evaluating parathyroidectomy of either moderate or high quality that show a beneficial or harmful effect of this treatment on mortality, CVD, hospitalization, fractures, or quality of life; on bone and cardiovascular outcome; or on biochemical outcomes. However, parathyroidectomy performed by an expert surgeon generally results in a marked, sustained reduction in levels of serum PTH, calcium, and phosphorus. Subtotal parathyroidectomy or total parathyroidectomy with autotransplantation effec-

tively reduces elevated levels of iPTH, calcium, phosphorus, and ALP. An improvement in these biochemical parameters is reported to be maintained at 1, 2, and up to 5 years postoperatively, despite a relatively high incidence of recurrent HPT or persisting hypoparathyroidism in some studies.^{401–404} There is no evidence that total parathyroidectomy with immediate ectopic parathyroid tissue reimplantation is superior or inferior to subtotal parathyroidectomy. Total parathyroidectomy without immediate parathyroid tissue reimplantation may be contraindicated in patients with CKD stage 5D on a waiting list for kidney transplantation.

Most patients who undergo parathyroidectomy exhibit an improvement in biochemical parameters, but comparisons between medical and surgical therapy for outcomes of morbidity and mortality are difficult to assess. In the absence of RCTs, the available observational studies that compare surgically and medically managed patients are open to important patient selection biases that limit the validity of their findings. Individuals considered for parathyroidectomy differ from those who enrolled in cinacalcet studies. The study with the largest sample size is that of Kestenbaum *et al.*,⁴⁰⁵ showing lower long-term mortality in patients who underwent parathyroidectomy compared with a matched cohort. However, this is a retrospective, observational study. Short-term, postoperative mortality was high at 3.1% and the better long-term outcome after parathyroidectomy may be due to selection bias, as in the study by Trombetti *et al.*⁴⁰⁶ In that study, patients undergoing parathyroidectomy were younger and had fewer comorbidities. However, when the authors proceeded toward a case-control analysis, this difference was no longer significant.

Owing to a lack of RCTs of medical vs surgical therapy of HPT, these management strategies are difficult to compare. For patients unsuitable for surgery or awaiting elective surgery, a case can be made for the availability of medical therapies, including cinacalcet. For patients able to undergo surgery, parathyroidectomy is generally considered when HPT is severe and refractory to medical management, usually after a therapeutic trial of calcitriol, a vitamin D analog, or cinacalcet as suggested above.

Parathyroidectomy could also be considered when medical management to reduce levels of iPTH results in unacceptable rises in levels of serum calcium and/or phosphorus (as occurs frequently using calcitriol or vitamin D analogs), or when medical management is not tolerated because of AEs. Determining what constitutes 'refractory HPT' may be difficult. Clearly, the higher the PTH, the less likely the gland is to involute in response to medical therapy. When severe HPT is present, with levels of PTH >800 pg/ml (85 pmol/l) using a second-generation PTH assay, 22% of patients are reported to achieve levels of iPTH <300 pg/ml (32 pmol/l) with cinacalcet therapy. On the other hand, 81% with mild HPT (iPTH 300–500 pg/ml (32–53 pmol/l)) and 60% with moderate HPT (iPTH 500–800 pg/ml (53–85 pmol/l)) are reported to achieve reductions in serum iPTH to <300 pg/ml (32 pmol/l).³⁹⁵

RESEARCH RECOMMENDATIONS

Well-designed RCTs on the use of vitamin D, calcitriol, and vitamin D analogs in CKD stages 3–5 and stage 5D are required to address a number of issues of clinical importance. These trials should include reporting of allocation concealment, blinding of participants, investigators and outcome assessments, patients lost to follow-up, and AEs:

- In a prospective RCT, does the use of vitamin D, calcitriol, or a vitamin D analog influence patient-level outcomes, including cardiovascular events, rates of hospital admission, parathyroidectomy, fracture, musculoskeletal pain, quality of life or, in CKD stages 3–5, the risk of progression or of requiring renal replacement therapy?
- In a prospective RCT, do any of the newer vitamin D analogs provide a survival advantage over the use of alfacalcidol or calcitriol?
- In a prospective RCT to assess the current dialysis population, do laboratory outcomes differ for newer vitamin D analogs vs doses of calcitriol or alfacalcidol, which are equipotent for PTH lowering?
- In a prospective RCT, what is the influence of cholecalciferol or ergocalciferol on patient-level outcomes, surrogate biochemical outcomes, and AEs in CKD stages 3–5 and stage 5D?
- In a prospective RCT, what is the effect of vitamin D, calcitriol, or vitamin D analogs vs placebo or control on bone outcomes, particularly on the normalization of bone histomorphometry?
- In the management of secondary HPT, particularly in relation to patient-level and bone outcomes, how do vitamin D, calcitriol, or vitamin D analogs compare in terms of efficacy and AEs with calcimimetic cinacalcet?
- When using vitamin D, calcitriol, or vitamin D analogs, does the route of administration or the dosing schedule influence efficacy or AEs?
- RCTs with a sufficient length of follow-up are required to determine whether clinical outcomes—including all-cause mortality, cardiovascular and cerebrovascular morbidity, fractures, bone pain, hospitalization, parathyroidectomy rate, and quality of life—are improved by cinacalcet administration in patients with HPT associated with CKD. There is an ongoing study, EVOLVE (NCT00345839, www.clinicaltrials.com), which is evaluating a primary end point of all-cause mortality, nonfatal cardiovascular events, time to mortality, and time to cardiovascular events after a

4-year follow-up. EVOLVE is due to report in 2012. AEs should be recorded to provide a balanced view of benefit vs harm.

- Further RCTs are required to directly compare treatment of HPT with cinacalcet vs calcitriol/vitamin D analogs, and to establish the optimal use of cinacalcet in combination with phosphate binders and vitamin D sterols.

Supplementary Table 24. Overview table of selected studies demonstrating the risk relationships between hormonal parameters of PTH, vitamin D, and mortality in CKD stages 3–5 and 5D.

Supplementary Table 25. Summary table of the treatment of CKD-MBD with calcitriol or vitamin D analogs vs placebo in CKD stages 3–5—description of population at baseline.

Supplementary Table 26. Summary table of the treatment of CKD-MBD with calcitriol or vitamin D analogs vs placebo in CKD stages 3–5—intervention and results.

Supplementary Table 27. Summary table of the treatment of CKD-MBD with calcitriol or vitamin D analogs vs placebo in CKD stages 3–5—bone biopsy results.

Supplementary Table 28. Adverse events of calcitriol or vitamin D analogs in CKD stages 3–5D.

Supplementary Table 29. Ongoing RCTs examining the effect of vitamin D, calcitriol, or vitamin D analogs on CKD-MBD in CKD stages 3–5.

Supplementary Table 30. Summary table of the treatment of CKD-MBD with calcitriol vs placebo or vitamin D analogs in CKD stage 5D—description of population at baseline.

Supplementary Table 31. Summary table of the treatment of CKD-MBD with calcitriol vs placebo or vitamin D analogs in CKD stage 5D—intervention and results.

Supplementary Table 32. Summary table of the treatment of CKD-MBD with calcitriol vs placebo or vitamin D analogs in CKD stage 5D—bone biopsy results.

Supplementary Table 33. Ongoing RCTs examining the effect of vitamin D, calcitriol, or vitamin D analogs on CKD-MBD in CKD stage 5D.

Supplementary Table 34. Summary table of RCTs examining the treatment of CKD-MBD with calcimimetics in CKD stage 5D—description of population at baseline.

Supplementary Table 35. Summary table of RCTs examining the treatment of CKD-MBD with calcimimetics in CKD stage 5D—intervention and results.

Supplementary Table 36. Summary table of RCTs examining the treatment of CKD-MBD with calcimimetics in CKD stage 5D—bone biopsy results.

Supplementary Table 37. Adverse events of calcimimetics vs placebo in CKD stage 5D.

Supplementary Table 38. Ongoing RCTs examining the effect of calcimimetics on CKD-MBD.

Supplementary material is linked to the online version of the paper at <http://www.nature.com/ki>

Table 30 | RCTs of calcitriol or other vitamin D analogs in children with CKD

Author (year)	N	Population	F/U	Study design	Arm 1	Arm 2	Outcomes
Salusky (1998) ¹⁸ Kuizon (1998) ³⁹⁸	46	PD	12 months	RCT	Oral calcitriol	Intraperitoneal calcitriol	Bone Bx, Ca, P, PTH, calcitriol
Schmitt (2003) ³⁹⁹	24	CKD 3–5	12 months	RCT	Daily calcitriol	Twice weekly calcitriol	iPTH, growth, Ca × P
Greenbaum (2005) ³⁹⁷	42	HD	12 weeks	RCT	Calcitriol	Placebo	PTH, Ca, Ca × P
Greenbaum (2007) ⁴⁰⁰	29	HD	12 weeks	RCT	Paricalcitol	Placebo	Ca, P, Ca × P, PTH

Bx, biopsy; Ca × P, calcium-phosphorus product; CKD, chronic kidney disease; F/U, follow-up; HD, hemodialysis; iPTH, intact parathyroid hormone; N, number of subjects; PD, peritoneal dialysis; PTH, parathyroid hormone; RCT, randomized controlled trial.

Table 31 | Evidence matrix of calcitriol or vitamin D analogs vs placebo in CKD stages 3–5

Outcome	Methodological quality									Adverse event reporting		
	A			B			C			Author	N (on agent)	F/U
	Author	N (on agent)	F/U	Author	N (on agent)	F/U	Author	N (on agent)	F/U			
Mortality	—	—	—	—	—	—	—	—	—	Coyne (2006) ³⁷⁷	220 (107)	6 months
Clinical CVD	—	—	—	—	—	—	—	—	—	Hamdy (1995) ⁹⁷	176 (89)	24 months
Hospitalization	—	—	—	—	—	—	—	—	—	Coburn (2004) ³⁷⁶	55 (27)	6 months
CKD clinical outcomes	—	—	—	—	—	—	—	—	—	Coburn (2004) ³⁷⁶	55 (27)	6 months
QoL	—	—	—	—	—	—	—	—	—	Nordal (1988) ¹⁰²	30 (15)	8 months
Fractures	—	—	—	—	—	—	—	—	—	—	—	—
PTx	—	—	—	—	—	—	—	—	—	—	—	—
Bone density	—	—	—	—	—	—	—	—	—	—	—	—
Bone histology	—	—	—	—	—	—	Hamdy (1995) ⁹⁷	134 (72)	24 months	—	—	—
Vascular/valvular calcification	—	—	—	—	—	—	Nordal (1988) ¹⁰²	30 (15)	8 months	—	—	—
GFR loss	—	—	—	—	—	—	Coyne (2006) ³⁷⁷	220 (107)	6 months	—	—	—
							Hamdy (1995) ⁹⁷	176 (89)	24 months	—	—	—
							Coburn (2004) ³⁷⁶	55 (27)	6 months	—	—	—
Lab: Ca, P, PTH	Coyne (2006) ³⁷⁷	220 (107)	6 months	Hamdy (1995) ⁹⁷	176 (89)	24 months	—	—	—	—	—	—
	Coburn (2004) ³⁷⁶	55 (27)	6 months	Kooienga (2009) ³⁷⁴	322 (214)	24 months	—	—	—	—	—	—
Lab: ALP, b-ALP	Coyne (2006) ³⁷⁷	220 (107)	6 months	Hamdy (1995) ⁹⁷	176 (89)	24 months	Kooienga (2009) ³⁷⁴	322 (214)	24 months	—	—	—
				Coburn (2004) ³⁷⁶	55 (27)	6 months	—	—	—	—	—	—
Lab: Bicarbonate	—	—	—	—	—	—	—	—	—	—	—	—
Adverse events	—	—	—	—	—	—	—	—	—	Coyne (2006) ³⁷⁷	220 (107)	6 months
										Hamdy (1995) ⁹⁷	176 (89)	24 months
										Coburn (2004) ³⁷⁶	55 (27)	6 months
										Nordal (1988) ¹⁰²	30 (15)	8 months

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; CKD, chronic kidney disease; CVD, cardiovascular disease; F/U, follow-up; GFR, glomerular filtration rate; N, number of subjects; PTH, parathyroid hormone; PTx, parathyroidectomy; QoL, quality of life.

Table 32 | Evidence profile of treatment of CKD-MBD with calcitriol or vitamin D analogs vs placebo in CKD stages 3-5

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations ^a	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	— AE from 3 RCTs	— 451 (223)	— Very serious limitations (–2)	—	—	—	Very low	Unable to assess	Critical
Clinical CVD and CeVD ^b	— AE from 1 RCT	— 55 (27)	— Very serious limitations (–2)	—	—	—	Very low	Unable to assess	Critical
All-cause hospitalization	—	—	—	—	—	—	—	—	High
CKD clinical outcomes	— AE from 3 RCTs	— 261 (131)	— Very serious limitations (–2)	—	—	—	Very low	Unable to assess	High
Quality of life	—	—	—	—	—	—	—	—	High
Fractures	—	—	—	—	—	—	—	—	High
PTx	—	—	—	—	—	—	—	—	High
Bone density	—	—	—	—	—	—	—	—	Moderate
Bone histology	2 RCTs	164 (87)	Very serious limitations (–2)	No important inconsistencies	Some uncertainty about directness (–1) ^c	—	Low	Osteitis fibrosa (high turnover) but also more cases of adynamic bone (low turnover). Mineralization improves with calcitriol. Volume is not different from placebo	Moderate
Vascular/valvular Calcification	—	—	—	—	—	—	—	—	Moderate
GFR Loss	3 RCTs	451 (223)	Very serious limitations (–2) ^d	No important inconsistencies	Direct	—	Low	No difference	Moderate
<i>Laboratory measurements</i>									
Calcium	—	—	No limitations ^e	No important inconsistencies ^f	Direct	—	High	Trend to or statistically significantly higher calcium with active vitamin D sterols	
Phosphorus	4 RCTs	773 (437)	No limitations ^e	No important inconsistencies ^f	Direct	—	High	Trend to elevated phosphorus with active vitamin D sterols	
PTH	—	—	No limitations ^e	No important inconsistencies ^f	Direct ^h	—	High	Active vitamin D sterols lower PTH	Moderate
Ca × P	2 RCTs	275 (134)	No limitations ^g	No important inconsistencies ^f	Direct	—	High	Trend to higher Ca × P with active vitamin D sterols	
ALP, b-ALP	3 RCTs	451 (223)	Serious limitations (–1) ⁱ	No important inconsistencies	Direct	—	Moderate	Statistically significantly lower ALP or b-ALP with active vitamin D sterol	
Bicarbonate	—	—	—	—	—	—	—	—	
Adverse Events	4 RCTs	481 (238)	—	—	—	—	—	One study of alfacalcidol vs placebo shows trend toward greater proportion of patients with episodes of hypercalcemia. No consistent reporting of GI and cardiac AEs	Depends on outcome
Balance of potential benefits and harm: No evidence regarding benefit for clinical outcomes Vitamin D sterols lower PTH. Trends toward higher serum phosphorus, calcium, and Ca × P and lower ALP and b-ALP Uncertainty regarding harm							Quality of overall evidence: High for biochemical outcomes Low for other surrogate outcomes Absent for patient-centered outcomes		

Table 32 | Continued

AE, adverse event; ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; Ca × P, calcium-phosphorus product; CeVD, cerebrovascular disease; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; CVD, cardiovascular disease; GFR, glomerular filtration rate; GI, gastrointestinal; N, number of subjects; PTH, parathyroid hormone; PTx, parathyroidectomy; RCT, randomized controlled trial.

^aOther considerations include imprecise or sparse data (–1), high probability of reporting bias (–1). For observational studies, other considerations include strong association (+1 or +2), dose–response gradient (+1), all plausible confounders would have reduced the effect (+1).

^bClinical cardiovascular and cerebrovascular disease.

^cThe use of aluminum-containing phosphate binders at baseline limits generalizability.

^dThree grade C.

^eTwo grade A, one grade B.

^fDirection of effect is consistent across studies.

^gTwo grade A.

^hHowever, limited certainty about the directness of PTH due to bias in PTH assays, and biological variability of PTH values and effect of different PTH fragments.

ⁱOne grade A, two grade B.

