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Editorial correspondence and manuscript submissions should be addressed to Bertram L. Kasiske, MD, Editor-in-Chief, *AJKD,* Hennepin Faculty Associates, 600 HFA Building, Room D508, 914 South 8th Street, Minneapolis, MN 55404. Telephone: (612) 347-7770

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## K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease

## K/DOQI Disclaimer

These Guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care, and should not be construed as one. Neither should they 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 Guidelines 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.

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These Guidelines, as well as other K/DOQI guidelines, can be accessed on the internet at: www.kdoqi.org

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AMGEN genzyme

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# Acronyms and Abbreviations

| | |
|---|---|
| ABD | Adynamic bone disease |
| ACI | Aortic calcification index |
| ADHR | Autosomal dominant hypophosphatemic rickets |
| AIs | Adequate intakes |
| APD | Aminohydroxypropylidene |
| AVN | Avascular necrosis |
| A$\beta_2$M | $\beta_2$-microglobulin amyloidosis |
| BCG | Bromocresol green method |
| BFR | Bone formation rate |
| BMD | Bone mineral density |
| CaR | Calcium-sensing receptors |
| CAPD | Continous ambulatory peritoneal dialysis |
| CCR | Creatinine clearance rate |
| CKD | Chronic kidney disease |
| DBP | Vitamin D-binding protein |
| DEXA | Dual energy X-ray absorptiometry |
| DFO | Desferrioxamine |
| DOQI | Dialysis Outcomes Quality Initiative |
| DRA | Dialysis-related amyloidosis |
| DRI | Dietary Reference Intake |
| EBCT | Electron beam computed tomography |
| ESRD | End stage renal disease |
| GFR | Glomerular filtration rate |
| ICMA | Immunochemiluminometric assay |
| IRMA | Immunoradiometric assay |
| K/DOQI | Kidney Disease Outcomes Quality Initiative |
| MCV | Mean cell volume |
| MDRD | Modification of Diet in Renal Disease |
| NKF | National Kidney Foundation |
| PTH | Parathyroid hormone |
| QCT | Quantitative computed tomography |
| RDA | Recommended dietary allowance |
| RDI | Recommended daily intake |
| ROC | Receiver operating characteristics |
| Tm | Tubular maximum |
| VDR | Vitamin D receptor |
| VDRE | Vitamin D receptor element, vitamin D-responsive element |

# K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease

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KECK School of Medicine
University of Southern California
Los Angeles, CA

*Vice-Chair:*
Jack W. Coburn, MD
VA Greater Los Angeles Healthcare System
Los Angeles, CA

### *Work Group Members*

Glenn M. Chertow, MD, MPH
University of California San Francisco
San Francisco, CA

Keith Hruska, MD
Barnes Jewish Hospital
St. Louis, MO

Craig Langman, MD
Children's Memorial Hospital
Chicago, IL

Hartmut Malluche, MD
University of Kentucky
Lexington, KY

Kevin Martin, MD, BCh
St. Louis University
St. Louis, MO

Linda M. McCann, RD, CSR, LD
Satellite Dialysis Centers
Rocklin, CA

James T. McCarthy, MD
Mayo Clinic
Rochester, MN

Sharon Moe, MD
Indiana University
Wishard Memorial
Indianapolis, IN

Isidro B. Salusky, MD
UCLA School of Medicine
Los Angeles, CA

Donald J. Sherrard, MD
VA Puget Sound Healthcare System
Seattle, WA

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Los Angeles, CA

Kline Bolton, MD
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### *ECRI*
### *Plymouth Meeting, PA*

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**Ex-Officio:**

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Thomas Hostetter, MD

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*Co-Chair Emeritus*

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Brian J.G. Pereira, MD, DM, MBA
Kerry Willis, PhD

## K/DOQI Guideline Development NKF Staff

Nadine Ferguson
Donna Fingerhut
Anthony Gucciardo
Margaret Klette
Doreen Mallard
Kerry Willis, PhD

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# Foreword

FROM ITS rudimentary beginnings in the 1960s, through its widespread and increasing availability to the present, dialysis has provided lifesaving replacement therapy for millions of individuals with end-stage renal disease (ESRD). Parallel advances in understanding the course of progressive kidney disease and its complications have resulted in the development of interventions that can slow the progression and ameliorate the complications of chronic kidney disease (CKD). Thus, while dialysis has made it possible to prolong the lives of patients with ESRD, today it is also possible to retard the course of progression of kidney disease, to treat accompanying comorbidities earlier, and to improve the outcomes and quality of life of all individuals afflicted with kidney disease, well before replacement therapy becomes necessary. Yet, the application of these advances remains inconsistent, resulting in variations in clinical practice and, sadly, in avoidable differences in patient outcomes.

In keeping with its longstanding commitment to improving the quality of care delivered to all patients with kidney disease and the firm conviction that substantial improvements in the quality and outcomes of their care are achievable, the National Kidney Foundation (NKF) launched in 1995 the Dialysis Outcomes Quality Initiative (DOQI), supported by an educational grant from Amgen, Inc., to develop clinical practice guidelines for dialysis. Since their publication in 1997, the DOQI Guidelines have had a significant and measurable impact on the care and outcomes of dialysis patients.[1,2] The frequency with which they continue to be cited in the literature and serve as the focus of national and international symposia is but a partial measure of their impact. The DOQI Guidelines have also been translated into more than a dozen languages; selected components of the Guidelines have been adopted in various countries across the world; and they have provided the basis of clinical performance measures developed and put into effect by the Health Care Financing Administration (now renamed the Center for Medicare and Medicaid Services [CMS] in the United States).