Table 33 | Evidence matrix for calcitriol vs vitamin D analogs in CKD stage 5D

Outcome	Methodological quality									Adverse event reporting		
	A			B			C			Author	N (on calcitriol)	F/U
	Author	N (on calcitriol)	F/U	Author	N (on calcitriol)	F/U	Author	N (on calcitriol)	F/U			
Mortality	—	—	—	—	—	—	—	—	—	Hayashi (2004) ³⁹¹	82 (47)	12 months
Clinical CVD and CeVD	—	—	—	—	—	—	—	—	—	—	—	—
All-cause hospitalization	—	—	—	—	—	—	—	—	—	—	—	—
QoL	—	—	—	—	—	—	—	—	—	—	—	—
Fractures	—	—	—	—	—	—	—	—	—	—	—	—
PTx	—	—	—	—	—	—	—	—	—	—	—	—
Bone density	—	—	—	—	—	—	—	—	—	—	—	—
Bone histology	—	—	—	—	—	—	—	—	—	—	—	—
Vascular/valvular calcification	—	—	—	—	—	—	—	—	—	—	—	—
Lab: Ca, P, PTH	—	—	—	Sprague (2003) ³⁹²	266 (133)	3–8 months	Hayashi (2004) ³⁹¹	91 (47)	12 months	—	—	—
Lab: ALP, b-ALP	—	—	—	—	—	—	Hayashi (2004) ³⁹¹	91 (47)	12 months	—	—	—
Lab: Bicarbonate	—	—	—	—	—	—	—	—	—	—	—	—
Adverse events	—	—	—	—	—	—	—	—	—	Sprague (2003) ³⁹² Hayashi (2004) ³⁹¹	266 (133) 91 (47)	3–8 months 12 months

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; CeVD, cerebrovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; F/U, follow-up; N, number of subjects; PTH, parathyroid hormone; PTx, parathyroidectomy; QoL, quality of life.

N randomized may be more than N analyzed; this evidence matrix does not include studies of calcitriol vs placebo in CKD stage 5D (refer to summary table entry for Baker (1986)¹⁰¹) or studies in pediatric patients (refer to summary table entry for Salusky (1998)¹⁸).

Table 34 | Evidence profile^a for calcitriol vs vitamin D analogs in CKD stage 5D

Outcome	No. of studies and study design	Total N (Calcitriol arm)	Methodological quality of studies	Consistency across studies	Directness of the evidence generalizability/applicability	Other considerations ^b	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	— AE from 1 RCT	91 (47)	Very serious limitations (–2)	—	—	—	Very low	Unable to assess	Critical
Clinical CVD and CeVD	—	—	—	—	—	—	—	—	Critical
All-cause hospitalization	—	—	—	—	—	—	—	—	High
Quality of life	—	—	—	—	—	—	—	—	High
Fractures	—	—	—	—	—	—	—	—	High
PTx	—	—	—	—	—	—	—	—	High
Bone density	—	—	—	—	—	—	—	—	Moderate
Bone histology	—	—	—	—	—	—	—	—	Moderate
Vascular/valvular Calcification	—	—	—	—	—	—	—	—	Moderate
<i>Laboratory measurements</i>									
Calcium and Ca × P	—	—	Serious limitations (–1) ^c	No important inconsistencies	Direct	—	Moderate	No difference ^d	
Phosphorus	—	—	Very serious limitations (–2) ^e	No important inconsistencies	Direct	—	Low	No difference in mean phosphorus or % with high phosphorus	
PTH	2 RCTs	357 (180)	Serious limitations (–1) ^c	No important inconsistencies ^f	Direct ^g	—	Moderate	No difference between calcitriol compared with maxacalcitol and paricalcitol in number of individuals achieving lower PTH outcome. Paricalcitol group of one study showed slightly reduced time to lower PTH outcome	Moderate
ALP, b-ALP	1 RCT	91 (47)	Very serious limitations (–2) ^h	NA	Direct	Sparse	Very low	Unable to assess	
Bicarbonate	—	—	—	—	—	—	—	—	
Adverse events	2 RCTs	357 (180)	—	—	—	—	—	Limited evidence; no difference in proportion of pts with hypercalcemia, hyperphosphatemia and/or elevated Ca × P	Depends on type of outcome

Balance of potential benefits and harm:

No evidence regarding benefit of calcitriol compared with other active vitamin D sterols for clinical outcomes. There is no difference between these treatments for Ca, P, or PTH

Quality of overall evidence:

Moderate to very low for biochemical outcomes
Absent for other surrogate outcomes
Absent for patient-centered outcomes

AE, adverse event; ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; Ca × P, calcium-phosphorus product; CeVD, cerebrovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; N, number of subjects; NA, not applicable; PTH, parathyroid hormone; pts, patients; PTx, parathyroidectomy; RCT, randomized controlled trial.

^aThis evidence profile does not include studies of calcitriol vs placebo in CKD stage 5D (refer to summary table entry for Baker (1986)¹⁰¹) or studies in pediatric patients (refer to summary table entry for Salusky (1998)¹⁸).

^bOther considerations include imprecise or sparse data (–1), high probability of reporting bias (–1). For observational studies, other considerations include strong association (+1 or +2), dose-response gradient (+1), all plausible confounders would have reduced the effect (+1).

^cOne grade B, one grade C.

^dSecondary, not prespecified analyses, of one study, Sprague (2003)³⁹² showed statistically significant difference in proportion of individuals with repeated episodes of high Ca or Ca × P.

^eTwo grade C. In study by Sprague (2003)³⁹² reportedly no difference in hyperphosphatemia, but definition or numbers were not provided.

^fFairly consistent between studies, that is, no difference for proportions.

^gHowever, limited certainty about the directness of PTH due to bias in PTH assays, and biological variability of PTH values and effect of different PTH fragments.

^hOne grade C.

Table 35 | Evidence matrix for calcimimetics in CKD stage 5D

Outcome	Methodological quality									Adverse event reporting		
	A			B			C			Author	N	F/U
	Author	N (on agent)	F/U	Author	N (on agent)	F/U	Author	N (on agent)	F/U			
Mortality	—	—	—	—	—	—	Cunningham (2005) ³⁸⁶	1184 (697)	6–12 months	Block (2004) ³⁸⁷	—	6 months
Clinical CVD and CeVD	—	—	—	—	—	—	—	—	—	Lindberg (2005) ³⁸⁸	—	6 months
Hospitalization	—	—	—	—	—	—	Cunningham (2005) ³⁸⁶	1184 (697)	6–12 months	—	—	—
QoL	—	—	—	—	—	—	Cunningham (2005) ³⁸⁶	876 (X ^a)	6–12 months	—	—	—
Fractures	—	—	—	—	—	—	Cunningham (2005) ³⁸⁶	1184 (697)	6–12 months	—	—	—
PTx	—	—	—	—	—	—	Cunningham (2005) ³⁸⁶	1184 (697)	6–12 months	—	—	—
Bone density	—	—	—	—	—	—	—	—	—	—	—	—
Bone histology	—	—	—	—	—	—	Malluche (2008) ³⁸⁹	48 (32)	24 months	—	—	—
Vascular/valvular Calcification	—	—	—	—	—	—	—	—	—	—	—	—
Lab: Ca, P, PTH	—	—	—	Block (2004) ³⁸⁷	741 (371)	6 months	—	—	—	—	—	—
				Lindberg (2005) ³⁸⁸	395 (294)	6 months						
				Moe (2005) ³⁹⁵	+0 ^b	6 months						
Lab: ALP, b-ALP	—	—	—	Block (2004) ³⁸⁷	741 (371)	6 months	—	—	—	—	—	—
Lab: Bicarbonate	—	—	—	—	—	—	—	—	—	—	—	—
Adverse events										Block (2004) ³⁸⁷	741 (371)	6 months
										Lindberg (2005) ³⁸⁸	396 (294)	6 months
										Malluche (2008) ³⁸⁹	48 (32)	24 months

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; CeVD, cerebrovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; F/U, follow-up; N, number of subjects; PTH, parathyroid hormone; PTx, parathyroidectomy; QoL, quality of life.

N analyzed may be less than N randomized.

^aUnclear reporting regarding the number of individuals who received study drug.

^bN for Moe (2005)³⁹⁵ is equal to the N from Block (2004)³⁸⁷ + Lindberg (2005)³⁸⁸.

Table 36 | Evidence profile for calcimimetics in CKD stage 5D

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies	Consistency across studies	Directness of the evidence generalizability/applicability	Other considerations ^a	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	1 report of 4 RCTs	1184 (697)	Very serious limitations (-2) ^b	NA	Direct	—	Low	HR 0.81 (CI 0.45–1.45) in 100 patient-years	Critical
Clinical CVD and CeVD	0	—	—	—	—	—	—	—	Critical
All-cause hospitalization	1 report of 4 RCTs	1184 (697)	Very serious limitations (-2) ^b	NA	Direct	—	Low	HR 1.03 (CI 0.87–1.22) in 100 patient-years	High
Quality of life	1 report of 4 RCTs	876 (ND)	Very serious limitations (-2) ^b	NA	Direct	—	Low	Statistically significant benefit in KDQOL Cognitive Functioning and in SF-36 Physical Component Summary, Bodily Pain and General Health Perception, No benefit for other SF-36 domains	High
Fractures	1 report of 4 RCTs	1184 (697)	Very serious limitations (-2) ^b	NA	Direct	Sparse data	Very Low	HR 0.46 (CI 0.22–0.95) in 100 patient-years	High
PTx	1 report of 4 RCTs	1184 (697)	Very serious limitations (-2) ^b	NA	Some uncertainty about directness ^c	Sparse data	Very Low	HR 0.07 (CI 0.01–0.55) in 100 patient-years	High
Bone density	0	—	—	—	—	—	—	—	Moderate
Bone histology	1 RCT	48 (19)	—	—	—	—	Very Low	Overall changes in biopsies were not very different between groups. No statistical comparisons	Moderate
Vascular/valvular Calcification	0	—	—	—	—	—	—	—	Moderate
<i>Laboratory measurements</i>									
Calcium			Serious limitations (-1) ^d	No major inconsistencies ^e	Direct	—	Moderate		
Phosphorus			Serious limitations (-1) ^d	No major inconsistencies ^e	Direct	—	Moderate		
Ca × P	3 reports of 3 RCTs	1136 (665)	Serious limitations (-1) ^d	No major inconsistencies ^e	Direct	—	Moderate	Improved ability to lower PTH while also lowering Ca, P	Moderate
PTH			Serious limitations (-1) ^d	No major inconsistencies ^e	Direct ^f	—	Moderate		
ALP, b-ALP	1 RCT	741 (391)	Serious limitations (-1) ^g	NA	Direct	—	Moderate	Lower b-ALP	
Bicarbonate	0	—	—	—	—	—	—	—	
Adverse events	3 reports of 3 RCTs	1136 (665)						Higher rates of nausea and vomiting which may limit ability to continue treatment	Depends on outcome
Balance of potential benefits and harm: Improved ability to lower PTH while also lowering Ca, P in short term (up to 1 year); uncertainty about benefit or harm for patient-centered clinical outcomes							Quality of overall evidence: Moderate for biochemical outcomes Very Low for other surrogate outcomes Low for patient-centered outcomes		

Table 36 | Continued

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; Ca × P, calcium–phosphorus product; CeVD, cerebrovascular disease; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; KDQOL, Kidney Disease Quality of Life Instrument; N, number of subjects; NA, not applicable; ND, not documented; PTH, parathyroid hormone; PTx, parathyroidectomy; RCT, randomized controlled trial; SF-36, Medical Outcomes Study Short Form 36.

^aOther considerations include imprecise or sparse data (–1), high probability of reporting bias (–1). For observational studies, other considerations include strong association (+1 or +2), dose–response gradient (+1), all plausible confounders would have reduced the effect (+1).

^bOne grade C.

^cProtocol indicated for parathyroidectomies.

^dThree grade B.

^eNo major inconsistencies between Block (2004)³⁸⁷ and Lindberg (2005)³⁸⁸.

^fHowever, limited certainty about the directness of PTH due to bias in PTH assays, and biological variability of PTH values and effect of different PTH fragments.

^gOne grade B.

Chapter 4.3: Treatment of bone with bisphosphonates, other osteoporosis medications, and growth hormone

Grade for strength of recommendation ^a	Strength	Wording	Grade for quality of evidence	Quality of evidence
Level 1	Strong	'We recommend...should'	A	High
Level 2	Weak	'We suggest...might'	B	Moderate
			C	Low
			D	Very low

^aIn addition the Work Group could also make ungraded statements (see Chapter 2 section on ungraded statements).

INTRODUCTION

Abnormal bone is a common component of CKD-MBD. Patients with CKD have an increased risk of fractures compared with age-matched controls, with a resultant significant disability and mortality.^{82,90,158} In children, linear height deficit (short stature) is one of the cardinal features of progressive CKD, and is also a component of CKD-MBD. Both fractures and abnormal linear growth can lead to a decreased quality of life, and therefore, treatments to reduce these complications of CKD-MBD are needed. However, clinical studies in patients with CKD stages 4-5 are very limited.

RECOMMENDATIONS

- 4.3.1 In patients with CKD stages 1-2 with osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, we recommend management as for the general population (1A).**
- 4.3.2 In patients with CKD stage 3 with PTH in the normal range and osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, we suggest treatment as for the general population (2B).**
- 4.3.3 In patients with CKD stage 3 with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy (2D).**
- 4.3.4 In patients with CKD stages 4-5D having biochemical abnormalities of CKD-MBD, and low BMD and/or fragility fractures, we suggest additional investigation with bone biopsy prior to therapy with antiresorptive agents (2C).**
- 4.3.5 In children and adolescents with CKD stages 2-5D and related height deficits, we recommend treatment**

with recombinant human growth hormone when additional growth is desired, after first addressing malnutrition and biochemical abnormalities of CKD-MBD (1A).

Summary of rationale for recommendations

- Patients with late stages of CKD have a high risk of fractures that are painful and disabling.
- In patients with age-related osteoporosis, surrogate measurements such as low BMD relate to clinical outcomes. This does not necessarily apply in patients with CKD stages 3-5D, in whom the fracture risk is high, regardless of BMD.
- In postmenopausal osteoporosis, medication-related increases in BMD are not always directly responsible for reductions in fracture incidence. Improved BMD does not necessarily parallel bone quality, which is an important factor contributing to bone fragility fractures.
- Studies evaluating medications for the treatment of postmenopausal osteoporosis (risedronate, alendronate, teriparatide, and raloxifene) specifically excluded patients with an elevated serum creatinine level, HPT, or abnormal ALPs. However, *post hoc* analyses found that these drugs had similar efficacy, improved BMD, and reduced fractures in individuals with a moderately reduced eGFR compared with those with a mildly decreased or normal eGFR.
- No studies meeting evidence-based criteria have evaluated these therapies in patients with CKD stages 3-5D who have biochemical evidence of CKD-MBD.
- There are multiple additional factors that contribute to fractures in patients with CKD stages 3-5D compared with those in the general population. The bone is frequently of abnormal quality because of metabolic abnormalities specific to CKD stages 3-5D and therapies

that are used. In addition, patients with CKD may have an increased risk of falling.

- The pathogenesis of bone disease in patients with CKD-MBD is different from that in postmenopausal osteoporosis; therefore, extrapolating results of studies from osteoporosis to patients with CKD stages 3–5D may not be valid, especially with concerns of long-term safety. Thus, when evaluating treatment options for low BMD and/or fracture prevention, patients with CKD stages 1–3 who have no evidence of CKD-MBD must be differentiated from patients with CKD stages 3–5D who do have evidence of CKD-MBD.
- In children, linear growth abnormalities are common and can be corrected with rhGH.

BACKGROUND

Fractures and bone quality

Fractures occur when the bone is subjected to a force that is greater than the bone strength. Bone strength reflects the integration of two main features: BMD and bone quality.^{407–409} These ‘quality’ factors include the rate of bone turnover or remodeling, bone shape and architecture, trabecular connectivity, mineralization, collagen cross-linking, crystal size, intrinsic biomechanical properties of strength and toughness, amount of microdamage, and viability of bone cells. For example, in some diseases such as osteopetrosis and skeletal fluorosis, bone fracture incidence is increased, despite high BMD, because bone quality is poor.

Bone quality in CKD

The pathogenesis of bone disease in patients with CKD-MBD is different from that in postmenopausal osteoporosis.⁴¹⁰ In patients with CKD-MBD, BMD does not predict fracture risk as it does in the general population (as detailed in Chapter 3.2), implying an abnormal bone quality. This limits the ability to extrapolate data from studies of patients with postmenopausal osteoporosis to patients with CKD-MBD. For example, in a report of 1429 bone biopsies from patients with CKD stage 5D, 52 patients had osteoporosis, and 49 of them had adynamic bone disease.⁴¹¹ Another biopsy study of patients with CKD found low bone volume in 46% of the patients, who were younger than the usual patients with idiopathic osteoporosis. Regression analysis revealed that the duration of amenorrhea, being Caucasian, and the OPG/RANK-L ratio influenced bone volume. This study also showed low bone-formation rates in those with low bone volumes.²³¹ Many patients with CKD have abnormal mineralization and increased osteoid. These findings are very different from studies of patients with postmenopausal osteoporosis, who frequently show increased bone turnover and rarely show abnormal mineralization.

Similarly, CKD-MBD may alter bone and cartilage structure and function in children, resulting in an abnormal linear growth in children. Thus, the management of bone disease in patients with CKD is challenging.