In the course of development of DOQI it became evident that, in order to further improve dialysis outcomes, it was necessary to improve the health status of those who reach ESRD, and that therein existed an even greater opportunity to improve outcomes for all individuals with kidney disease, from earliest kidney injury through the various stages of progression to kidney failure, when replacement therapy becomes necessary. It was on this basis that in the fall of 1999, the Board of Directors of the NKF approved a proposal to move the clinical practice guideline initiative into a new phase, in which its scope would be enlarged to encompass the entire spectrum of kidney disease. This enlarged scope increases the potential impact of improving outcomes of care from the hundreds of thousands on dialysis to the millions of individuals with kidney disease who may never require dialysis. To reflect these expanded goals, the reference to "dialysis" in DOQI was changed to "disease," and the new initiative was termed the Kidney Disease Outcomes Quality Initiative (K/DOQI).

The objectives of K/DOQI are ambitious and its challenges considerable. As a first and essential step it was decided to adhere to the guiding


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principles that were instrumental to the success of DOQI. The first of these principles was that the development of guidelines would be scientifically rigorous and based on a critical appraisal of the available evidence. Secondly, the participants involved in developing the guidelines would be multidisciplinary. This was especially crucial because the broader nature of the new guidelines will require their adoption across several specialties and disciplines. Thirdly, the Work Groups charged with developing the guidelines would be the final authority on their content, subject to the requirements that they be evidence-based whenever possible, and that the rationale and evidentiary basis of each guideline be explicit. By vesting decision-making authority in highly regarded experts from multiple disciplines, the likelihood of developing clinically applicable and sound guidelines is increased. Finally, the guideline development process would be open to general review, in order to allow the chain of reasoning underlying each guideline to undergo peer review and debate prior to publishing. It was believed that such a broad-based review process would promote a wide consensus and support of the guidelines among health-care professionals, providers, managers, organizations, and patients.

To provide a unifying focus to K/DOQI, it was decided that its centerpiece would be a set of clinical practice guidelines on the evaluation, classification, and stratification of CKD. This initial set of guidelines provided a standardized terminology for the evaluation and classification of kidney disease; the proper monitoring of kidney function from initial injury to end stage; a logical approach to stratification of kidney disease by risk factors and comorbid conditions; and consequently a basis for continuous care and therapy throughout the course of CKD. The Chronic Kidney Disease: Evaluation, Classification, and Stratification Guidelines were published in February 2002.[3]

K/DOQI also includes interventional, disease-specific guidelines, based on the staging and classification developed by the CKD: Evaluation, Classification, and Stratification Guidelines. Work on 2 of these interventional Guidelines was begun in 2000. We are proud to present one of these interventional Guidelines for your review and comments. The Work Group appointed to develop the Guidelines screened over 22,300 potentially relevant articles; over 4,100 were subjected to preliminary review; about 470 were then selected for formal structured review of content and methodology. While considerable effort has gone into the development of the Guidelines and every attention has been paid to detail and scientific rigor, it is only the ongoing review and ratification that assures their clinical applicability and practical utility. The current Guidelines have been through three extensive reviews and represented herein is the product with incorporation of these comments.

Ultimately, we also ask for your suggestions for implementation of these Guidelines. It is hoped that implementation plans, currently being developed, will ensure the same acceptance of K/DOQI by nephrologists as well as by the broader spectrum of professionals who provide primary care for kidney disease as that which DOQI received from those who provide dialysis care.

On behalf of the NKF, we would like to acknowledge the immense effort and contributions of those who have made these Guidelines possible. In particular, we wish to acknowledge the following: the members of the Work Group charged with developing the Guidelines, without whose tireless effort and commitment these Guidelines would not have been possible; the members of the Support Group, whose input at monthly conference calls was instrumental in resolving the problems encountered over the time it has taken to reach this stage; the members of the K/DOQI Advisory Board, whose insights and guidance were essential in broadening the applicability of the Guidelines; Amgen, Inc., which had the vision and foresight to appreciate the merits of the K/DOQI initiative and to provide the unrestricted funds necessary for its launching in 2000; Abbott Renal Care, which shared the K/DOQI objective to improve the care of patients with CKD and as Primary Sponsor of the present set of Guidelines provided an unrestricted grant for their development; Genzyme Therapeutics, which as Associate Sponsor provided an unrestricted grant to support the completion of these Guidelines; and the NKF staff assigned to K/DOQI who worked so diligently in attending to the innumerable details that needed attention at every stage of Guideline develop-

ment and in meeting our nearly impossible deadlines.

A special debt of gratitude goes to Shaul G. Massry, MD, Chair of the Work Group, whose seminal contributions to the understanding of parathyroid gland, bone disease, and phosphate metabolism in CKD and personal commitment to K/DOQI provided the leadership, intellectual rigor, and invaluable expertise in synthesizing these Guidelines; and to ECRI, for providing crucial methodological rigor and staff support in developing the evidentiary basis of the Guidelines.

In a voluntary and multidisciplinary undertaking of such magnitude, many others have made valuable contributions to these Guidelines but cannot be individually acknowledged here. To each and every one of them we extend our sincerest appreciation.

***Garabed Eknoyan, MD***
***NKF–K/DOQI Co-Chair***

***Adeera Levin, MD***
***NKF–K/DOQI Co-Chair***

***Nathan W. Levin, MD***
***NKF–K/DOQI Co-Chair Emeritus***

# INTRODUCTION

Disturbances in mineral and bone metabolism are common in patients with CKD. A large body of evidence indicates that these derangements are associated with increased mortality and morbidity. These patients have bone pain, increased incidence of bone fractures and deformity, myopathy and muscle pain, and ruptures of tendons. Hyperphosphatemia also appears to be associated with increased mortality, and elevated blood levels of PTH exert significant adverse effects on the function of almost every organ.

Importantly, the long-term effects of these derangements on soft tissue calcification have become an area of growing concern in the care of CKD patients. Calcification of the lung leads to impaired pulmonary function, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, and right-side congestive heart failure. Calcification of the myocardium, coronary arteries, and cardiac valves results in congestive heart failure, cardiac arrhythmias, ischemic heart disease, and death. Vascular calcification leads to ischemic lesions, soft-tissue necrosis, and difficulties for kidney transplantation.