Gonadal hormones and bone strength

Many women with CKD have hypoestrogenism, and thus it may seem logical to administer patients estrogen. In postmenopausal women from the general population, estrogen-replacement therapy has been conclusively shown to reduce the incidence of hip, vertebral, and nonvertebral fractures.⁴¹² However, the combined administration of estrogen and progestin may also increase the risk of breast cancer, thromboembolic events, and coronary and cerebrovascular disease, with risks dependent on age and years since menopause.⁴¹³ A current theory is that estrogen can help prevent CACs if given to women who have normal coronary arteries, but can cause plaque rupture and myocardial infarctions in women who already have coronary artery disease.⁴¹⁴ Given that women with CKD frequently have coronary artery disease, the Work Group felt that these drugs should be used with caution. In premenopausal women with CKD, there are not enough data to make any recommendations with regard to estrogen use. Similarly, men with advanced CKD may have reduced testosterone levels,⁴¹⁵ which also may contribute to abnormal bone. However, there are no studies that have specifically evaluated the effect of testosterone therapy on bone in CKD patients.

Abnormal height and CKD

Linear height deficit (short stature) is one of the cardinal features of progressive CKD in pediatric patients. On the basis of the NAPRTCS 2006 Data Report,²⁵² more than one-third of patients are less than the third percentile for height. Baseline kidney function, by height Z-score, shows that there are patients with severe height deficits, even though they have a relatively good function (> 25 ml/min). Of patients with a calculated CrCl between 50 and 75 ml/min, 18.2% (379/1720) had a height Z-score worse than -1.88. The mechanisms of linear growth failure include the presence of chronic metabolic acidosis, renal osteodystrophy, nutrient wasting, chronic inflammation, functional hypogonadism (in some adolescents), and dysregulation of the growth hormone–insulin-like growth factor-1 endocrine axis. Since 1988, rhGH has been licensed by the Food and Drug Administration in the United States for the treatment of linear growth failure in children with CKD.

RATIONALE

4.3.1 In patients with CKD stages 1–2 with osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, we recommend management as for the general population (1A).

Although osteoporosis is a major cause of disability among older men and women, studies from around the world have reported that many patients with osteoporotic fractures are not receiving treatment. The majority of patients with fragility fractures admitted to hospitals are not treated.⁴¹⁶ The disease is considered to be a consequence of aging, despite the fact that therapies can reduce fracture incidence

and improve the quality of life. Approximately 85% of elderly women with postmenopausal osteoporosis have CKD.¹²²

Often patients with osteoporosis and CKD stages 1–2 are ignored, even though studies show that medications can reduce fractures and improve the quality of life. The Work Group felt it was important to indicate that bisphosphonates, raloxifene, and teriparatide could be used in these patients with early CKD, who otherwise would be appropriate candidates for therapy in the absence of CKD.

Osteoporosis in the general population

Overview. It was beyond the scope of this report to review all the studies on osteoporosis. The WHO has developed a clinical risk prediction algorithm that will help physicians determine the risk of a fracture within the subsequent decade (<http://www.shef.ac.uk/FRAX/index.htm>; last accessed on 25 March 2009); treatment decisions will depend on the cost and long-term studies on efficacy and safety; moreover, the exact thresholds for intervention are not yet determined.¹⁸⁵ Currently, it is cost effective to prescribe alendronate for patients with a BMD *T*-score lower than -2.5 or who have experienced a vertebral compression fracture or non-traumatic hip fracture.⁴¹⁷ In patients with osteoporosis, the approved drugs reduce fracture incidence by about 50%. A recent meta-analysis did not find any drug that was superior to others.⁴¹⁸ We focus on medications for which there are data in patients with CKD. It is important to remember that vitamin D and calcium supplements have been used as co-therapies in all of the major clinical trials.

Importance of bone turnover. Idiopathic osteoporosis, seen most often in elderly men and women, has a multifactorial pathophysiology. The bone turnover, for example, ranges from high to suppressed. Within the cancellous bone, the trabeculae become thin and disconnected, and lose the normal plate-like structure.⁴¹⁹ Further perforations of the trabecular plates can lead to an accelerated loss of strength. Medications that inhibit the osteoclastic resorption of the bone prevent this deterioration of bone strength.⁴²⁰ Most of the currently effective medications for osteoporosis (bisphosphonates, estrogen, calcitonin, and raloxifene) act by inhibiting resorption; as a consequence, bone formation is secondarily decreased. Thus, there are only minor changes, if any, in bone volume. Fractures are prevented because trabecular perforations are prevented. The decreased bone resorption and formation also leads to more mineralization in the bone, so that the bone becomes harder. This may also contribute to improving bone strength,⁴²¹ although over-mineralization is associated with more brittle bone.⁴²²

The reason BMD increases in patients with osteoporosis who are treated with antiresorbing medications is that bone becomes more mineralized. In clinical trials of antiresorbing medications, the decrease in fracture rate is not entirely explained by changes in BMD. Changes in the serum markers of bone cell activity suggest that fracture reduction is more closely related to a decrease in bone turnover than to an increase in BMD.^{247,249}

In clinical trials of osteoporosis medications, fracture rates are decreased by about 50%. This suggests that about half of the individuals did not respond to therapy, and investigators would like to identify which patients are most likely to have a benefit. A recent *post hoc* evaluation of a large alendronate study found fracture benefit in women with the highest tertile of baseline bone turnover markers, but no difference in fracture rate in those with baseline low markers of bone turnover.²⁴⁸

Bisphosphonates

Overview. Bisphosphonates have been studied extensively and have been shown to effectively decrease bone fractures in patients with osteoporosis in studies with durations up to 5 years.

Pharmacokinetics. Several features with regard to bisphosphonate actions and pharmacokinetics are important in the context of CKD. Bisphosphonates bind very tightly to mineral, with a half-life of over 10 years.⁴²³ In patients with normal kidney function, about half of the administered dose is bound to the bone and the rest is excreted within several hours by the kidney, hence most of the tissues have only a brief exposure to the drugs.⁴²³ Serum calcium decreases and PTH increases.

Vascular calcifications. Although bisphosphonates are usually prescribed for bone diseases, the first-generation bisphosphonate (etidronate) inhibits calcification and has been used to treat ectopic calcifications. Vascular calcifications are an important component of CKD-MBD, and therefore, the effects of bisphosphonates on extraskeletal calcifications are important, and there may be differences between etidronate and the newer aminobisphosphonates. The effect of ibandronate on aortic calcifications was also studied in two 3-year RCTs involving 474 women with postmenopausal osteoporosis. One trial used oral doses and the other i.v. doses. Aortic calcifications increased significantly in both studies in the women taking ibandronate, although a similar increase was also seen in the patients taking a placebo.⁴²⁴ Another study of CACs, measured using EBCT, found increased calcium deposition in 56 elderly women after 2 years of alendronate, but the rate was not significantly greater than that in control women.⁴²⁵ There are no published studies of aminobisphosphonates and vascular calcification in patients with CKD stages 4–5D, although the older bisphosphonate etidronate did prevent arterial calcification progression in a small uncontrolled study of dialysis patients.⁴²⁶

Adverse events. Oral doses commonly cause upper gastrointestinal irritation. Intravenous dosing commonly causes an acute-phase reaction with fever, leukopenia, and bone pain. Severe hypocalcemia has been reported when these medications are administered to patients with a vitamin D deficiency.^{427,428}

Unusual adverse effects of bisphosphonates include osteonecrosis of the jaw, ocular inflammation, atrial fibrillation, esophageal ulceration, bone pain, and nephrotic

syndrome. It is important to realize that the clinical trials in patients with osteoporosis that show a decreased incidence of fractures with bisphosphonates have controls for only 5 years. Currently, there is a debate with regard to the possibility of oversuppression of bone formation with long-term use of bisphosphonates. There are several anecdotal reports of unusual fractures in patients who took bisphosphonates and whose bone biopsies showed no tetracycline labels. There may be a higher risk of subtrochanteric fractures, noted in a small study from Singapore⁴²⁹ and New York.⁴³⁰ Ten-year observational studies of patients who have taken bisphosphonates, however, have not revealed any increased incidence of fractures.⁴³¹ Further follow-up of these patients will be important.

Intermittent administration of 1–34 PTH

The only currently available medication that increases the formation of new bone is teriparatide (recombinant human 1–34 PTH). This anabolic drug has a totally different mechanism of action than bisphosphonates: the BMD increases because there is more bone.^{432,433} The duration of the anabolic effect of PTH is about 12–18 months; thereafter, bone-formation rates return to baseline.⁴³² An earlier or concurrent use of bisphosphonates attenuates the anabolic effect within cancellous bone.^{434,435} Teriparatide is particularly effective in cancellous bone.¹²⁵ Early studies suggested that PTH could increase cancellous bone at the expense of cortical bone;⁴³⁶ the effects have been shown to be complex in cortical bone, with an increase in cortical thickness,⁴³² as well as an increase in cortical porosity⁴³⁷ and a decrease in the volumetric density of the hip as measured by quantitative computed tomography (qCT).⁴³⁴ Bone density at the radius decreases with teriparatide.^{125,434,435} This could have implications for the treatment of patients with CKD, who frequently have lower BMD at the radius compared with other skeletal sites (see Chapter 3.2). Furthermore, it is not known if 1–34 PTH will be anabolic in patients who already have high PTH, or in patients with PTH resistance.

Raloxifene

Raloxifene is a selective estrogen receptor modulator that is approved for treatment of postmenopausal osteoporosis. Several large clinical trials have documented a reduction in vertebral fracture incidence, but not in nonvertebral fractures.^{438,439} This drug acts through estrogen receptors in the bone, but is antagonistic to estrogen effects in the breast and uterus. Similar to estrogen, there is enhanced coagulation and more frequent episodes of thrombophlebitis. The lipid profile improves (lower low-density lipoprotein cholesterol and higher high-density lipoprotein cholesterol), but the effect on CVD in women with preexisting coronary artery disease is similar to that of placebo. In women who have documented coronary artery disease or a history of myocardial infarction, the risk of a fatal stroke was increased with raloxifene.⁴³⁹ The incidence of strokes was not increased in studies of women with osteoporosis or of women with

a high risk of breast cancer. The incidence of breast cancer, particularly estrogen-receptor-positive cases, is about half of that seen with placebo and similar to the beneficial effect on breast cancer found with tamoxifen.⁴⁴⁰ Side effects include hot flashes and leg cramps. Raloxifene is not indicated in premenopausal women because it may interfere with native estrogen.

4.3.2 In patients with CKD stage 3 with PTH in the normal range and osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, we suggest treatment as for the general population (2B).

There are no clinical trials of antiresorbing drugs specifically designed for patients with CKD stages 3–5, and such patients were specifically excluded from most osteoporosis treatment trials. However, because of the use of serum creatinine, and not GFR, as an inclusion criteria, patients with CKD stages 3–4 by eGFR were inadvertently enrolled in these studies. Importantly, in all of these studies, patients were excluded if the PTH was elevated or if there were other biochemical abnormalities of CKD–MBD. Specifically, *post hoc* analyses of trials of bisphosphonates, teriparatide, or raloxifene have evaluated the effect of these agents on BMD and fractures, and are discussed below.

Bisphosphonates in CKD

Two *post hoc* analyses of trials in patients with osteoporosis have been published (**Tables 37, 38** and *Supplementary Tables 39–42*). Miller *et al.*¹²⁶ reported a pooled analysis of nine trials using risedronate for treatment of osteoporosis. The primary trials were designed to exclude patients with significant systemic disease, hence individuals with serum creatinine >1.1 times the upper limit of normal were excluded. The individuals were elderly; therefore, most of them had some age-related decline in renal function as estimated by the Cockcroft and Gault method. There were 4071 patients with CKD stage 3, with a mean age of 77 years, and 572 patients with CKD stage 4, with a mean age of 83 years, with a mean serum creatinine of 1.3 mg/dl. These patients showed a reduction in vertebral fracture rates and improvements in bone density, which were similar to those with eGFR above 80 ml/min per 1.73 m²; however, in the CKD stage 4 patients, there was no difference in the femoral neck bone density with risedronate compared to placebo. In most of the primary studies, one-third of the patients were treated with 2.5 mg/d of risedronate, but these patients were not included in this pooled analysis. Bone biopsies were measured in 57 patients, but only 14 had moderate decreases in eGFR and none had CKD stage 4. Mineralizing surface decreased 68% with risedronate. No data with regard to other aspects of the bone biopsies were reported. An important limitation of this study is that the nonvertebral fracture rates were not mentioned, even though they are included in the primary reports.

This study provides C-quality evidence that risedronate is effective in elderly women with age-related CKD stage 3. Dropout rates were not represented and the end points from the studies were different; nevertheless, the results were pooled. Finally, the fracture data were incomplete as paired X-ray data were not uniformly available. These results may not apply to men or younger women. The evidence for efficacy in CKD stage 4 is weak, because these women did not show the classical bone abnormalities seen in patients with CKD stage 4. First, they were excluded if serum PTH or ALP values were higher than normal. Second, the mean eGFR was 27 ml/min per 1.73 m² and the interquartile range was 24.5–28.7 ml/min per 1.73 m², hence the eGFR was barely lower than that in CKD stage 4. Third, the mean age was 83 years, by which time the Cockcroft–Gault method becomes less accurate. Using the MDRD method, the average woman in the CKD stage 4 group had an eGFR of 42 ml/min per 1.73 m², hence most of these women did not meet the KDOQI definition of CKD stage 4. Fourth, fewer than half of the patients in the CKD stage 4 group had vertebral fractures measured. Finally, patients with severe CKD usually have more bone loss in the cortical bone (measured at the femoral neck) relative to cancellous bone (measured at the spine). Femoral neck bone density did not show any improvement with risedronate in the CKD stage 4 group.

A similar *post hoc* analysis of an osteoporosis trial was reported by Jamal *et al.*¹²⁷ Data from the alendronate fracture intervention trial were re-analyzed according to GFR as estimated by a modified equation using lean body mass from dual-energy X-ray absorptiometry studies. Verification of this method was not included in the report. In this study, as well as in the one conducted by Miller *et al.*,¹²⁶ the intent of the original trial was to exclude women with kidney disease, but because of their age many individuals did have mild-to-moderate decreases in eGFR. Data extrapolated from a figure in the paper show that fewer than 20 individuals had CKD stage 4, and those with abnormal serum calcium, PTH, or ALP values were excluded. This makes it unlikely that any patient had CKD-MBD. The authors found that the women with an eGFR less than 45 ml/min per 1.73 m² had similar improvements in BMD and decreases in relative fracture risk than those with higher eGFR. The original study was powered to detect differences in fracture rates, but there was inadequate power to detect a fracture benefit in this subgroup analysis. The study was graded as C quality, as the sample size was small and dropout rates were not provided.

Teriparatide in CKD

Miller *et al.*¹²⁶ reported a *post hoc* study that used data from the Fracture Prevention Trial¹²⁵ (Supplementary Tables 43–45) to evaluate patients with postmenopausal osteoporosis, excluding patients with a serum creatinine > 2 mg/dl. Using the Cockcroft–Gault formula, the patients were divided on the basis of kidney function into normal (GFR > 80 ml/min per 1.73 m², *N* = 885), mildly impaired (GFR 50–79 ml/min per 1.73 m², *N* = 444), or moderately impaired (GFR

30–49 ml/min per 1.73 m², *N* = 83); five patients with an eGFR less than 30 ml/min per 1.73 m² were in the study, but not in the analysis. These women did not carry a diagnosis of kidney disease, and they were thin and elderly. Importantly, the study excluded individuals with elevations in serum calcium, phosphorus, or PTH, or with vitamin D deficiency. The two treatment arms (different doses of teriparatide) were combined in the analysis. The study found that vertebral fracture incidence, detected by changes in radiographs, was greater in individuals with an abnormal renal function compared with those with a normal renal function for all levels of abnormal GFR; however, this difference was not found for nonvertebral fragility fracture. Teriparatide reduced vertebral fracture incidence in all groups; there were no nonvertebral fractures in the group with a moderately decreased eGFR. In addition, teriparatide improved lumbar spine BMD, femoral neck BMD, and collagen cross-link biomarkers in a similar manner in normal, mild, and moderately impaired GFR. The treatment increased serum calcium and uric acid in all subgroups, but the percentage of patients with hypercalcemia and hyperuricemia was greater in the moderately impaired GFR group.

Owing to the *post hoc* nature of this study, the different groupings of GFR depending on the end point of the study, and the inability to generalize to the ‘usual’ CKD stage 3 patient because of the exclusion criteria of abnormal biochemistries of CKD-MBD, the study was considered to be of low (‘C’) quality. In women with postmenopausal osteoporosis who have normal serum biochemistry levels, CKD stages 2–3 do not seem to be a contraindication to teriparatide therapy.

Raloxifene in CKD

A *post hoc* study used data from the Multiple Outcomes of Raloxifene Evaluation trial to evaluate the efficacy of raloxifene in patients with reduced kidney function (Supplementary Tables 43–45).⁴⁴¹ The original trial included 7705 postmenopausal women aged 31–80 year. Women were randomly assigned to receive placebo, raloxifene 60 mg/d, or raloxifene 120 mg/d, in addition to daily calcium supplements of 500 mg and 400–600 IU of vitamin D. The trial included women at least 2 years postmenopausal, with osteoporosis defined by low BMD or radiographical evidence of vertebral fractures. Women with a serum creatinine level > 2.6 mg/dl (225 μmol/l) at baseline were excluded. For the *post hoc* analysis, some sites that did not use the central lab for creatinine were excluded, with a total of 7316 postmenopausal women being included. CKD was defined using the Cockcroft–Gault formula, and divided by kidney function into CrCl > 60 ml/min (*N* = 2343), CrCl 45–59 ml/min (*N* = 3293), or CrCl < 45 ml/min (*N* = 1480). In the latter group, the median CrCl was 40.6 (range 20–44.9) and only 55 individuals had CrCl < 30 ml/min; thus, this group represents CKD stage 3 patients. Importantly, the study excluded individuals with elevations in serum PTH, or with vitamin D deficiency, and the levels of PTH were normal in all of the

CKD groups. The two treatment arms (different doses of raloxifene) were combined in the analysis. The study found that femoral neck and spine BMD increased with raloxifene compared with treatment using placebo. The femoral neck BMD increase was greatest in patients with lower CrCl compared with those in other kidney disease groups, but this difference disappeared when the MDRD formula was used instead of that of Cockcroft–Gault. There was a significant reduction in vertebral fractures in the overall cohort of raloxifene-treated patients, with no difference in the three (CrCl) groups. The odds ratio for vertebral fracture was 0.60 for those with a normal kidney function, 0.54 with eGFR 45–59 ml/min per 1.73 m², and 0.74 if eGFR was <45 ml/min per 1.73 m². In the latter group, this was not significant, but only 282 women were in that group. In contrast, there was no difference in nonvertebral fracture incidence in raloxifene-treated patients compared with those on placebo in the overall cohort (consistent with the results of the primary study), or within the groups defined by eGFR. AEs were greater in patients with a reduced kidney function, but there was no difference based on treatment assignment. This study was graded to be of ‘B’ quality, limited because of the *post hoc* analyses.

4.3.3 In patients with CKD stage 3 with biochemical abnormalities of CKD–MBD and low BMD and/or fragility fractures, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy (2D).

At CKD stage 3, some patients have already developed abnormalities of CKD–MBD, in particular, secondary HPT. The large randomized trials of osteoporosis medications detailed above excluded those with known kidney disease, but many of the patients had early CKD stage 3. As kidney disease progresses, bone disease changes from idiopathic osteoporosis to renal osteodystrophy. This disease progression has not been characterized very well and is probably variable from patient to patient, but it seems to begin around a GFR of 40–50 ml/min per 1.73 m², when the biochemical manifestations of CKD–MBD initially appear.^{28,233} The clinical trials of bisphosphonates, raloxifene, and teriparatide have excluded individuals with abnormal PTH values, hence the beneficial effects of these therapies cannot be assumed to apply to patients whose disease has progressed to those stages of CKD when biochemical abnormalities, and related bone remodeling abnormalities start to appear (that is, CKD–MBD, see Chapter 3.2). Given the heterogeneity of this population in terms of progressive CKD, duration of CKD, and severity of CKD–MBD, these patients must be evaluated on an individual basis. The Work Group recommends that secondary HPT be addressed first, as in Chapter 4.2. In patients in whom HPT has been corrected, the GFR is stable, and the risk of a fracture outweighs the potential long-term risk of inducing an irreversible low bone turnover, therapy

with bisphosphonates may be considered. However, bisphosphonates are likely to prevent fractures only in those patients who have increased bone resorption. Therefore, the Work Group recommends consideration of a bone biopsy whenever feasible.

4.3.4 In patients with CKD stages 4–5D, having biochemical abnormalities of CKD–MBD, and low BMD and/or fragility fractures, we suggest additional investigation with bone biopsy prior to therapy with antiresorptive agents (2C).

The effectiveness of long-term bisphosphonate, teriparatide, or raloxifene therapy in CKD stages 4–5D with biochemical abnormalities of CKD–MBD is currently unknown. The Work Group could therefore not recommend the routine use of these agents, especially in light of safety concerns that are highlighted below.

Bisphosphonates in CKD stages 4–5D

A small study of 12 dialysis patients given pamidronate found reduced serum calcium and increased PTH.⁴⁴² A recent abstract presented by Amerling *et al.*⁴⁴³ found that patients with CKD stages 2–5 who were taking oral alendronate had low-turnover bone disease with absent tetracycline uptake. These patients had all been referred to the renal clinic. Thus, the bisphosphonates could cause adynamic bone disease in patients with CKD–MBD. This is an important consideration for patients with CKD–MBD stage 5D, in whom the prevalence of low-turnover bone disease is high (28% of patients, range 4–60%; see Chapter 3.2).

We have no definite evidence that bisphosphonates are harmful to patients with CKD stages 4–5. Bisphosphonates could potentially be beneficial to those with a low bone density and a high bone turnover, with well-controlled serum PTH and minerals. An RCT is needed for this population. In addition, the pharmacodynamics of these drugs in CKD should be better defined.

Teriparatide in CKD stages 4–5D

There are no data on teriparatide in patients with CKD stage 3 who have biochemical abnormalities (high serum PTH, abnormal serum ALPs or 25(OH)D), and also no data in patients with CKD stages 4–5. There is a theoretical concern that preexisting HPT would be exacerbated by teriparatide, and the anabolic effects may not be able to overcome the resorptive effects. Moreover, patients with CKD–MBD show resistance to skeletal actions of PTH, hence they may not respond to intermittent injections of usual 1–34 PTH doses. One could speculate that teriparatide might be useful in patients with surgical hypoparathyroidism and adynamic bone disease, but there is currently no evidence to support this.

Raloxifene in CKD stages 4–5D

There was a single RCT evaluating raloxifene in dialysis patients,⁴⁴⁴ with 25 patients randomized to 60 mg/d

raloxifene and 25 randomized to placebo for 1 year. The patients were postmenopausal by at least 2 years, and the BMD *T*-score was below -2.0 s.d. In the raloxifene-treated patients, the results showed a significant improvement in lumbar spine, but not hip BMD, after 1 year. Serum levels of pyridinoline (a marker of bone resorption) and of low-density lipoprotein cholesterol decreased after 6 months in the raloxifene-treated patients compared with those on placebo. There were no side effects noted. This study was graded of 'B' quality because of small sample size and the question of generalizability of the end point of BMD, as BMD in dialysis patients may not predict fracture risk as it does in the general population. This small study was not felt to be adequate for raloxifene to be recommended for routine use in dialysis patients.

From the physiological point of view, raloxifene is expected to be beneficial to bone in postmenopausal women with CKD-MBD, and reduction in breast cancer could be an important additional benefit. However, raloxifene increases the risk of thromboembolism, and larger studies are needed to determine whether the risks of thromboembolism or dialysis access thrombosis are seen in women with CKD stage 5D. There are also insufficient data with regard to the pharmacokinetics of raloxifene in dialysis patients. The drug is excreted through hepatic metabolism, unlike bisphosphonates. The effect of abnormal protein binding has not been studied, but this is an important factor for estrogen. The free estradiol levels in women with CKD stage 5D are twice as high as in women with normal kidney function when given the same dose.²⁰⁴ Most importantly, the patients enrolled in the MORE trial⁴⁴¹ had no biochemical evidence of CKD-MBD, and thus fracture efficacy may not be generalizable to patients with CKD stages 3–5D with CKD-MBD, in whom bone quality may be altered for reasons other than estrogen deficiency.

4.3.5 In children and adolescents with CKD stages 2–5D and related height deficits, we recommend treatment with recombinant human growth hormone when additional growth is desired, after first addressing malnutrition and biochemical abnormalities of CKD-MBD (1A).

There was a 2006 Cochrane Review on the use of rhGH in children with CKD.¹⁹ We searched using PEDS PICCOD criteria to determine if there were additional RCT studies not included or published, and found none. The Cochrane article¹⁹ reviewed 15 RCTs (629 children) that compared rhGH therapy with placebo. No studies have been published since then. These studies showed an improvement in height s.d. score, height velocity, and height velocity s.d. score. Depending on the study, the effects were evaluated at 6, 12, or 24 months, with positive results at all time points. However, across all growth outcomes, there was a consistent pattern of waning effect with longer duration of treatment. Thus, rhGH

administration is efficacious in standard measures of growth in children. Available RCT data suggest that children with CKD should be treated with 28 IU/m²/week of rhGH. Compared with a dose of 14 IU/m²/week, the larger dose increases height by about 1.5 cm/year over 1 year, but increasing the dose to 56 IU/m²/week did not result in a statistically significant improvement in growth indices. However, these conclusions are based on only 18 patients. There are limited bone biopsy data in children treated with rhGH. The consistency of the positive benefits of rhGH across studies and in AEs was considered a high-quality evidence, leading to a strong guideline recommending its use in children with CKD height deficits.

The benefits to growth need to be balanced with AEs and the difficulty of adhering to a daily subcutaneous injection regimen. In a recent case series of children with CKD treated with rhGH for 2 years, children who responded to rhGH reported that they would choose treatment again, and those who did not respond generally reported that they would not choose treatment again.⁴⁴⁵ These data suggest that treatment response overrides concerns about injections. Adherence to treatment was time dependent, so that 41% of parents reported noncompliance at 1 year, whereas 91% reported missing injections at 2 years (when response to treatment had waned). When most parents are asked to trade-off the growth potential of their children against the burden of daily injections, they opt for rhGH treatment. In general, AEs were usually minor.

RESEARCH RECOMMENDATIONS

The following research studies are needed:

- A randomized, placebo-controlled clinical trial of men and women with CKD stages 4–5D, with controlled serum PTH, phosphorous, and calcium but low bone density, treated with bisphosphonates. The study should evaluate bone density, bone biopsy in at least a subset, serum PTH, calcium and ALP, fracture incidence, and measures of vascular calcification.
- A pharmacokinetic study of postmenopausal women with CKD stage 5D should evaluate serum levels of raloxifene and teriparatide after administration.
- An RCT in women with CKD stages 4–5D comparing the effects of raloxifene vs placebo on bone density, bone biopsy in at least a subset, serum PTH, calcium, phosphorous, ALP, cholesterol, incidence of fractures, breast cancer, heart disease, stroke, and blood/access clots.
- A prospective study of patients with CKD stage 5D with adynamic bone disease and low serum PTH levels using teriparatide to determine markers of bone formation and resorption, bone biopsies, and serum calcium/phosphorous/ALP.
- An RCT of pediatric CKD-MBD patients treated with rhGH therapy compared with those on placebo to evaluate bone histomorphometry, height, skeletal age, and fractures.

SUPPLEMENTARY MATERIALS

Supplementary Table 39. Summary table of the treatment of CKD-MBD with bisphosphonates in CKD stages 3–5—description of population at baseline.

Supplementary Table 40. Summary table of the treatment of CKD-MBD with bisphosphonates in CKD stages 3–5—intervention and results.

Supplementary Table 41. Adverse events of bisphosphonates in CKD stages 3–5.

Supplementary Table 42. Ongoing RCTs examining the effect of bisphosphonates on CKD-MBD.

Supplementary Table 43. Summary table of the treatment of CKD-MBD with other bone treatments in CKD stages 3–5 and 5D—description of population at baseline.

Supplementary Table 44. Summary table of the treatment of CKD-MBD with other bone treatments in CKD stages 3–5 and 5D—intervention and results.

Supplementary Table 45. Adverse events of other bone treatments in CKD stages 3–5 and 5D.

Supplementary material is linked to the online version of the paper at <http://www.nature.com/ki>

Table 37 | Evidence matrix of bisphosphonates vs placebo/control in CKD stages 3–5

Outcome	Methodological quality of outcome									Adverse event reporting		
	A			B			C			Author	N (on agent)	F/U
	Author	N (on agent)	F/U	Author	N (on agent)	F/U	Author	N (on agent)	F/U			
Mortality	—	—	—	—	—	—	—	—	—	—	—	—
Clinical CVD	—	—	—	—	—	—	—	—	—	—	—	—
Hospitalization	—	—	—	—	—	—	—	—	—	—	—	—
CKD clinical outcomes	—	—	—	—	—	—	—	—	—	—	—	—
QoL	—	—	—	—	—	—	—	—	—	—	—	—
Clinical fractures	—	—	—	—	—	—	Jamal (2007) ¹²⁷	581 (X ^a)	36 months	—	—	—
Radiological fractures	—	—	—	—	—	—	Jamal (2007) ¹²⁷	581 (X ^a)	36 months	—	—	—
							Miller (2005) ¹²⁶	2658 (X ^a)	22–25 months			
PTx	—	—	—	—	—	—	—	—	—	—	—	—
Bone density	—	—	—	—	—	—	Jamal (2007) ¹²⁷	581 (X ^a)	36 months	—	—	—
							Miller (2005) ¹²⁶	4643 (2335)	22–25 months			
Bone histology	—	—	—	—	—	—	—	—	—	—	—	—
Vascular/valvular calcification	—	—	—	—	—	—	—	—	—	—	—	—
GFR loss	—	—	—	—	—	—	Miller (2005) ¹²⁶	4643 (2335)	22–25 months	—	—	—
Lab: Ca, P	—	—	—	—	—	—	Miller (2005) ¹²⁶	4643 (2335)	22–25 months	—	—	—
Lab: ALP, b-ALP	—	—	—	—	—	—	—	—	—	—	—	—
Lab: PTH, Vit D, Bicarb	—	—	—	—	—	—	—	—	—	—	—	—
Adverse events	—	—	—	—	—	—	—	—	—	Miller (2005) ¹²⁶	4643 (2335)	25 months

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; CKD, chronic kidney disease; CVD, cardiovascular disease; F/U, follow-up; GFR, glomerular filtration rate; N, number of subjects; PTH, parathyroid hormone; PTx, parathyroidectomy; QoL, quality of life.

N randomized may be higher than N analyzed.

^aUnclear reporting regarding the number of individuals who received study drug.

Table 38 | Evidence profile of bisphosphonates vs placebo/control in CKD stages 3–5

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations ^a	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	—	—	—	—	—	—	—	—	Critical
Clinical CVD and CeVD ^b	—	—	—	—	—	—	—	—	Critical
All-cause hospitalization	—	—	—	—	—	—	—	—	High
CKD clinical outcomes	—	—	—	—	—	—	—	—	High
Quality of life	—	—	—	—	—	—	—	—	High
<i>Fractures</i>									
Clinical	1 RCT	581 (?)	Very serious limitations (–2) ^c	NA	Some uncertainty ^d	Sparse (–1) ^e	Very low	No statistically significant difference	High
Radiological	1 MA of 9 RCTs + 1 RCT	3239 (?)	Serious limitations (–1) ^f	No important inconsistencies	Some uncertainty ^d	None	Low	Likely benefit. Benefit in MA and consistent point estimate in additional RCT	High
PTx	—	—	—	—	—	—	—	—	High
Bone density	1 MA of 9 RCTs + 1 RCT	5224 (2335+?)	Serious limitations (–1) ^f	No important inconsistencies	Some uncertainty ^d	None	Low	Overall benefit in BMD in lumbar and femoral sites	Moderate
Bone histology	—	—	—	—	—	—	—	—	Moderate
Vascular/valvular calcification	—	—	—	—	—	—	—	—	Moderate
GFR loss	1 MA of 9 RCTs	4643 (2335)	Serious limitations (–1) ^g	No important inconsistencies	Some uncertainty ^d	None	Low	Overall no significantly greater loss of kidney function over 1–2 years of follow-up	Moderate
<i>Laboratory measurements</i>									
Calcium	1 MA of 9 RCTs	4643 (2335)	Serious limitations (–1) ^g	NA	Some uncertainty ^d	None	Low	No statistically significant difference	
Phosphorus	—	—	Serious limitations (–1) ^g	NA	Some uncertainty ^d	None	Low	—	Moderate
Ca × P	—	—	—	—	—	—	—	—	
PTH	—	—	—	—	—	—	—	—	
25 OH Vit D	—	—	—	—	—	—	—	—	
1,25 Vit D	—	—	—	—	—	—	—	—	
ALP, b-ALP	—	—	—	—	—	—	—	—	
Adverse events	CKD: 1 RCTs Non-CKD: Trials, Case Reports, Reviews, etc.	4643+ (2335+)	—	—	—	—	—	In non-CKD patients, a number of clinical and laboratory AEs, some of them potentially severe, have been reported ^h . Evidence from trials of CKD patients is limited	Depends on outcome
Balance of potential benefits and harm: Benefits and harm cannot be determined with any certainty							Quality of overall evidence: Low for biochemical outcomes Low for other surrogate outcomes Absent for patient-centered outcomes		

AE, adverse event; ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; BMD, bone mineral density; Ca × P, calcium-phosphorus product; CeVD, cerebrovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate; MA, meta-analysis; N, number of subjects; NA, not applicable; PTH, parathyroid hormone; PTx, parathyroidectomy; RCT, randomized controlled trial.

^aOther considerations include imprecise or sparse data (–1), high probability of reporting bias (–1). For observational studies, other considerations include strong association (+1 or +2), dose-response gradient (+1), all plausible confounders would have reduced the effect (+1).