The processes causing disordered mineral metabolism and bone disease have their onset in the early stages of CKD, continue throughout the course of progressive loss of kidney function, and may be influenced beneficially or adversely by the various therapeutic approaches now used. Thus, prevention of the disturbances in mineral and bone metabolism and their management early in the course of chronic kidney disease are extremely important in improving the quality of life and longevity of CKD patients.

The present clinical practice guidelines were developed to provide an integrated clinical action plan to the management of this complex problem throughout the course of CKD. In the guidelines, the stages of CKD are defined according to the K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification (Table 1).

**Table 1. Stages of Chronic Kidney Disease**

| Stage | Description | GFR (mL/min/1.73 m²) |
|---|---|---|
| 1 | Kidney damage with normal or ↑ GFR | ≥90 |
| 2 | Kidney damage with mild ↓ GFR | 60-89 |
| 3 | Moderate ↓ GFR | 30-59 |
| 4 | Severe ↓ GFR | 15-29 |
| 5 | Kidney failure | <15 (or dialysis) |

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m² for ≥3 months. Kidney damage is defined as pathological abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

The target population of these guidelines is adults (age 18 years and over) with CKD. While many of the recommendations made apply to all ages, there are sufficient issues unique to children and adolescents that a subcommittee of the Work Group of pediatricians has been constituted to address these issues. A separate set of these guidelines targeted to children and adolescents will be published separately.

The guidelines are based on a systematic review of the literature through January 1st, 2001. In formulating the guidelines, the rationale and evidentiary basis of each recommendation was made explicit. When all components of the rationale for a guideline were based on published evidence, the guidelines were labeled "Evidence." When no definite evidence existed or the evidence was considered inconclusive, and either the guideline or steps in its rationale were based on judgment they were labeled "Opinion." As such, it is the available literature that determined the labeling of each guideline. As a result, of the 111 recommendations made in these guidelines, about one third are evidence based and two thirds are opinion based. This distribution is true whether one considers the recommendations made for CKD stages 3 and 4 patients or for those in stage 5 who are already on maintenance dialysis. There are 8 recommendations in the guideline for the kidney transplant recipient; all of these 8 statements are opinion based.

Concerning opinion based statements, it is important to note that prior to their publication, a final draft of the guidelines was subjected to a broad-based review by experts, organizations, and the public. Thus, the chain of reasoning and recommendation of each opinion based guideline was exposed to open debate, with the final published product reflecting a wide consensus of healthcare professionals, providers, managers, organizations, associations, and patients.

No clinical practice guidelines, irrespective of

the rigor of their development, can accomplish the intended improvement in outcomes without an implementation plan. Since the majority of the recommendations made in this set of guidelines are based on opinion, it is imperative that evaluation of their clinical outcomes be made a component of their implementation. In addition, the paucity of evidence based information in this field requires that a more integrated approach to research efforts be planned and conducted to provide answers to the many issues that remain to be elucidated. Actually, these are components of the implementation of these guidelines that has already been initiated. A coordinated approach to ongoing research and evaluation of the outcomes of the recommendations made should provide the answers necessary for the future updating of these guidelines.

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**Conversion Factors of Metric Units to SI Units**

| Test | Metric Unit | Conversion Factor | SI Units |
|---|---|---|---|
| Calcium (serum) | mg/dL | 0.25 | mmol/L |
| Calcium ionized (serum) | mg/dL | 0.25 | mmol/L |
| Phosphorus (serum) | mg/dL | 0.32 | mmol/L |
| Magnesium (serum) | mg/dL | 0.41 | mmol/L |
| Creatinine (serum) | mg/dL | 83.30 | $\mu$mol/L |
| BUN (serum) | mg/dL | 0.36 | mmol/L |
| Albumin (serum) | g/dL | 10.00 | g/L |
| Alkaline phosphatase (serum) | IU/L | 0.02 | $\mu$kat/L |
| Intact parathyroid hormone (serum) | pg/mL | 0.11 | pmol/L |
| 25(OH)D (serum or plasma) | ng/mL | 2.5 | nmol/L |
| $1.25(OH)_2D$ (serum or plasma) | pg/mL | 2.4 | pmol/L |

NOTE. Metric Units x Conversion Factor = SI Units

# GUIDELINE STATEMENTS

## GUIDELINE 1. EVALUATION OF CALCIUM AND PHOSPHORUS METABOLISM (p S52)

**1.1 Serum levels of calcium, phosphorus, and intact plasma parathyroid hormone (PTH) should be measured in all patients with CKD and GFR <60 mL/min/1.73 m$^2$. (EVIDENCE) The frequency of these measurements should be based on the stage of chronic kidney disease (Table 14). (OPINION)**

**Table 14. Frequency of Measurement of PTH and Calcium/Phosphorus by Stage of CKD**

| CKD Stage | GFR Range (mL/min/1.73 m$^2$) | Measurement of PTH | Measurement of Calcium/Phosphorus |
|---|---|---|---|
| 3 | 30-59 | Every 12 months | Every 12 months |
| 4 | 15-29 | Every 3 months | Every 3 months |
| 5 | <15 or dialysis | Every 3 months | Every month |

**1.2 These measurements should be made more frequently if the patient is receiving concomitant therapy for the abnormalities in the serum levels of calcium, phosphorus, or PTH, as detailed in Guidelines 4, 5, 7, and 8, and in transplant recipient, Guideline 16.**

**1.3 Measurement of plasma PTH levels may be done less frequently for those with levels within the low end of the target levels (Table 15). (OPINION)**

**1.4 The target range of plasma levels of intact PTH in the various stages of CKD are denoted in Table 15.**

**Table 15. Target Range of Intact Plasma PTH by Stage of CKD**

| CKD Stage | GFR Range (mL/min/1.73 m$^2$) | Target "intact" PTH (pg/mL [pmol/L]) |
|---|---|---|
| 3 | 30-59 | 35-70 [3.85-7.7 pmol/L] (OPINION) |
| 4 | 15-29 | 70-110 [7.7-12.1 pmol/L] (OPINION) |
| 5 | <15 or dialysis | 150-300 [16.5-33.0 pmol/L] (EVIDENCE) |