^bClinical cardiovascular and cerebrovascular disease.

^cOne grade C.

^dThe majority of patients in the studies were postmenopausal women with eGFR below 60 ml/min per 1.73 m² and excluded those with known kidney disease or SCr 122 μmol/l (1.27 mg/dl) or >1.1 times the upper limit of normal.

^eOne study with less than 1000 patients.

^fTwo grade C.

^gOne grade C.

^hGI upset, esophageal ulcers, bone pain, osteonecrosis of the jaw, osteomalacia, acute phase reaction to i.v. drugs (fever, myalgias, and transient leucopenia), atrial fibrillation, nephrotic syndrome, ocular inflammation, hypocalcemia, increased PTH, and hyperphosphatemia.

Chapter 5: Evaluation and treatment of kidney transplant bone disease

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Grade for strength of recommendation ^a	Strength	Wording	Grade for quality of evidence	Quality of evidence
Level 1	Strong	'We recommend...should'	A	High
Level 2	Weak	'We suggest...might'	B	Moderate
			C	Low
			D	Very low

^aIn addition the Work Group could also make ungraded statements (see Chapter 2 section on ungraded statements).

INTRODUCTION

As the number and survival of kidney transplant recipients increase, new challenges arise for overall management. Chronic kidney disease–mineral and bone disorder (CKD–MBD) is a common morbidity in patients with a kidney transplant, and pre-existing CKD–MBD may adversely affect bone health, even with normal kidney allograft function. In addition, most kidney transplant recipients have some degree of CKD, and thus CKD–MBD may be present. However, transplant-specific therapies, especially corticosteroids, may further affect CKD–MBD management.

RECOMMENDATIONS

5.1 In patients in the immediate post-kidney-transplant period, we recommend measuring serum calcium and phosphorus at least weekly, until stable (1B).

5.2 In patients after the immediate post-kidney-transplant period, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (not graded).

Reasonable monitoring intervals would be:

- In CKD stages 1–3T, for serum calcium and phosphorus, every 6–12 months; and for PTH, once, with subsequent intervals depending on baseline level and CKD progression.
- In CKD stage 4T, for serum calcium and phosphorus, every 3–6 months; and for PTH, every 6–12 months.
- In CKD stage 5T, for serum calcium and phosphorus, every 1–3 months; and for PTH, every 3–6 months.
- In CKD stages 3–5T, measurement of alkaline phosphatases annually, or more frequently in the presence of elevated PTH (see Chapter 3.2).

In CKD patients receiving treatments for CKD–MBD, or in whom biochemical abnormalities are

identified, it is reasonable to increase the frequency of measurements to monitor for efficacy and side-effects (not graded).

It is reasonable to manage these abnormalities as for patients with CKD stages 3–5 (not graded) (see Chapters 4.1 and 4.2).

5.3 In patients with CKD stages 1–5T, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and interventions (2C).

5.4 In patients with CKD stages 1–5T, we suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).

5.5 In patients with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73 m², we suggest measuring BMD in the first 3 months after kidney transplant if they receive corticosteroids or have risk factors for osteoporosis as in the general population (2D).

5.6 In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73 m² and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidol, or bisphosphonates be considered (2D).

- We suggest that treatment choices be influenced by the presence of CKD–MBD, as indicated by abnormal levels of calcium, phosphorus, PTH, alkaline phosphatases, and 25(OH)D (2C).
- It is reasonable to consider a bone biopsy to guide treatment, specifically before the use of bisphosphonates due to the high incidence of adynamic bone disease (not graded).

There are insufficient data to guide treatment after the first 12 months.

- 5.7 In patients with CKD stages 4–5T, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population and BMD does not predict the type of kidney transplant bone disease (2B).
- 5.8 In patients with CKD stages 4–5T with a known low BMD, we suggest management as for patients with CKD stages 4–5 not on dialysis, as detailed in Chapters 4.1 and 4.2 (2C).

Summary of rationale for recommendations

- The risk of fractures after kidney transplant is high.
- The etiology of transplant bone disease is multifactorial and most patients have pre-existing CKD–MBD.
- In non-kidney-transplant recipients, a low BMD or loss of BMD predicts fracture, but data are lacking for kidney transplant recipients.
- There are no randomized controlled trial (RCT) data examining bone-specific therapies on patient-level outcomes, including mortality or fractures, in patients receiving kidney transplantation.
- Treatment with calcium, calcitriol, or vitamin D analogs, and/or bisphosphonates, has been suggested to improve BMD in kidney transplant recipients. However, bone biopsy studies are limited.
 - A small study of calcitriol showed worsened bone turnover, but improved mineralization.
 - A small study of treatment with bisphosphonates showed worsened bone turnover and mineralization.
- It is unclear how to identify those kidney transplant patients who would benefit more or less from specific treatments, making it difficult to assess the risk–benefit ratio of those treatments.
- The absence of RCTs that show fracture prevention and heterogeneity within post-kidney-transplantation bone disease prevents the generalization of therapeutic strategies across patients and extrapolation from non-kidney-transplant studies. Therefore, this remains a weak recommendation.

BACKGROUND

Biochemical abnormalities

Biochemical abnormalities are common after transplant, but less documented than in patients on dialysis. It is probably useful to distinguish the time period immediately after kidney transplant, with rapidly changing GFR and concomitantly given therapies, from the subsequent time period when a more stable graft function has been achieved. The magnitude of CKD–MBD before transplant, the degree of kidney function recovery, and the effects of immunosuppressive and other therapies create a heterogeneous patient population. The scope and magnitude of the biochemical abnormalities of CKD–MBD fluctuate dramatically in the early post-transplant period compared with the late post-transplant period, the latter depending on the level of kidney

function. Hypophosphatemia occurs in a large proportion of patients immediately after transplantation, but once kidney function has become stabilized, serum phosphorus returns to the normal range in most of them. Serum calcium tends to increase after transplant and then stabilizes at the higher end of the normal range within 2 months. PTH levels decrease significantly during the first 3 months after transplant but typically stabilize at elevated values after 1 year. Low levels of 1,25(OH)₂D typically do not reach normal values until almost 18 months after transplant.⁴⁴⁶ There are no large databases in which these data are routinely collected and therefore can be systematically evaluated. Thus, most reports are single-center studies.

Bone

Abnormalities of bone are nearly uniformly observed, but the etiology and pathology are widely variable. Post-transplant bone disease represents an important complication observed in a substantial proportion of patients. Early studies have shown a rapid decrease in BMD in the first 6–12 months after successful kidney transplantation, and continued loss—albeit at a lower rate—for many years.⁴⁴⁷ As a consequence, fractures are common and associated with substantial morbidity.

The etiology of transplant bone disease is multifactorial. Patients come to transplantation with pre-existing bone disease of CKD (CKD–MBD), which is not always improved by transplantation. In addition, new insults to bone occur, including the potentially deleterious effects of various immunosuppressive agents, the impaired kidney function (CKD) frequently observed in kidney transplant patients, and other factors particular to each patient, such as post-menopausal status, presence of diabetes, smoking, physical activity, and duration of dialysis and transplantation.⁴⁴⁸ Previous studies in kidney transplant patients have shown a correlation between the cumulative dose of glucocorticoids and BMD. On the basis of a few bone biopsy studies in transplant patients, glucocorticoids seem to be the primary determinant of subsequent bone volume and turnover. Thus, the cumulative and mean prednisone dose correlated negatively with bone turnover, whereas there was no correlation with cyclosporine cumulative dose or serum PTH.⁴⁴⁹ The possible role of calcineurin inhibitors, such as cyclosporine or tacrolimus, remains incompletely studied, with contradictory reports on their effects on bone turnover.⁴⁴⁹

Vascular calcification

Arterial calcification is also common after a kidney transplant, but is often due to the effects of the uremic state and dialysis rather than the transplant itself and, overall, is poorly studied in this population. In renal transplant recipients (CKD stages 1–5T), only one prevalence study was identified, showing a prevalence of calcification of 24.4%.⁴⁵⁰ Although this cross-sectional study was large ($n = 1117$), calcification was assessed by a postero-anterior

plain abdominal X-ray examination of the aorto-iliac region, which is likely to be less sensitive than computed tomography-based imaging methods and gives only semi-quantitative information. In addition, one of the major difficulties in interpreting calcification in the transplant population is the carryover effect from CKD stage 5 or stage 5D. Currently, only one preliminary study is available, suggesting that the progression of cardiovascular calcification may be halted after renal transplantation.⁴⁵¹ Thus, much remains to be learned.

The following tables are found at the end of this chapter: **Table 39** summarizes the RCTs of treatments in children with CKD (stages 1–5T). The evidence matrix, a table that describes the methodologic quality of the included studies, and the evidence profile, a table that provides an overall assessment of the quality of the evidence and balance of potential benefits and harm are **Tables 40, 41** for calcitriol or vitamin D analogs; and **Tables 42, 43** for bisphosphonates. Studies of treatments for CKD-MBD in transplant recipients reviewed for this topic are further described in detail in the *Supplementary Tables 46–53*.

RATIONALE

5.1 In patients in the immediate post-kidney-transplant period, we recommend measuring serum calcium and phosphorus at least weekly, until stable (1B).

Similar to what has been described for CKD stage 3–5 patients with CKD-MBD, in kidney transplant recipients, serum levels of calcium, phosphorus, total CO₂, and PTH should be closely monitored in all patients regardless of graft function. During the first week after kidney transplantation, serum levels of calcium and phosphorus should be measured at least weekly. Many, if not most, kidney transplant recipients develop persistently low levels of serum phosphorus (<3.1 mg/dl or 1.0 mmol/l) in the post-transplant period. They should be considered for treatment with phosphate supplementation. However, phosphate administration is not without risk, and caution should be exerted, as it may exacerbate an already existing secondary hyperparathyroidism (HPT). Therefore, every attempt should be made to prescribe the minimum doses. Patients with severe secondary HPT before the transplant will continue to have excessive PTH secretion from large hyperplastic glands. With a new kidney, there will now be enhanced renal reabsorption of calcium and hypercalcemia may ensue. Also, there will be reduced tubular phosphate reabsorption. Thus, during the immediate post-transplant period, wide fluctuations of serum calcium and phosphorus may be seen and thus frequent monitoring is needed.

5.2 In patients after the immediate post-kidney-transplant period, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (not graded).

Reasonable monitoring intervals would be:

- In CKD stages 1–3T, for serum calcium and phosphorus, every 6–12 months; and for PTH, once, with subsequent intervals depending on baseline level and CKD progression.
- In CKD stage 4T, for serum calcium and phosphorus, every 3–6 months; and for PTH, every 6–12 months.
- In CKD stage 5T, for serum calcium and phosphorus, every 1–3 months; and for PTH, every 3–6 months.
- In CKD stages 3–5T, measurement of alkaline phosphatases annually, or more frequently in the presence of elevated PTH (see Chapter 3.2).

In CKD patients receiving treatments for CKD-MBD, or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for efficacy and side-effects (not graded).

It is reasonable to manage these abnormalities as for patients with CKD stages 3–5 (not graded) (see Chapters 4.1 and 4.2).

Patients with a kidney transplant usually have some degree of CKD and, therefore, CKD-MBD may be present. However, there are no clinical trials that have specifically addressed the optimal frequency of monitoring in the CKD or CKD transplant population. Thus, on the basis of the prevalence of abnormalities and the risks associated with those abnormalities, the management of the biochemical abnormalities of CKD-MBD after transplant should be similar to that proposed for nontransplant CKD.

A recent study of 303 kidney transplant recipients in the United States found that 11–25% of patients had abnormal serum calcium or CaXP in the first year after transplant, and 24% of recipients with an eGFR between 40 and 60 ml/min per 1.73 m² had intact PTH levels >130 pg/ml (13.8 pmol/l) at 1 year after kidney transplant.⁴⁵² Another series from the United Kingdom⁴⁵³ evaluated 244 kidney transplant recipients: 104 in the first year, and the remainder more than 1 year after transplant. Hypercalcemia was present in 40% of recently transplanted recipients and 25% of long-term patients. Hypophosphatemia was very common in the immediate post-transplant period, but normalized within the first year in most series, although a urinary phosphate leak often remained despite normal serum levels.⁴⁵⁴ A larger cohort from Switzerland⁴⁵⁵ evaluated 823 kidney transplant recipients, on average 7 years after transplant. They found that only 27% of the population had a PTH within normal range (that is, 15–65 pg/ml (1.6–6.9 pmol/l)), whereas 70% had HPT (PTH >65 pg/ml (>6.9 pmol/l)) and 2.8% were hypoparathyroid (PTH <15 pg/ml (<1.6 pmol/l)). Serum phosphorus was within normal range in 74% of the patients (0.85–1.45 mmol/l), and increased in only 3.6% of the patients. Finally, serum calcium was within normal range in most patients (85.9%), with only 2.8 and 11.3% of the patients being hypocalcemic and

hypercalcemic, respectively. Thus, disorders of mineral metabolism may persist many years after transplantation.

There is a paucity of data describing the risk relationship of biochemical abnormalities of CKD-MBD and mortality in patients after kidney transplantation. A study in Austria of 773 patients with kidney transplant found no relationship between serum calcium, phosphorus, or PTH and mortality.⁴⁵⁶ However, they did find that patients with the highest quintile of phosphorus had increased risk of kidney allograft loss. Similarly, those with the highest quintile of calcium also had increased risk of kidney allograft loss, which is similar to other reports in which hypercalcemia was associated with both graft loss and recipient death.⁴⁵² Clearly, more data are needed to fully understand the possible significance of these relationships.

From a management perspective, there are no RCTs that specifically enrolled transplant recipients who met our inclusion criteria. Thus, approaches similar to those in nontransplant CKD should be taken, with some special considerations. Hypercalcemia after kidney transplantation is usually due to HPT that persists from the preceding CKD period. Increased serum calcium concentration can persist for years after transplantation. In patients with nonsuppressible nodular parathyroid hyperplasia, persistently elevated PTH levels after restoration of normal renal function with a transplant may have a primary role in maintaining a high bone turnover. Parathyroid gland hyperplasia, especially autonomous parathyroid growth, does not easily resolve after establishment of sufficient renal function, except in mild cases or when secondary to vitamin D deficiency. In 30–50% of transplant recipients, abnormal PTH secretion persists. When it causes hypercalcemia, it may require parathyroidectomy.^{457–460} In general, the same principles we have discussed for the management of patients with CKD stages 3–5 with CKD-MBD will apply for patients with CKD stages 3–5T.

5.3 In patients with CKD stages 1–5T, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and interventions (2C).

25(OH)D levels were measured in 244 renal transplant recipients and divided into two groups: 104 recently transplanted (less than 1 year) and 140 long term.⁴⁵³ Vitamin D insufficiency (15–30 ng/ml or 40–75 nmol/l) was present in 29 and 43% of recent and long-term kidney transplant recipients, deficiency (4.8–15.6 ng/ml or 12–39 nmol/l) in 56 and 46%, and severe deficiency (<4.8 ng/ml or 12 nmol/l) in 12 and 5%, respectively. Thus, vitamin D deficiency is common after transplant, and an initial assessment of status is reasonable.

5.4 In patients with CKD stages 1–5T, we suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).

Vitamin D deficiency and insufficiency are associated with cardiovascular disease, autoimmune disorders, malignancies,

bone disease and musculoskeletal weakness, and insulin resistance.⁴⁶¹ Unfortunately, there are no RCTs of vitamin D supplementation in patients with a kidney transplant evaluating end points other than bone health (see recommendation 5.6 for bone health). However, given the magnitude of vitamin D deficiency and the high prevalence of many of the disorders associated with vitamin D deficiency in the general population, the Work Group felt that it was reasonable to treat deficiency, if found. Thus, supplementation with either ergocalciferol or cholecalciferol is recommended, but the optimal treatment regimen is not known,⁴⁶² and neither is the sufficient level of calcidiol well defined (see Chapter 3.1). It is also important to point out that the primary source of vitamin D is sunlight, and that the increased risk of skin cancer in kidney transplant patients mandates the use of appropriate sun-screen protection, further increasing the need for oral intake of vitamin D.⁴⁶³

5.5 In patients with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73 m², we suggest measuring BMD in the first 3 months after kidney transplant if they receive corticosteroids, or have risk factors for osteoporosis as in the general population (2D).

Post-transplant bone disease is a complex disorder that extends beyond simple alterations in BMD. It includes systemic and local derangements of bone and mineral metabolism that can be detected and treated appropriately. The management of bone disease after kidney transplantation should take into account its pathophysiology, with particular focus on three different phases: (i) optimal treatment of CKD-MBD before kidney transplantation; (ii) prevention of bone loss during the first year after transplantation; and (iii) treatment of decreased bone mass thereafter.

There are no studies that directly address fracture prevention, hospitalizations, or mortality related to CKD-MBD in kidney transplant recipients. There is only one study that shows low BMD, as assessed by dual energy X-ray absorptiometry (DXA), to be predictive of fracture risk in kidney transplant recipients. This recent study evaluated 238 renal transplant patients with CKD stages 1–5T who underwent 670 DXA investigations of the hip. Fractures were assessed by a questionnaire. Osteopenia and an absolute bone density below 0.9 g/cm² in the hip region conferred an increased risk of fracture.⁴⁶⁴ However, the Work Group felt that this study was inadequate to determine whether DXA had a high enough predictive value of fracture to be routinely used, because of the bias of repeated DXA evaluations counted as independent measures and the nonsystematic assessment of fractures. It is worth noting that reductions in BMD have been associated with an increased fracture rate in studies of osteoporosis in women in association with postmenopausal status, in men treated with glucocorticoids, and in heart- or liver-transplant recipients. However, the etiology of post-transplant kidney bone disease is likely influenced by CKD-MBD from the pretransplant dialysis period, and ongoing CKD-MBD after transplant, given that most patients

have some impairment of kidney function. Thus, the studies from the general population and other solid organ transplantation may not be generalizable to the kidney transplant population. In addition, there are no treatments in these patients that show fracture reduction (see Recommendation 5.6). Thus, the Work Group felt that DXA should be reserved for high-risk populations, including those receiving significant doses of corticosteroids, or those with risk factors for osteoporosis in the general population (see Chapter 3.2). In addition, the Work Group felt that DXA screening after transplant should only be done in individuals with a well-functioning allograft (CKD stages 1–3T), as patients with CKD stages 4–5T will be more likely to have abnormal bone quality from CKD–MBD, with unknown impact on the predictive value of DXA.

5.6 In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73 m² and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidol, or bisphosphonates be considered (2D).

- We suggest that treatment choices be influenced by the presence of CKD–MBD, as indicated by abnormal levels of calcium, phosphorus, PTH, alkaline phosphatases, and 25(OH)D (2C).
- It is reasonable to consider a bone biopsy to guide treatment, specifically before the use of bisphosphonates due to the high incidence of adynamic bone disease (not graded).

There are insufficient data to guide treatment after the first 12 months.

As detailed below, unfortunately, there are no RCTs that show the beneficial or harmful effects of bone-protective agents on patient-level outcomes, in particular fractures, hospitalizations, or mortality. Studies that examined the effects of calcitriol or vitamin D analogs to prevent transplant bone disease found an improvement in BMD and no adverse events (AEs) of bone.^{465–468} Studies that examined the effects of bisphosphonates to prevent transplant bone disease found an improvement in BMD,^{165,469} but possible AEs of bone histology, increasing the risk of adynamic bone disease.⁴⁶⁹ There are only inconsistent or low-quality data showing positive effects of vitamin D, calcitriol, vitamin D analogs, or bisphosphonates on BMD in established transplant bone disease.^{470,471} Given that BMD is not a well-validated surrogate marker of fracture risk in the transplant patient (and is not even an accepted end point for drug treatments in the general population), and that no studies evaluate fracture as an end point in transplant recipients, this recommendation can only be weak. In addition, clinicians should be aware of the complexity and heterogeneity of transplant bone disease and consider the use of bone biopsy and other biochemical abnormalities of CKD–MBD to guide therapeutic choices rather than only focusing on DXA.

Preventive therapy

Use of vitamin D, calcitriol, and its analogs. Each of the trials in which vitamin D, calcitriol, or its analogs were administered as preventive therapy assessed changes in BMD as the primary outcome.

There were no studies evaluating vitamin D therapy specifically in kidney transplant recipients that met our inclusion criteria, but a meta-analysis published in 1999, in patients treated with steroids for multiple reasons, supported efficacy in improving BMD of the lumbar spine.⁴⁶⁵ This meta-analysis compared all RCTs lasting at least 6 months (and reporting extractable results) of patients receiving oral corticosteroids and treated with vitamin D. The study found a moderate beneficial effect of vitamin D plus calcium vs no therapy or vs calcium alone (nine trials: effect size 0.60; 95% CI 0.34, 0.85; $P < 0.0001$). In a comparison of vitamin D with other osteoporosis therapies, bisphosphonates were more effective than vitamin D (six trials: effect size 0.57; 95% CI 0.09, 1.05). Thus, the Work Group felt that vitamin D supplementation is a reasonable and safe treatment choice for patients with low BMD.

In three studies in renal transplant recipients,^{466–468} a positive change in BMD was observed in the calcitriol and alfacalcidol groups vs the ‘no treatment’ or placebo groups. No fracture data were recorded in any of these studies. The RCTs are detailed in **Tables 40, 41** and *Supplementary Tables 46–49*. No clinically important clinical outcomes such as mortality, hospitalizations, or fractures were evaluated. Only BMD as a surrogate marker for fractures was determined. In addition, most of the studies either lacked or did not define randomization, or there were inconsistencies between the text and the tables. Some studies did not provide any baseline data or the data were incomplete. Thus, the overall quality of the evidence was classified as low. As reported, no significant AEs were observed, except for mild hypercalcemia in the study by Josephson *et al.*⁴⁶⁸ No patients were withdrawn from the study because of secondary effects. No deleterious effect on kidney graft function was observed.

Bisphosphonates. Two studies in 152 patients evaluated the role of bisphosphonates as preventive therapy after kidney transplantation (**Tables 42, 43**; *Supplementary Tables 50–53*).

Protocols between the studies were different, making overall comparisons nearly impossible. In the study of Coco *et al.*,⁴⁶⁹ patients received IV pamidronate at baseline and at 1, 2, 3, and 6 months after transplantation. Rapid decrease of lumbar spine BMD was prevented in the pamidronate group. No changes in hip BMD were observed. There were no differences in the number of fractures between the groups after 1 year. The bone biopsy data are detailed below. The second study by Grotz *et al.*¹⁶⁵ evaluated IV ibandronate at baseline and at 3, 6, and 9 months after transplantation. Loss of trabecular and cortical bone assessed by BMD was prevented by ibandronate. Fewer vertebral deformities by X-ray were observed in the ibandronate group than in the controls. No significant side effects or decreased GFR were reported.

In the study by Coco *et al.*,⁴⁶⁹ bone biopsies were performed at the time of transplant in 21 patients and in 14 patients after 6 months, six in the pamidronate group and eight in the control group. The mean activation frequency after 6 months was significantly lower in the pamidronate-treated patients than in the controls. All of the pamidronate patients had adynamic bone disease on the 6-month biopsy; four patients with initial HPT and one with mixed uremic osteodystrophy developed adynamic disease. In the control group, three of eight patients had adynamic bone disease and the rest were mixed. The bone turnover improved in five of eight (62%) patients among the control biopsies and in none of the pamidronate biopsies. It worsened in one control biopsy (12%) and in five of six (83%) pamidronate biopsies. Mineralization lag time determination was not available for the first biopsy. In the second biopsy, three subjects had prolonged mineralization lag time, indicating either osteomalacia or very little tetracycline uptake. In the control group, none of the biopsies had increased osteoid thickness, although several had elevated mineralization lag time. The data provided do not allow a clear interpretation of mineralization. Mean bone volume was normal in both groups. In the pamidronate group, there was no change from baseline. The mean bone volume in the control group decreased from 28.6 to 25.7 (10%), but this was not significant. Overall, the histology suggests development of adynamic bone disease in these patients, but the results are limited by a small number of subjects with a short follow-up time. It is also not clear whether the potential benefit from preserving bone volume and fracture reduction outweighs the potential harm of decreased bone formation and/or prolonged mineralization.

Overall, the quality of the preventive studies with bisphosphonates was ranked as moderate. Some of the studies showed limited fracture data and/or bone biopsy information. The observation in the study by Coco *et al.* that patients showed early evidence and progression to adynamic bone disease in some patients should raise caution about the indiscriminate use of bisphosphonates in renal transplant patients.

Long-term treatment

Calcitriol. There was only one study in long-term renal transplant patients (those patients >12 months from transplant) that evaluated the effect of calcitriol plus calcium carbonate vs no treatment (Tables 40, 41).⁴⁷⁰ This study enrolled 45 patients, with only 30 of them completing the trial. This RCT met our inclusion criteria because bone biopsies were an evaluated end point. The mean time after transplantation was 118.7 months in the treatment group and 133 months in the control group. Although significant improvement in BMD was observed after 1 year in the treatment group, no differences were observed between the treatment and nontreatment groups. No fracture data were reported. Thus, the overall quality of the evidence is low. After 1 year of treatment, patients in the treatment group had a

suppression of serum PTH, together with an increase in serum calcium (but within normal limits), as compared with the no-treatment group. The bone biopsy results showed that bone turnover was better in 43% of the control biopsies and 12% of the calcitriol biopsies, but worse in 28% of the control biopsies and 50% of the calcitriol biopsies. The study also described a decrease in osteoclast surfaces that represents a secondary index of turnover. Therefore, if a decrease in the osteoclast surface is accompanied by a drop in the bone formation rate into the adynamic range, then the overall turnover is worse.

No evidence of AEs was recorded with respect to changes in serum calcium, phosphorus, or intact PTH. No patients were withdrawn from the study because of AEs. A gradual decrease in GFR assessed by creatinine clearance was observed in both the control and treatment groups.

Bisphosphonates. Only one study examined the effect of bisphosphonates in long-term kidney transplant patients with established osteopenia or osteoporosis (Tables 42, 43). Jeffery *et al.* evaluated 117 patients with reduced BMD (T score ≤ -1). Patients were randomized to daily oral alendronate and calcium vs calcitriol and calcium.⁴⁷¹ There was no untreated control group in this study. One year of therapy was completed by 90 patients. Both treatments showed significant increases in lumbar spine and femur BMD. No differences between groups were shown. No information was provided on the number of patients who did not finish the study. No significant AEs or alterations in kidney function were reported. The quality of evidence of this study was ranked between moderate and low.

In a recent, nonrandomized controlled study by Conley *et al.*, the use of bisphosphonates was retrospectively evaluated in 554 kidney transplant patients who had at least two BMD analyses. Patients who received bisphosphonates after the first year of transplantation showed improved BMD, but did not have a reduced fracture rate when compared with those who did not receive the antiresorptive agents.⁴⁷²

Thus, the Work Group could not make any recommendations for long-term treatment strategies.

SPECIAL CONSIDERATIONS IN CHILDREN

One study reviewed treatments provided to 60 pediatric renal transplant patients (CKD stages 1–5T).⁴⁷³ In this four-arm study (see Table 39), the effect of alfacalcidol \pm calcitonin on BMD, as assessed by DXA, and on selected biochemical markers was compared to that of alendronate. No differences were found. No fracture data were collected. Another 30 patients from the same investigators were given either alfacalcidol or placebo therapy and DXA, and selected biochemistries were assessed.⁴⁷⁴ It is not clear whether these patients were separate from those reported in the first study cited above. Again, there were no differences in outcomes. Given the paucity of data about CKD stages 1–5T, and the inherent inaccuracy in the use of DXA in pediatric CKD, there is insufficient evidence to recommend specific

treatments for post-transplant renal bone disease in children at this point in time.

5.7 In patients with CKD stages 4–5T, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population and BMD does not predict the type of kidney transplant bone disease (2B).

In patients with CKD stages 4–5T, there is an increased likelihood of more severe underlying bone abnormalities of CKD-MBD that further decrease the utility of DXA in determining the underlying bone disorder. The data supporting routine use of DXA in a well-functioning allograft are weak (see above), and thus the Work Group felt that the additional confounder of CKD-MBD did not allow a recommendation for routine use of DXA in these patients.

5.8 In patients with CKD stages 4–5T with known low BMD, we suggest management as for patients with CKD stages 4–5 not on dialysis, as detailed in Chapters 4.1 and 4.2 (2C).

Despite not recommending routine DXA in patients with CKD stages 4–5T, the Work Group acknowledged that these patients might still have undergone such an assessment. When the DXA reveals low BMD, the patients should be fully evaluated and managed as for patients without a kidney transplant as detailed in Chapters 4.1 and 4.2. Importantly, these patients should be referred to as having low BMD, as opposed to osteoporosis,⁴⁷⁵ as the latter term often leads to treatments as in the general population with osteoporosis such as bisphosphonates. However, bisphosphonates can decrease bone turnover and therefore may theoretically worsen adynamic bone disease. As detailed in Chapters 3.2 and 4.3, bisphosphonates accumulate in bone for many years, and thus patients should be evaluated with a bone biopsy to ensure normal turnover before their use.

RESEARCH RECOMMENDATIONS

- Prospective studies in patients with CKD stages 3–5T should be performed to determine the level of BMD that is predictive of fractures and whether or not the predictive value is affected by other parameters of CKD-MBD, such as HPT.
- RCTs should be performed in patients with CKD stages 3–5T with low BMD at the time of kidney transplant to evaluate the effects of bisphosphonates or calcitriol and vitamin D analogs. The study should be of sufficient time (at least 1 year) to evaluate the effect on BMD change and patient-level outcomes, such as hospitalization, fractures, all-cause mortality, cardiovascular morbidity and mortality, and quality of life.
- RCTs should be performed in patients with CKD stages 3–5T with low serum calcidiol levels at the time of kidney transplant to evaluate the effect of vitamin D supplementation on change in BMD and patient-level outcomes, such as all-cause mortality, hospitalization, fracture, cardiovascular morbidity and mortality, and quality of life.

SUPPLEMENTARY MATERIAL

Supplementary Table 46. Summary table of RCTs examining treatment of CKD-MBD with calcitriol or vitamin D in CKD stages 1–5T—description of population at baseline.

Supplementary Table 47. Summary table of RCTs examining treatment of CKD-MBD with calcitriol or vitamin D in CKD stages 1–5T—intervention and results.

Supplementary Table 48. Summary table of RCTs examining treatment of CKD-MBD with calcitriol or vitamin D in CKD stages 1–5T—bone biopsy results.

Supplementary Table 49. Adverse events of vitamin D, calcitriol, or vitamin D analogs in CKD stages 1–5T.

Supplementary Table 50. Summary table of RCTs examining treatment of CKD-MBD with bisphosphonates vs control or calcitriol in CKD stages 1–5T—description of population at baseline.

Supplementary Table 51. Summary table of RCTs examining the treatment of CKD-MBD with bisphosphonates vs control or calcitriol in CKD stages 1–5T—intervention and results.

Supplementary Table 52. Summary table of RCTs examining the treatment of CKD-MBD with bisphosphonates vs control or calcitriol in CKD stages 1–5T—bone biopsy results.

Supplementary Table 53. Adverse events of bisphosphonates in CKD stages 1–5T.

Supplementary material is linked to the online version of the paper at <http://www.nature.com/ki>

Table 39 | RCTs of treatments for CKD-MBD in children with CKD stages 1–5T

Author (year)	N	Population	F/U	Study design	Arm 1 (arm 3)	Arm 2 (arm 4)	Outcomes
El-Husseini (2004) ⁴⁷³	60	CKD 1–5T	12 months	RCT	Alfacalcidol (calcitonin)	Alendronate (control)	DXA, Biochemical markers
El-Husseini (2004) ⁴⁷⁴	30	CKD 1–5T	12 months	RCT	Alfacalcidol	Control	DXA, Ca, P, PTH, CrCl

CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; CrCl, creatinine clearance; DXA, dual energy X-ray absorptiometry; F/U, follow-up; N, number of subjects; PTH, parathyroid hormone; RCT, randomized controlled trial.

Table 40 | Evidence matrix of calcitriol or vitamin D analogs vs placebo or calcium alone in CKD stages 1–5T

Outcome	Methodological quality									Adverse event reporting		
	A			B			C			Author	N (on agent)	F/U
	Author	N (on agent)	F/U	Author	N (on agent)	F/U	Author	N (on agent)	F/U			
Mortality	—	—	—	—	—	—	—	—	—	—	—	—
Clinical CVD	—	—	—	—	—	—	—	—	—	—	—	—
Hospitalization	—	—	—	—	—	—	—	—	—	—	—	—
CKD clinical outcomes	—	—	—	—	—	—	—	—	—	De Sevaux (2002) ^{466 a} Torres (2004) ^{467 a} Cuento-Manzano (2007) ^{470 b}	113 (65) 90 (45) 45 (23)	6 months 12 months 12 months
QoL	—	—	—	—	—	—	—	—	—	—	—	—
Fractures	—	—	—	—	—	—	—	—	—	De Sevaux (2002) ^{466 a} Torres (2004) ^{467 a} Cuento-Manzano (2000) ^{470 b}	113 (65) 90 (45) 45 (23)	6 months 12 months 12 months
PTx	—	—	—	—	—	—	—	—	—	—	—	—
Bone density	—	—	—	Torres (2004) ^{467 a}	90 (45)	12 months	De Sevaux (2002) ^{466 a} Josephson (2004) ^{468 a}	113 (65) 64 (26)	6 months 12 months	—	—	—
Bone histology	—	—	—	—	—	—	Cuento-Manzano (2000) ^{470 b}	30 (16)	12 months	—	—	—
Vascular/valvular calcification	—	—	—	—	—	—	—	—	—	—	—	—
GFR loss	—	—	—	—	—	—	De Sevaux (2002) ^{466 a} Torres (2004) ^{467 a}	113 (65) 90 (45)	6 months 12 months	—	—	—
Lab: Ca, P, PTH, ALP, b-ALP	—	—	—	De Sevaux (2002) ^{466 a} Torres (2004) ^{467 a}	113 (65) 90 (45)	6 months 12 months	—	—	—	—	—	—
Lab: Bicarbonate	—	—	—	Torres (2004) ^{467 a}	90 (45)	12 months	—	—	—	—	—	—
Adverse events	—	—	—	—	—	—	—	—	—	De Sevaux (2002) ^{466 a} Torres (2004) ^{467 a} Josephson (2004) ^{468 a} Cuento-Manzano (2000) ^{470 b}	113 (65) 90 (45) 64 (26) 45 (23)	6 months 12 months 12 months 12 months

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; CKD, chronic kidney disease; CVD, cardiovascular disease; F/U, follow-up; GFR, glomerular filtration rate; N, number of subjects; PTH, parathyroid hormone; PTx, parathyroidectomy; QoL, quality of life.