## GUIDELINE 2. ASSESSMENT OF BONE DISEASE ASSOCIATED WITH CKD (p S57)

**2.1 The most accurate diagnostic test for determining the type of bone disease associated with CKD is iliac crest bone biopsy with double tetracycline labeling and bone histomorphometric analysis. (EVIDENCE)**

**2.2 It is not necessary to perform bone biopsy for most situations in clinical practice. However, a bone biopsy should be considered in patients with kidney failure (Stage 5) who have:**

**2.2a Fractures with minimal or no trauma (pathological fractures); (OPINION)**

**2.2b Intact plasma PTH levels between 100 and 500 pg/mL (11.0 to 55.0 pmol/L) (in CKD Stage 5) with coexisting conditions such as unexplained hypercalcemia, severe bone pain, or unexplained increases in bone alkaline phosphatase activity; (OPINION)**

**2.2c Suspected aluminum bone disease, based upon clinical symptoms or history of aluminum exposure. (OPINION) (See Guideline 11)**

**2.3 Bone radiographs are not indicated for the assessment of bone disease of CKD, (EVIDENCE) but they are useful in detecting severe peripheral vascular calcification (OPINION) and bone disease due to $\beta_2$ microglobulin amyloidosis. (See Guideline 10) (EVIDENCE)**

**2.4 Bone mineral density (BMD) should be measured by dual energy X-ray absorptiometry (DEXA) in patients with fractures and in those with known risk factors for osteoporosis. (OPINION)**

## GUIDELINE 3. EVALUATION OF SERUM PHOSPHORUS LEVELS (p S62)

**3.1 In CKD patients (Stages 3 and 4), the serum level of phosphorus should be maintained at or above 2.7 mg/dL (0.87 mmol/L) (EVIDENCE) and no higher than 4.6 mg/dL (1.49 mmol/L). (OPINION)**

**3.2 In CKD patients with kidney failure (Stage 5) and those treated with hemodialysis or peritoneal dialysis, the serum levels of phosphorus should be maintained between 3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L). (EVIDENCE)**

## GUIDELINE 4. RESTRICTION OF DIETARY PHOSPHORUS IN PATIENTS WITH CKD (p S63)

**4.1 Dietary phosphorus should be restricted to 800 to 1,000 mg/day (adjusted for dietary protein needs) when the serum phosphorus levels are elevated >4.6 mg/dL (1.49 mmol/L) at Stages 3 and 4 of CKD, (OPINION) and >5.5 mg/dL (1.78 mmol/L) in those with kidney failure (Stage 5). (EVIDENCE)**

**4.2 Dietary phosphorus should be restricted to 800 to 1,000 mg/day (adjusted to dietary protein needs) when the plasma levels of intact PTH are elevated above target range of the CKD Stage (see Table 15 in Guideline 1). (EVIDENCE)**

**4.3 The serum phosphorus levels should be monitored every month following the initiation of dietary phosphorus restriction. (OPINION)**

## GUIDELINE 5. USE OF PHOSPHATE BINDERS IN CKD (p S70)

***In CKD Patients (Stages 3 and 4):***

**5.1 If phosphorus or intact PTH levels cannot be controlled within the target range (see Guidelines 1, 3), despite dietary phosphorus restriction (see Guideline 4), phosphate binders should be prescribed. (OPINION)**

**5.2 Calcium-based phosphate binders are effective in lowering serum phosphorus levels (EVIDENCE) and may be used as the initial binder therapy. (OPINION)**

***In CKD Patients with Kidney Failure (Stage 5):***

**5.3 Both calcium-based phosphate binders and other noncalcium-, nonaluminum-, and nonmagnesium-containing phosphate-binding agents (such as sevelamer HCl) are effective in lowering serum phosphorus levels (EVIDENCE) and either may be used as the primary therapy. (OPINION)**

**5.4 In dialysis patients who remain hyperphosphatemic (serum phosphorus >5.5 mg/dL [1.78 mmol/L]) despite the use of either of calcium-based phosphate binders or other noncalcium-, nonaluminum-, nonmagnesium-containing phosphate-binding agents, a combination of both should be used. (OPINION)**

**5.5 The total dose of elemental calcium provided by the calcium-based phosphate binders should not exceed 1,500 mg/day (OPINION), and the total intake of elemental calcium (including dietary calcium) should not exceed 2,000 mg/day. (OPINION)**

**5.6 Calcium-based phosphate binders should not be used in dialysis patients who are hypercalcemic (corrected serum calcium of >10.2 mg/dL [2.54 mmol/L]), or whose plasma PTH levels are <150 pg/mL (16.5 pmol/L) on 2 consecutive measurements. (EVIDENCE)**

**5.7 Noncalcium-containing phosphate binders are preferred in dialysis patients with severe vascular and/or other soft-tissue calcifications. (OPINION)**

**5.8 In patients with serum phosphorus levels >7.0 mg/dL (2.26 mmol/L), aluminum-based phosphate binders may be used as a short-term therapy (4 weeks), and for one course only, to be replaced thereafter by other phosphate binders. (OPINION) In such patients, more frequent dialysis should also be considered. (EVIDENCE)**

## GUIDELINE 6. SERUM CALCIUM AND CALCIUM-PHOSPHORUS PRODUCT (p S77)

***In CKD Patients (Stages 3 and 4):***

**6.1 The serum levels of corrected total calcium should be maintained within the "normal" range for the laboratory used. (EVIDENCE)**

***In CKD Patients With Kidney Failure (Stage 5):***

**6.2 Serum levels of corrected total calcium should be maintained within the normal range for the laboratory used, preferably toward the lower end (8.4 to 9.5 mg/dL [2.10 to 2.37 mmol/L]). (OPINION)**

**6.3 In the event corrected total serum calcium level exceeds 10.2 mg/dL (2.54 mmol/L), therapies that cause serum calcium to rise should be adjusted as follows:**