Note: Number randomized may be higher than number analyzed; this evidence matrix does not include studies of cholecalciferol vs control in CKD stages 1–5T (refer to summary table entry for Wissing, 2005).

^aEarly post-transplant (prevention).

^bLong-term kidney transplant recipients.

Table 41 | Evidence profile^a of calcitriol or vitamin D analogs vs placebo or calcium alone in CKD stages 1–5T

Outcome	Number of studies and study design	Total N (N on study drug)	Methodological quality of studies	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations ^b	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	—	—	—	—	—	—	—	—	Critical
Clinical CVD and CeVD	—	—	—	—	—	—	—	—	Critical
All-cause hospitalization	—	—	—	—	—	—	—	—	High
CKD clinical outcomes	AEs from 3 RCTs	248 (133)	Very serious limitations (–2)	—	—	—	Very low	Unable to assess	High
Quality of life	—	—	—	—	—	—	—	—	High
Fractures	AEs from 2 RCTs	203 (110)	Very serious limitations (–2)	—	—	—	Very Low	Unable to assess	High
PTx	—	—	—	—	—	—	—	—	High
Bone density	3 RCTs (early)	267 (135)	Very serious limitations (–2) ^c	No major inconsistencies	Direct	—	Low	Two studies showed statistically significant improvement of BMD. One was inconclusive	Moderate
Bone histology	1 RCT (LT)	30 (16)	Very serious limitations (–2) ^c	NA	Direct	Sparse data	Very low	Calcitriol caused more adynamic disease and placebo showed more improvement in turnover. Mineralization better with calcitriol, therefore overall results are complex	Moderate
Vascular/valvular calcification	—	—	—	—	—	—	—	—	Moderate
GFR loss	2 RCTs (early)	203 (110)	Very serious limitations (–2) ^d	NA	Direct	—	Low	Similar levels of CrCl at 6 months or 1 year	Moderate
<i>Laboratory measurements</i>									
Calcium	2 RCTs (early)	203 (110)	Serious limitations (–1) ^e	No major inconsistencies	Direct	—	Moderate	—	—
Phosphorus	2 RCTs (early)	203 (110)	Serious limitations (–1) ^e	No major inconsistencies	Direct	—	Moderate	Two studies show no difference in Ca, P, or ALP. One study showed no change in PTH, the other showed lower PTH with treatment.	Moderate
Ca × P	—	—	—	—	—	—	—	—	—
PTH	2 RCTs (early)	203 (110)	Serious limitations (–1) ^e	No major inconsistencies	Direct ^f	—	Moderate	One study showed no difference in bicarbonate	Moderate
ALP, b-ALP	2 RCTs (early)	203 (110)	Serious limitations (–1) ^e	No major inconsistencies	Direct	—	Moderate	—	—
Bicarbonate	1 RCT (early)	90 (45)	Serious limitations (–1) ^g	NA	Direct	Sparse data	Low	—	—
Adverse events	3 RCTs (early) 1 RCT (late)	267 (135) 30 (16)	—	—	—	—	—	Hypercalcemia was seen more in treatment arms in two studies and lead to a 3% discontinuation on one of the studies. No conclusions can be made with any certainty regarding graft function, acute rejection, new fractures or bone symptoms	Depends on outcome

Balance of Potential Benefits and Harm:

No evidence of benefit
Potential for hypercalcemia

Quality of Overall Evidence:

Moderate for biochemical outcomes
Low for other surrogate outcomes
Absent for patient-centered outcomes

AE, adverse event; ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; BMD, bone mineral density; CaXP, calcium-phosphorus product; CeVD, cerebrovascular disease; CKD, chronic kidney disease; CrCl, creatinine clearance; CVD, cardiovascular disease; GFR, glomerular filtration rate; LT, long term; N, number of subjects; NA, not applicable; PTH, parathyroid hormone; PTx, parathyroidectomy; RCT, randomized controlled trial.
^aThis evidence profile does not include studies of cholecalciferol vs control in CKD stages 1–5T (refer to summary table entry for Wissing, 2005).

^bOther considerations include: Imprecise or sparse data (–1), high probability of reporting bias (–1). For observational studies: other considerations include: strong association (+1 or +2), dose–response gradient (+1), all plausible confounders would have reduced the effect (+1).

^cOne grade B, two grade C.

^dTwo grade C.

^eTwo grade B.

^fHowever, limited certainty about the directness of PTH due to bias in PTH assays, and biological variability of PTH values and effect of different PTH fragments.

^gOne grade B.

Table 42 | Evidence matrix of bisphosphonates vs control in CKD stages 1–5T

Outcome	Methodological quality									Adverse event reporting		
	A			B			C			Author	N (on agent)	F/U
	Author	N (on agent)	F/U	Author	N (on agent)	F/U	Author	N (on agent)	F/U			
Mortality	—	—	—	—	—	—	—	—	—	Grotz (2001) ¹⁶⁵	80 (40)	12 months
Clinical CVD	—	—	—	—	—	—	—	—	—	—	—	—
Hospitalization	—	—	—	—	—	—	—	—	—	—	—	—
CKD clinical outcomes	—	—	—	—	—	—	—	—	—	Grotz (2001) ¹⁶⁵	80 (40)	12 months
QoL	—	—	—	—	—	—	—	—	—	—	—	—
Clinical fractures	—	—	—	—	—	—	Grotz (2001) ¹⁶⁵	80 (40)	12 months	—	—	—
Radiological fractures	—	—	—	—	—	—	Grotz (2001) ¹⁶⁵	80 (40)	12 months	—	—	—
							Coco (2003) ⁴⁶⁹	72 (36)	12 months			
PTx	—	—	—	—	—	—	—	—	—	—	—	—
Bone density	Grotz (2001) ¹⁶⁵	80 (40)	12 months	Coco (2003) ⁴⁶⁹	50 (X ^a)	12 months	—	—	—	—	—	—
Bone histology	—	—	—	Coco (2003) ⁴⁶⁹	50 (X ^a)	12 months	—	—	—	—	—	—
Vascular/valvular calcification	—	—	—	—	—	—	—	—	—	—	—	—
GFR loss	—	—	—	—	—	—	Grotz (2001) ¹⁶⁵	80 (40)	12 months	—	—	—
							Coco (2003) ⁴⁶⁹	72 (36)	12 months			
Lab: Ca, P, PTH	—	—	—	Grotz (2001) ¹⁶⁵	80 (40)	12 months	—	—	—	—	—	—
				Coco (2003) ⁴⁶⁹	72 (36)	12 months						
Lab: ALP, b-ALP	—	—	—	Grotz (2001) ¹⁶⁵	80 (40)	12 months	—	—	—	—	—	—
				Coco (2003) ⁴⁶⁹	72 (36)	12 months						
Adverse events										Grotz (2001) ¹⁶⁵	80 (40)	12 months
										Coco (2003) ⁴⁶⁹	72 (36)	12 months

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; CKD, chronic kidney disease; CVD, cardiovascular disease; F/U, follow-up; GFR, glomerular filtration rate; N, number of subjects; PTH, parathyroid hormone; PTx, parathyroidectomy; QoL, quality of life.

Note: N analyzed may be less than N randomized; This evidence matrix does not include studies of bisphosphonate vs vitamin D in CKD stages 1–5T (refer to summary table entry for Jeffery, 2003).

^aUnclear reporting regarding the number of individuals who received study drug.

Table 43 | Evidence profile^a for the treatment of CKD-MBD with bisphosphonates vs control in CKD stages 1-5T

Outcome	Number of studies and study design	Total N (N on study drug)	Methodological quality of studies	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations ^b	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	AE from 1 RCT	80 (40)	Very serious limitations (-2)	—	—	—	Very low	Unable to assess	Critical
Clinical CVD and CeVD ^c	—	—	—	—	—	—	—	—	Critical
All-cause hospitalization	—	—	—	—	—	—	—	—	High
CKD clinical outcomes	AE from 1 RCT	80 (40)	Very serious limitations (-2)	—	—	—	Very low	Unable to assess	High
Quality of life	—	—	—	—	—	—	—	—	High
<i>Fractures</i>									
Clinical	1 RCT	80 (40)	Very serious limitations (-2) ^d	NA	Direct	Sparse data	Very low	Unable to assess	High
Radiological	2 RCTs	152 (76)	Very serious limitations (-2) ^e	No major inconsistencies ^f	Direct	Sparse data	Very low	Unable to assess	High
PTx	—	—	—	—	—	—	—	—	High
Bone density	2 RCTs	152 (76)	Serious limitations (-1) ^g	No major inconsistencies	Direct	—	Moderate	Treatment arms show improvement in BMD at different sites. Effect size is variable	Moderate
Bone histology	1 RCT	50 (X)	—	—	—	—	—	Pamidronate biopsies developed adynamic bone but volume was slightly better	Moderate
Vascular/ valvular calcification	—	—	—	—	—	—	—	—	Moderate
GFR loss	2 RCTs	152 (76)	Serious limitations (-2) ^h	No major inconsistencies	Direct	—	Low	Similar levels of CrCl at 1 year	Moderate
<i>Laboratory measurements</i>									
Calcium	2 RCTs	152 (76)	Serious limitations (-1) ⁱ	No major inconsistencies	Direct	—	Moderate	—	—
Phosphorus	2 RCTs	152 (76)	Serious limitations (-1) ^j	No major inconsistencies	Direct	—	Moderate	—	—
PTH	2 RCTs	152 (76)	Serious limitations (-1) ^j	No major inconsistencies	Direct ^k	—	Moderate	No significant difference over 1 year follow-up	Moderate
CaXP	—	—	—	—	—	—	—	—	—
ALP, b-ALP	2 RCTs	152 (76)	Serious limitations (-1) ⁱ	—	—	—	Moderate	—	—
Adverse events	—	—	—	—	—	—	—	One study in early transplant shows a statistically significant reduction in acute rejection episodes with ibandronate vs Ca. Trend toward greater GI discomfort with bisphosphonates compared with control	Depends on outcome

Balance of Potential Benefits and Harm:

Evidence regarding benefit of bisphosphonates in BMD at different sites
 No evidence demonstrating a difference in GFR loss, Ca, P or PTH
 Limited data showing association with acute rejection or GI discomfort

Quality of Overall Evidence:

Moderate for biochemical outcomes
 Moderate for other surrogate outcomes
 Absent for patient-centered outcomes

AE, adverse event; ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; BMD, bone mineral density; CaXP, calcium-phosphorus product; CeVD, cerebrovascular disease; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; CrCl, creatinine clearance; CVD, cardiovascular disease; GFR, glomerular filtration rate; GI, gastrointestinal; N, number of subjects; NA, not applicable; PTH, parathyroid hormone; PTx, parathyroidectomy; RCT, randomized controlled trial.

^aThis evidence profile does not include studies of bisphosphonate vs vitamin D in CKD stages 1-5T (refer to summary table entry for Jeffery, 2003).

^bOther considerations include: Imprecise or sparse data (-1), high probability of reporting bias (-1). For observational studies: other considerations include: strong association (+1 or +2), dose-response gradient (+1), all plausible confounders would have reduced the effect (+1).

^cClinical cardiovascular and cerebrovascular disease.

^dOne grade C.

^eTwo grade C.

^fConsistencies in direction on effect.

^gOne grade A, one grade B.

^hTwo grade C.

ⁱTwo grade B.

^jTwo grade B.

^kHowever, limited certainty about the directness of PTH due to bias in PTH assays, and biological variability of PTH values and effect of different PTH fragments.

Chapter 6: Summary and research recommendations

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As detailed throughout this guideline, there is a paucity of high-quality studies evaluating the clinical benefit of various treatments given to patients with chronic kidney disease—mineral and bone disorder (CKD–MBD). **Table 44** summarizes the number and quality of randomized controlled trials by end points. More detailed summaries are provided in **Table 45** and (*Supplementary Tables 54 and 55*). As CKD–MBD is unique to patients with CKD stages 3–5D and stages 1–5T, we unfortunately do not have treatment studies in the general population that we can apply to the management of our patients. The Work Group *a priori* decided that we should focus only on randomized controlled trials with at least 6 months' duration and sufficient sample size to guide treatment decisions. Therefore, additional randomized controlled trials of shorter duration are not included in this table. However, it is unlikely that these shorter studies provided high-quality evidence on clinical end points. Owing to the paucity of randomized controlled trials in this field, the Work Group made the attempt to also use observational studies with large sample size of treatment effects that were relevant to the guideline treatment questions, under the condition that they showed a relative risk of >2.0 or <0.5

for patient-centered outcomes. No observational treatment studies meeting these criteria were identified.

This guideline contains mostly level 2 recommendations. These are formulated on the basis of the expert judgment of the Work Group and the review of evidence that is either of low quality or that does not examine patient-centered end points. As detailed in Chapter 2, there are important differences in the implications for level 1 and level 2 recommendations (Chapter 2).

The grading of recommendations adopted for the guideline is shown in **Table 46** (also shown in Chapter 2).

It is important to reinforce that level 2 recommendations are not meant to be used for quality performance measures by dialysis providers or payers. Level 2 recommendations should also not be considered mandatory for a specific therapeutic approach. Instead, level 2 recommendations are meant to guide clinicians in caring for patients, and these recommendations must be validated by future research. It is also important that the grade for the strength of the recommendation and the quality of the evidence corresponding to each statement (see Chapter 2) be included whenever a recommendation is reproduced or communicated.

Table 44 | Summary of cumulative evidence matrix with patient-centered outcomes, other surrogate outcomes, and biochemical outcomes

Outcome	Methodological quality of outcome			Total
	A Number of studies	B Number of studies	C Number of studies	
Patient-centered outcomes				
Mortality	—	2	1	15
Clinical CVD	—	—	—	
Hospitalization	—	—	2	
CKD clinical outcomes	—	—	—	
QoL	—	—	1	
Fractures	—	1	7	
PTx	—	—	1	
Other surrogate outcomes				
BMD	1	6	7	47
Bone histomorphometry	2	5	6	
Vascular/valvular calcification	—	5	3	
GFR loss	—	—	12	
Biochemical outcomes				
Lab: Serum Ca, P	3	19	7	71
Lab: Serum ALP, b-ALP	1	12	5	
Lab: PTH, Vit D, bicarb	1	20	3	
Total	8	70	55	

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; Bicarb, bicarbonate; BMD, bone mineral density; Ca, calcium; CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate; P, phosphorus; PTH, parathyroid hormone; PTx, parathyroidectomy; QoL, quality of life; Vit D, vitamin D.