**6.3a In patients taking calcium-based phosphate binders, the dose should be reduced or therapy switched to a noncalcium-, nonaluminum-, nonmagnesium-containing phosphate binder. (OPINION) See Guideline 5.**

**6.3b In patients taking active vitamin D sterols, the dose should be reduced or therapy discontinued until the serum levels of corrected total calcium return to the target range (8.4 to 9.5 mg/dL [2.10 to 2.37 mmol/L]). (OPINION) See Guideline 8B.**

**6.3c If hypercalcemia (serum levels of corrected total calcium >10.2 mg/dL [2.54 mmol/L]) persists despite modification of therapy with vitamin D and/or discontinuation of calcium-based phosphate binders, dialysis using low dialysate calcium (1.5 to 2.0 mEq/L) may be used for 3 to 4 weeks. (OPINION) See Guideline 9.**

***In CKD Patients (Stages 3 to 5):***

**6.4 Total elemental calcium intake (including both dietary calcium intake and calcium-based phosphate binders) should not exceed 2,000 mg/day. (OPINION) See Guideline 5.**

**6.5 The serum calcium-phosphorus product should be maintained at <55 $mg^2/dL^2$. (EVIDENCE) This is best achieved by controlling serum levels of phosphorus within the target range. (OPINION) See Guidelines 3, 4, and 5.**

**6.6 Patients whose serum levels of corrected total calcium are below the lower limit for the laboratory used (<8.4 mg/dL [2.10 mmol/L]) should receive therapy to increase serum calcium levels if:**

**6.6a There are clinical symptoms of hypocalcemia such as paresthesia, Chvostek's and Trousseau's signs, bronchospasm, laryngospasm, tetany, and/or seizures (OPINION); or**

**6.6b The plasma intact PTH level is above the target range for the CKD Stage. (See Table 15 in Guideline 1.) (OPINION)**

**6.7 Therapy for hypocalcemia should include calcium salts such as calcium carbonate (EVIDENCE) and/or oral vitamin D sterols. (EVIDENCE) See Guideline 8B.**

## GUIDELINE 7. PREVENTION AND TREATMENT OF VITAMIN D INSUFFICIENCY AND VITAMIN D DEFICIENCY IN CKD PATIENTS (Algorithm 1) (p S84)

***In CKD Patients (Stages 3 and 4):***

**7.1 If plasma intact PTH is above the target range for the stage of CKD (Table 15, Guideline 1) serum 25-hydroxyvitamin D should be measured at first encounter. If it is normal, repeat annually. (EVIDENCE)**

**7.2 If the serum level of 25-hydroxyvitamin D is <30 ng/mL, supplementation with vitamin $D_2$ (ergocalciferol) should be initiated (Table 26). (OPINION)**

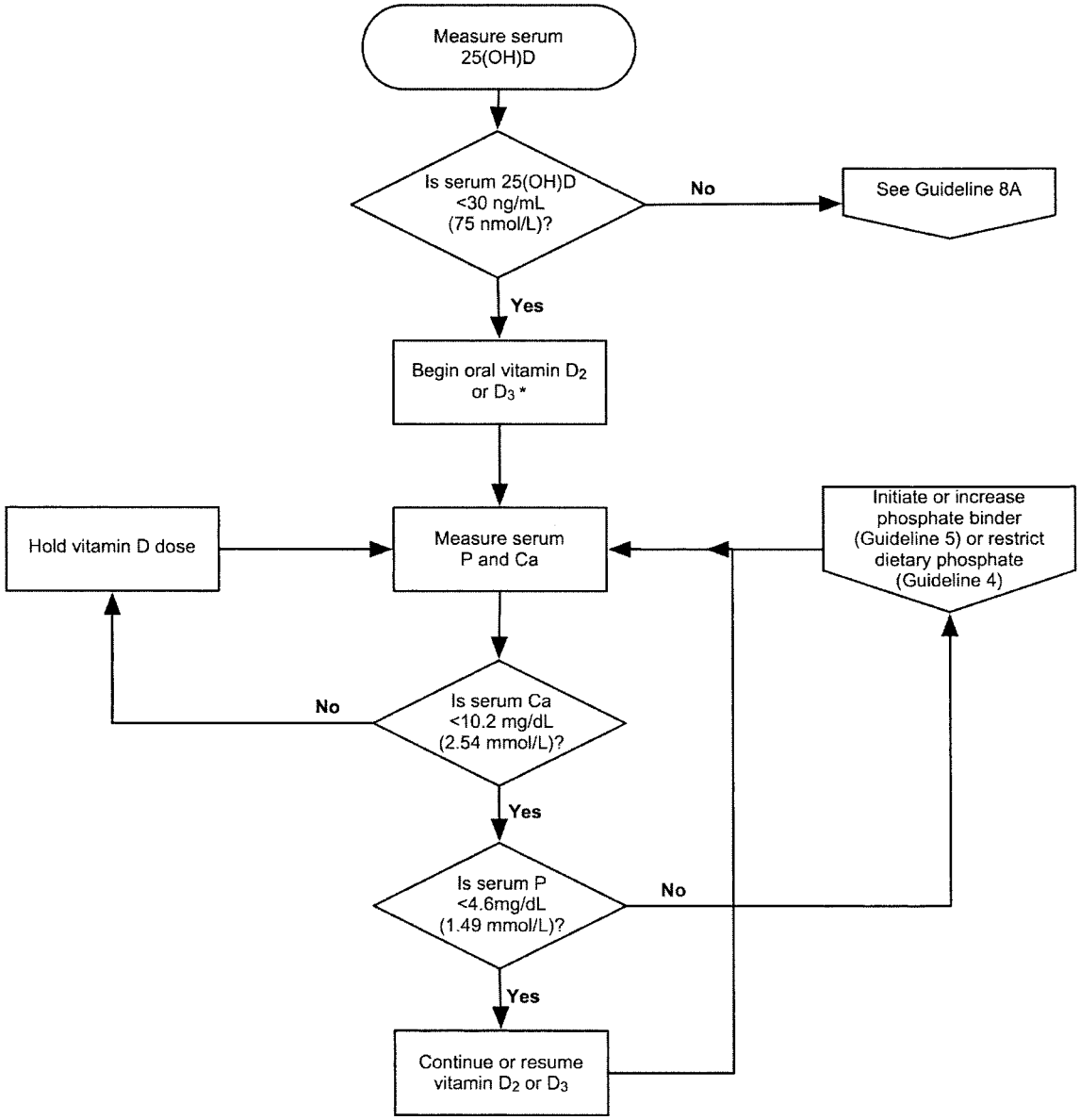
**7.3 Following initiation of vitamin D therapy:**

**7.3a The use of ergocalciferol therapy should be integrated with the serum calcium and phosphorus (Algorithm 1).**

**7.3b The serum levels of corrected total calcium and phosphorus should be measured at least every 3 months. (OPINION)**

**7.3c If the serum levels of corrected total calcium exceeds 10.2 mg/dL (2.54 mmol/L), discontinue ergocalciferol therapy and all forms of vitamin D therapy. (OPINION)**

In CKD patients with serum P <4.6 mg/dL (1.99 mmol/L), serum Ca <9.5 mg/dL (2.37 mmol/L), and serum PTH in the higher level of the target range for CKD stage (Stage 3: 35-70 pg/mL [3.85-7.7 pmol/L]; Stage 4: 70-110 pg/mL [7.7-12.1 pmol/L])




* Vitamin $D_2$ (ergocalciferol) may be safer than $D_3$ (cholecalciferol). When the 25(OH)D level is <15 ng/ml (37 nmol/L), 50,000 IU weekly for 4 doses followed by monthly for 4 doses is effective. With 25(OH)D levels of 20-30 ng/mL (50-75 nmol/L), 50,000 IU monthly for 6 months is recommended

**Algorithm 1. Vitamin D supplementation in CKD (Stages 3 and 4).**

**Table 26. Recommended Supplementation for Vitamin D Deficiency/Insufficiency in Patients with CKD Stages 3 and 4**

| Serum 25(OH)D (ng/mL) [nmol/L] | Definition | Ergocalciferol Dose (Vitamin $D_2$) | Duration (months) | Comment |
|---|---|---|---|---|
| <5 [12] | Severe vitamin D deficiency | 50,000 IU/wk orally x 12 wks; then monthly | 6 months | Measure 25(OH)D levels after 6 months |
| | | 500,000 IU as single I.M. dose | | Assure patient adherence; measure 25(OH)D at 6 months |
| 5-15 [12-37] | Mild vitamin D deficiency | 50,000 IU/wk x 4 weeks, then 50,000 IU/month orally | 6 months | Measure 25(OH)D levels after 6 months |
| 16-30 [40-75] | Vitamin D insufficiency | 50,000 IU/month orally | 6 months | |

**7.3d If the serum phosphorus exceeds 4.6 mg/dL, add or increase the dose of phosphate binder. (See Guidelines 4 and 5.) If hyperphosphatemia persists, discontinue vitamin D therapy. (OPINION)**

**7.3e Once patients are replete with vitamin D, continued supplementation with a vitamin-D–containing multi-vitamin preparation should be used with annual reassessment of serum levels of 25-hydroxyvitamin D, and the continued assessment of corrected total calcium and phosphorus every 3 months. (OPINION)**

***In CKD Patients With Kidney Failure (Stage 5):***

**7.4 Therapy with an active vitamin D sterol (calcitriol, alfacalcidol, paricalcitol, or doxercalciferol) should be provided if the plasma levels of intact PTH are >300 pg/mL. (OPINION) See Guideline 8B.**

## GUIDELINE 8. VITAMIN D THERAPY IN CKD PATIENTS (p S89)

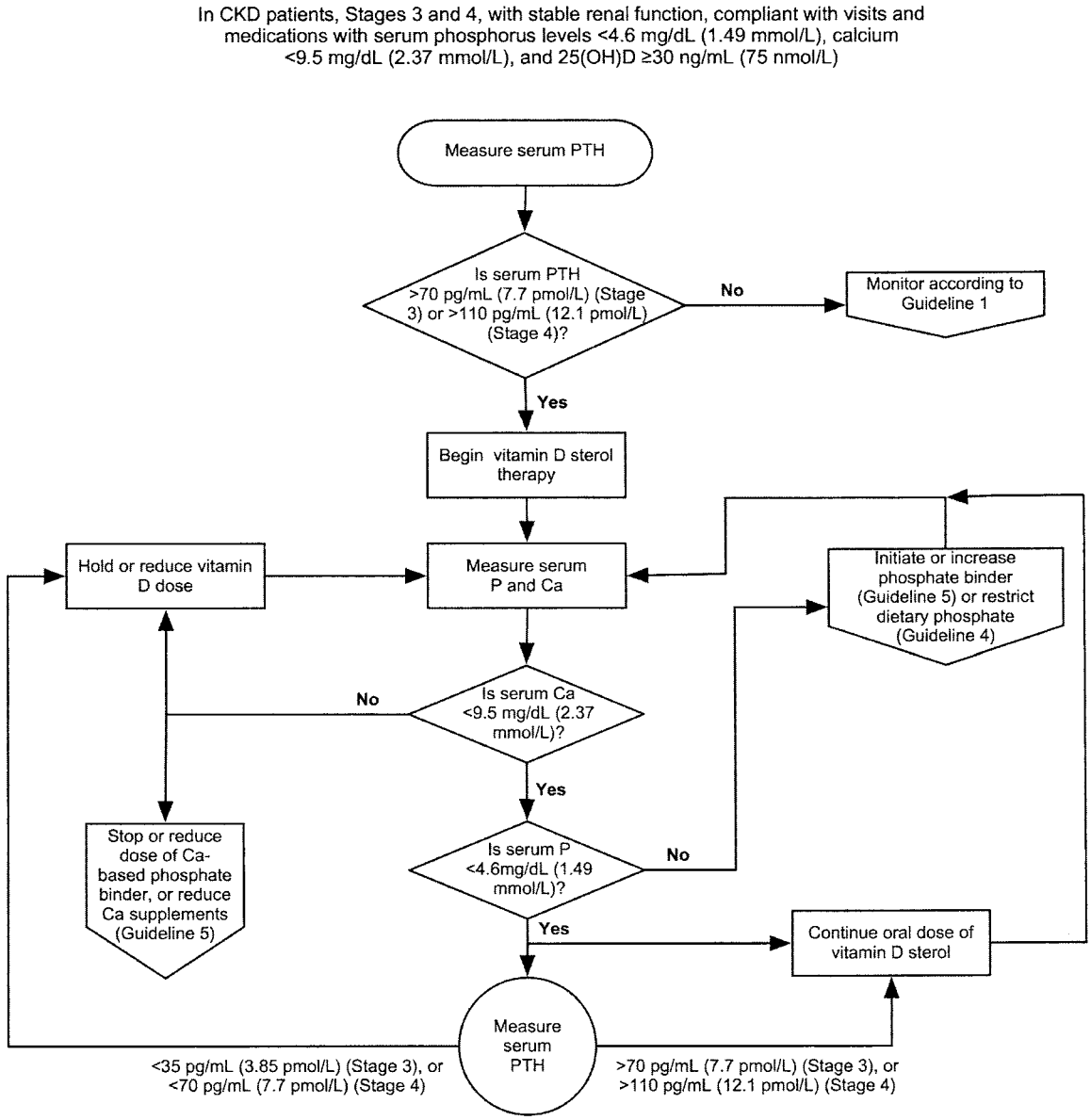
**This Guideline encompasses 2 parts: Guideline 8A, which deals with active vitamin D sterol therapy in CKD Stages 3 and 4, and Guideline 8B, which deals with CKD Stage 5.**