Table 45 | Cumulative evidence matrix for all treatment studies by outcome

Outcome	Methodological quality of outcome								
	A			B			C		
	Author	N (on agent)	F/U	Author	N (on agent)	F/U	Author	N (on agent)	F/U
Mortality	—	—	—	Block (2007) ²⁶⁵ St Peter (2008) ^{267 a}	127 (60) 2102 (1051)	44 months 28 months	Cunningham (2005) ³⁸⁶	1184 (697)	6–12 months
Clinical CVD	—	—	—	—	—	—	—	—	—
Hospitalization	—	—	—	—	—	—	Cunningham (2005) ³⁸⁶ Suki (2007) ^{266 a}	1184 (697) 2103 (1053)	6–12 months 20 months
CKD clinical outcomes	—	—	—	—	—	—	—	—	—
QoL	—	—	—	—	—	—	Cunningham (2005) ³⁸⁶	1184 (697)	6–12 months
Fractures	—	—	—	Ishani (2008) ⁴⁴¹	4973 (3293)	36 months	Miller (2005) ¹²⁶ Cunningham (2005) ³⁸⁶ Baker (1986) ¹⁰¹ Jamal (2007) ¹²⁷ Grotz (2001) ¹⁶⁵ Coco (2003) ⁴⁶⁹ Miller (2007) ⁴⁷⁶	2658 (X ^b) 1184 (697) 76 (38) 581 (X ^b) 80 (40) 72 (36) 731 (485)	22–25 months 6–12 months 60 months 36 months 12 months 12 months 21 months
PTx	—	—	—	—	—	—	Cunningham (2005) ³⁸⁶	1184 (697)	6–12 months
Bone density	Grotz (2001) ¹⁶⁵	80 (40)	12 months	Coco (2003) ⁴⁶⁹ Jeffery (2003) ⁴⁷¹ Torres (2004) ⁴⁶⁷ Wissing (2005) ⁴⁷⁷ Hernandez (2003) ⁴⁴⁴ Ishani (2008) ⁴⁴¹	50 (X ^b) 117 (46) 90 (45) 90 (46) 50 (25) 4973 (3293)	12 months 12 months 12 months 12 months — 36 months	Miller (2005) ¹²⁶ Jamal (2007) ¹²⁷ Raggi (2005) ³⁴⁶ Asmus (2005) ³⁴⁴ De Sevaux (2002) ⁴⁶⁶ Josephson (2004) ⁴⁶⁸ Miller (2007) ⁴⁷⁶	4643 (2335) 581 (X ^b) 111 (51) 114 (55) 113 (65) 64 (26) 731 (485)	22–25 months 36 months 12 months 21 months 6 months 12 months 21 months
Bone histology	Ferreira (2008) ¹⁰⁴ Barreto (2008) ²⁸⁸	91 (44) 101 (41)	13.5 months 12 months	Freemont (2005) ¹³ Spasovski (2006) ⁹⁸ Salusky (2005) ¹⁷ Malluche (2008) ¹⁰³	63 (30) 24 (12) 29 (15) 211 (51)	12 months 12 months 8 months 24 months	Hamdy (1995) ⁹⁷ Nordal (1988) ¹⁰² Baker (1986) ¹⁰¹ Salusky (1998) ¹⁸ Coco (2003) ⁴⁶⁹ Cuento-Manzano (2000) ⁴⁷⁰ Malluche (2008) ³⁸⁹	134 (72) 30 (15) 76 (38) 46 (16) 72 (36) 30 (16) 48 (32)	24 months 8 months 60 months 12 months 12 months 12 months 24 months
Vascular/Valvular Calcification	—	—	—	Quinibi (2008) ²⁸⁷ Chertow (2002) ^{284/} Chertow (2003) ³⁵⁷ Raggi (2004) ³⁴⁵ Block (2005) ²⁸⁵ Russo (2007) ²⁸⁶	203 (103) 200 (99) — 132 (62) 148 (73) 90 (30)	12 months 12 months — 12 months 18 months 24 months	Baker (1986) ¹⁰¹ Asmus (2005) ³⁴⁴ Barreto (2008) ²⁸⁸	76 (38) 114 (55) 101 (41)	60 months 21 months 12 months
GFR loss	—	—	—	—	—	—	Miller (2005) ¹²⁶ Coyne (2006) ³⁷⁷ Hamdy (1995) ⁹⁷ Coburn (2004) ³⁷⁶ Grotz (2001) ¹⁶⁵ Coco (2003) ⁴⁶⁹ Jeffery (2003) ⁴⁷¹ De Sevaux (2002) ⁴⁶⁶ Torres (2004) ⁴⁶⁷ Miller (2007) ⁴⁷⁶ Wissing (2005) ⁴⁷⁷ Russo (2007) ²⁸⁶	4643 (2335) 220 (107) 176 (89) 55 (27) 80 (40) 72 (36) 117 (46) 113 (65) 90 (45) 731 (485) 90 (46) 90 (30)	22–25 months 6 months 24 months 6 months 12 months 12 months 12 months 6 months 12 months 21 months 12 months 24 months
Lab: Ca, P	Coyne (2006) ³⁷⁷ Coburn (2004) ³⁷⁶ Culleton (2007) ³¹⁴	220 (107) 55 (27) 52 (26)	6 months 6 months 6 months	Block (2004) ³⁸⁷ Lindberg (2005) ³⁸⁸ Moe (2005) ³⁹⁵ Baker (1986) ¹⁰¹ Hamdy (1995) ⁹⁷ Sprague (2003) ³⁹² Freemont (2005) ¹³ Chertow (2002) ²⁸⁴ Block (2005) ²⁸⁵ Grotz (2001) ¹⁶⁵ Coco (2003) ⁴⁶⁹ De Sevaux (2002) ⁴⁶⁶	741 (371) 395 (294) 0 ^a 76 (38) 176 (89) 266 (133) 98 (49) 200 (99) 148 (73) 80 (40) 72 (36) 113 (65)	6 months 6 months 6 months 60 months 24 months 3–8 months 12 months 12 months 18 months 12 months 12 months 6 months	Miller (2005) ¹²⁶ Hayashi (2004) ³⁹¹ Finn (2006) ³⁴⁹ Suki (2007) ²⁶⁶ Asmus (2005) ³⁴⁴ Barreto (2008) ²⁸⁸	4643 (2335) 91 (47) 1359 (682) 2103 (1053) 114 (55) 101 (41)	22–25 months 12 months 24 months 20 months 24 months 12 months

Table 45 | Continued

Outcome	Methodological quality of outcome								
	A			B			C		
	Author	N (on agent)	F/U	Author	N (on agent)	F/U	Author	N (on agent)	F/U
				Torres (2004) ⁴⁶⁷	90 (45)	12 months			
				Wissing (2005) ⁴⁷⁷	90 (46)	12 months			
				Russo (2007) ²⁸⁶	90 (30)	24 months			
				Quinibi (2008) ²⁸⁷	203 (103)	12 months			
				Ferreira (2008) ¹⁰⁴	91 (44)	13.5 months			
				Malluche (2008) ¹⁰³	211 (51)	24 months			
				Kooienga (2009) ³⁷⁴	322 (214)	24 months			
Lab: ALP, b-ALP	Coyne (2006) ³⁷⁷	220 (107)	6 months	Block (2004) ³⁸⁷	741 (371)	6 months	Raggi (2005) ³⁴⁶	111 (51)	12 months
				Coburn (2004) ³⁷⁶	55 (27)	6 months	Hayashi (2004) ³⁹¹	91 (47)	12 months
				Hamdy (1995) ⁹⁷	176 (89)	24 months	Finn (2006) ³⁴⁹	1359 (682)	24 months
				Baker (1986) ¹⁰¹	76 (38)	60 months	Barreto (2008) ²⁸⁸	101 (41)	12 months
				Grotz (2001) ¹⁶⁵	80 (40)	12 months	Kooienga (2009) ³⁷⁴	322 (214)	24 months
				Coco (2003) ⁴⁶⁹	72 (36)	12 months			
				Russo (2007) ²⁸⁶	90 (30)	24 months			
				De Sevaux (2002) ⁴⁶⁶	113 (65)	6 months			
				Torres (2004) ⁴⁶⁷	90 (45)	12 months			
				Quinibi (2008) ²⁸⁷	203 (103)	12 months			
				Ferreira (2008) ¹⁰⁴	91 (44)	13.5 months			
				Malluche (2008) ¹⁰³	211 (51)	24 months			
Lab: PTH, Vit D, Bicarb	Coyne (2006) ³⁷⁷	220 (107)	6 months	Block (2004) ³⁸⁷	741 (371)	6 months	Finn (2006) ³⁴⁹	1359 (682)	24 months
				Lindberg (2005) ³⁸⁸	395 (294)	6 months	Asmus (2005) ³⁴⁴	114 (55)	24 months
				Moe (2005) ³⁹⁵	0 ^a	6 months	Hayashi (2004) ³⁹¹	91 (47)	12 months
				Baker (1986) ¹⁰¹	76 (38)	60 months			
				Hamdy (1995) ⁹⁷	176 (89)	24 months			
				Sprague (2003) ³⁹²	266 (133)	3–8 months			
				Freemont (2005) ¹³	98 (49)	12 months			
				Chertow (2002) ²⁸⁴	200 (99)	12 months			
				Block (2005) ²⁸⁵	148 (73)	18 months			
				Grotz (2001) ¹⁶⁵	80 (40)	12 months			
				Coco (2003) ⁴⁶⁹	72 (36)	12 months			
				De Sevaux (2002) ⁴⁶⁶	113 (65)	6 months			
				Torres (2004) ⁴⁶⁷	90 (45)	12 months			
				Wissing (2005) ⁴⁷⁷	90 (46)	12 months			
				Culleton (2007) ³¹⁴	52 (26)	6 months			
				Russo (2007) ²⁸⁶	90 (30)	24 months			
				Quinibi (2008) ²⁸⁷	203 (103)	12 months			
				Ferreira (2008) ¹⁰⁴	91 (44)	13.5 months			
				Malluche (2008) ¹⁰³	211 (51)	24 months			
				Choncol (2009) ³⁷⁹	404 (302)	8 months			

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; Bicarb, bicarbonate; Ca, calcium; CKD, chronic kidney disease; CVD, cardiovascular disease; F/U, follow-up; GFR, glomerular filtration rate; N, number of subjects; P, phosphorus; PTH, parathyroid hormone; PTx, parathyroidectomy; QoL, quality of life; Vit D, vitamin D.

All single studies of a specific comparison are shown in gray.

^aN for Moe (2005)³⁹⁵ study is equal to the N from Lindberg (2005)³⁸⁸+Block (2004)³⁸⁷

^bUnclear reporting regarding the number of individuals who received the study drug.

Table 46 | Grading of recommendations

Grade for strength of recommendation ^a	Strength	Wording	Grade for quality of evidence	Quality of evidence
Level 1	Strong	'We recommend...should'	A	High
Level 2	Weak	'We suggest...might'	B	Moderate
			C	Low
			D	Very low

^aIn addition the Work Group could also make ungraded statements (See Chapter 2 section on ungraded statements).

Only then will the true state of the evidence be recognized by all.

Given that the majority of the recommendations in this document are level 2, it should be obvious that much additional high-quality research is needed in the field of CKD-MBD to resolve uncertainties and allow the formula-

tion of more level 1 recommendations in the future. In each of the individual chapters, there are several research recommendations. The Work Group also felt that it was important to prioritize research, and determined that future studies such as those below are of critical importance to advance the field and improve patient care.

- Develop a risk-stratification tool based on CKD-MBD components and evaluate its predictive accuracy for clinical outcomes in patients with CKD stages 3–5, 5D, and 3–5T.
- Determine whether, in patients with CKD-MBD, a single measurement of bone mineral density (measured by dual energy X-ray absorptiometry or quantitative computed tomography) and serial changes in bone mineral density can predict fractures.
- Determine whether the presence or absence of vascular/valvular calcification in patients with CKD-MBD is an appropriate stratification and selection tool to identify individuals who may benefit from specific interventions.
- Determine whether the effect of an intensive CKD-MBD treatment approach (for example, protocol-driven combination therapy to achieve specific serum phosphorus and parathyroid hormone targets) vs a less intensive treatment approach (for example, protocol-driven combination therapy allowing higher serum phosphorus and parathyroid hormone targets) vs standard care improves clinical outcomes in patients with CKD stages 3–5D.
- Determine whether treating down to normal serum phosphorus levels (as compared with phosphorus levels of 5.5–6.5 mg/dl; 1.78–2.10 mmol/l) with the use of combinations of different phosphate binders and other approaches improves clinical outcomes in patients with CKD stages 4–5D and 4–5T.
- Determine whether treatment to a lower vs higher serum parathyroid hormone target improves or worsens clinical outcomes in patients with CKD stages 3–5, CKD stage 5D, and CKD stages 3–5T.
- Determine whether treatment with vitamin D (ergocalciferol or cholecalciferol) or calcidiol [25(OH)D], compared with calcitriol or vitamin D analogs, improves clinical outcomes in patients with CKD stages 3–5, CKD stage 5D, and CKD stages 1–5T.
- Determine which phosphate binders and other serum phosphorus-lowering treatments are able to improve survival in patients with CKD stages 3–5D and CKD stages 3–5T.
- Determine whether treatment with bisphosphonates, teriparatide, or raloxifene reduces fractures or vascular calcification in patients with CKD stages 3–5D and CKD stages 1–5T.
- Determine whether strategies to reverse adynamic bone disease by measures such as endogenous stimulation of parathyroid hormone secretion (for example, using low-calcium dialysate) or exogenous teriparatide administration, affect clinical outcomes in patients with CKD stages 4–5D or CKD stages 1–5T, compared with placebo.

SUPPLEMENTARY MATERIAL

Supplementary Table 54. Summary of cumulative evidence matrix of adverse events.

Supplementary Table 55. Adverse event reporting.

Supplementary material is linked to the online version of the paper at <http://www.nature.com/ki>

Biographic and disclosure information

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Advisor/Consultant: Amgen; DiaSorin; Genzyme; INEOS; Litholink; Shire

Royalties: Amgen

Speaker: Amgen; Genzyme

Grant/Research Support: Amgen; Genzyme; INEOS; Shire

Tilman B Drüeke, MD, FRCP (Work Group Co-Chair), is Inserm Research Director Emeritus and former Associate Professor of Medicine at Hôpital Necker in Paris, France. He began his medical studies at the University of Frankfurt in 1961 and graduated from the Medical School of Tübingen in 1967. Dr Drüeke later completed his postdoctoral and research fellowships at the Department of Nephrology, Hôpital Necker. Since 1983, he has been Director of Research at Inserm. From 1986 to 1998, he was the director of Inserm Unit 90 at Hôpital Necker. In 1998, he was elected as Fellow of the Royal College of Physicians of Edinburgh. He is an honorary member of the Gesellschaft für Nephrologie and of the Polish Society of Nephrology. He was elected as Professor honoris causa by Saints Cyril and Methodius University, Skopje, Republic of Macedonia, in 2008. He was a council member of the Société de Néphrologie (SN), European Renal Association-European Dialysis and Transplant Association (ERA-EDTNA), and International Society of Nephrology (ISN), and a member of the Scientific Program Committee of the American Society of Nephrology in 1999 and 2009. His nephrology interests include chronic renal failure,

hemodialysis, metabolic and endocrine abnormalities of chronic kidney disease (CKD), and cardiovascular diseases. He served as Editor-in-Chief for *NDT* (1999–2005) and currently serves as Associate Editor for *CJASN*. Dr Drüeke is also an editorial board member for *Journal of the American Society of Nephrology* and *Kidney International*, a reviewer for numerous other journals, and the author of more than 450 peer-reviewed articles.

Advisor/Consultant: Amgen; Fresenius Medical care; Genzyme; INEOS; Leo; Mitsubishi; Roche; Theraclion

Speaker: Amgen; Chugai; Genzyme; Kirin; Roche

Grant/Research Support: Amgen; Genzyme; Shire

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Advisor/Consultant: Amgen; Cytochroma; Genzyme

Speaker: Genzyme

Grant/Research Support: Amgen; Fresenius; Genzyme; Novartis; Shire

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Advisor/Consultant: Amgen; Shire

Speaker: Abbott; Genzyme; Shire

Grant/Research Support: Abbott; Amgen

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Advisor/Consultant: Abbott; Amgen; Genzyme; Shire/Orphan Australia

Speaker: Abbott; Amgen

Grant/Research Support: Roche

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Advisor/Consultant: Abbott Japan; Bayer Japan; Kyowa Hakko Kirin Co. Ltd; Novartis Pharma Co. Ltd

Speaker: Bayer Japan; Chugai Pharmaceutical Co. Ltd; Kyowa Hakko Kirin Co. Ltd

Grant/Research Support: Chugai Pharmaceutical Co. Ltd; Kyowa Hakko Kirin Co. Ltd

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Advisor/Consultant: Abbott; Genzyme

Speaker: Genzyme

Grant/Research Support: Abbott; Genzyme; Mantecorp

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Advisor/Consultant: Abbott; Amgen; Fresenius Medical Care; Genzyme; Shire

Speaker: Abbott; Amgen; Fresenius Medical Care; Genzyme; Shire

Grant/Research Support: Abbott; Amgen; Genzyme

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Advisor/Consultant: Genzyme

Speaker: Abbott; Genzyme

Grant/Research Support: Amgen

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Advisor/Consultant: Abbott; Amgen; Genzyme; Ortho Biotech; Shire

Speaker: Abbott; Amgen; Genzyme; Ortho Biotech; Shire

Grant/Research Support: Abbott; Amgen; Genzyme; Ortho Biotech; Shire

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Advisor/Consultant: Amgen; Genzyme

Speaker: Amgen; Baxter Healthcare; The France Foundation; Genzyme; Prime Medica

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Advisor/Consultant: Zymogenetics

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Grant/Research Support: Abbott Laboratories Ltd; Baxter Renal

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Advisor/Consultant: Fresenius Medical Care; Genzyme; Novartis; Roche

Speaker: Fresenius Medical Care; Genzyme; Novartis; Roche

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Advisor/Consultant: Abbott; Amgen; Genzyme, Vifor

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Grant/Research Support: Amgen; Genzyme

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Speaker: Amgen; Ortho Biotech; Roche

Grant/Research Support: Ortho Biotech; Roche

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*Advisor/Consultant: Astellas; Litholink; Novartis; Wyeth
Grant/Research Support: Bristol Myers Squibb; Merck-Schering Plough*

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