## GUIDELINE 8A. ACTIVE VITAMIN D THERAPY IN PATIENTS WITH STAGES 3 AND 4 CKD (Algorithm 2) (p S89)

**8A.1 In patients with CKD Stages 3 and 4, therapy with an active oral vitamin D sterol (calcitriol, alfacalcidol, or doxercalciferol) is indicated when serum levels of 25(OH)-vitamin D are >30 ng/mL (75 nmol/L) and plasma levels of intact PTH are above the target range for the CKD stage (see Table 15, Guideline 1). (EVIDENCE) The initial doses are provided in Table 27.**

**Table 27. Serum Levels of PTH, Calcium and Phosphate Required for Initiation of Oral Vitamin D Sterol Therapy, and Recommended Initial Doses in Patients with Stages 3 and 4 CKD**

| Plasma PTH pg/mL or [pmol/L] | Serum Ca mg/dL [mmol/L] | Serum P mg/dL [mmol/L] | Dose Oral Calcitriol | Dose Oral Alfacalcidol | Dose Oral Doxercalciferol |
|---|---|---|---|---|---|
| >70 [7.7] (CKD Stage 3) Or >110 [ 12.1] (CKD Stage 4) | <9.5 [2.37] | <4.6 [1.49] | 0.25 μg/day | 0.25 μg/day | 2.5 μg 3x/week |




Oral active vitamin D sterols available include calcitriol, alfacalcidol, and doxercalciferol; calcitriol (USA, Canada) and alfacalcidol (Canada and Europe) are approved for use in CKD, Stages 3 and 4. Initial doses should be low (calcitriol 0.25 µg/day or alfacalcidol, 0.25 µg/day). The dose of calcitriol should rarely exceed 0.5 µg/day and then only if the corrected levels of calcium increase by less than 0.2-0.3 mg/dL.

**Algorithm 2. Management of CKD patients (Stages 3 and 4) with active Vitamin D sterols.**

**8A.1a Treatment with an active vitamin D sterol should be undertaken only in patients with serum levels of corrected total calcium <9.5 mg/dL (2.37 mmol/L) and serum phosphorus <4.6 mg/dL (1.49 mmol/L). (OPINION)**

**8A.1b Vitamin D sterols should not be prescribed for patients with rapidly worsening kidney function or those who are noncompliant with medications or follow-up. (OPINION)**

**Table 28. Recommended Initial Dosing for Vitamin D Sterols by Serum Levels of Intact PTH, Calcium, Phosphorus, and Ca-P Product**

| Plasma PTH pg/mL or [pmol/L] | Serum Ca mg/dL [mmol/L] | Serum P mg/dL [mmol/L] | Ca-P Product | Dose per HD Calcitriol†* | Dose per HD Paricalcitol* | Dose per HD Doxercalciferol†* |
|---|---|---|---|---|---|---|
| 300-600 [33-66] | <9.5 [2.37] | <5.5 [1.78] | <55 | IV: 0.5-1.5 μg Oral: 0.5-1.5 μg | 2.5-5.0 μg | Oral: 5 μg IV: 2 μg |
| 600-1000 [66-110] | <9.5 [2.37] | <5.5 [1.78] | <55 | IV: 1.0-3.0 μg Oral: 1-4 μg | 6.0-10 μg | Oral: 5-10 μg IV: 2-4 μg |
| >1000 [110] | <10.0 [2.50] | <5.5 [1.78] | <55 | IV: 3.0-5.0 μg Oral: 3-7 μg | 10-15 μg | Oral: 10-20 μg IV: 4-8 μg |

*Intravenous; † Oral

**8A.2 During therapy with vitamin D sterols, serum levels of calcium and phosphorus should be monitored at least every month after initiation of therapy for the first 3 months, then every 3 months thereafter. Plasma PTH levels should be measured at least every 3 months for 6 months, and every 3 months thereafter. (OPINION)**

**8A.3 Dosage adjustments for patients receiving active vitamin D sterol therapy should be made as follows:**

**8A.3a If plasma levels of intact PTH fall below the target range for the CKD stage (Table 15, Guideline 1), hold active vitamin D sterol therapy until plasma levels of intact PTH rise to above the target range, then resume treatment with the dose of active vitamin D sterol reduced by half. If the lowest daily dose of the active vitamin D sterol is being used, reduce to alternate-day dosing. (OPINION)**

**8A.3b If serum levels of corrected total calcium exceed 9.5 mg/dL (2.37 mmol/L), hold active vitamin D sterol therapy until serum calcium returns to <9.5 mg/dL (2.37 mmol/L), then resume treatment at half the previous dose. If the lowest daily dose of the active vitamin D sterol is being used, reduce to alternate-day dosing. (OPINION)**

**8A.3c If serum levels of phosphorus rise to >4.6 mg/dL (1.49 mmol/L), hold active vitamin D therapy, initiate or increase dose of phosphate binder until the levels of serum phosphorus fall to ≤4.6 mg/dL (1.49 mmol/L); then resume the prior dose of active vitamin D sterol. (OPINION)**

## GUIDELINE 8B. VITAMIN D THERAPY IN PATIENTS ON DIALYSIS (CKD STAGE 5) (p S92)

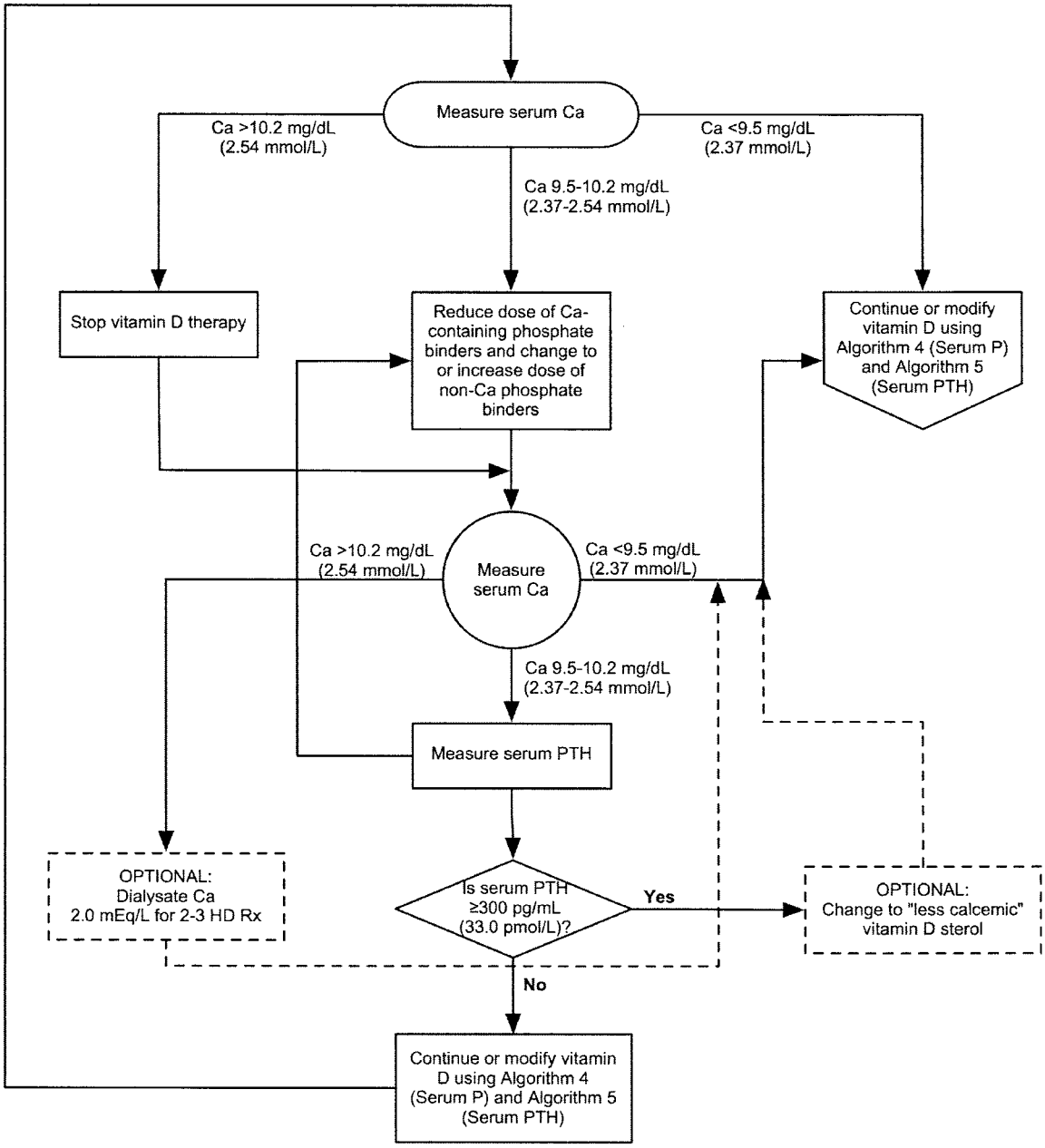
**8B.1 Patients treated with hemodialysis or peritoneal dialysis with serum levels of intact PTH levels >300 pg/mL should receive an active vitamin D sterol (such as calcitriol, alfacalcidol, paricalcitol, or doxercalciferol; see Table 28) to reduce the serum levels of PTH to a target range of 150 to 300 pg/mL. (EVIDENCE)**

**8B.1a The intermittent, intravenous administration of calcitriol is more effective than daily oral calcitriol in lowering serum PTH levels. (EVIDENCE)**

**8B.1b In patients with corrected serum calcium and/or phosphorus levels above the target range (see Guidelines 3 and 6, respectively), a trial of alternative vitamin D analogs, such as paricalcitol or doxercalciferol may be warranted. (OPINION)**

**8B.2 When therapy with vitamin D sterols is initiated or the dose is increased, serum levels of calcium and phosphorus should be monitored at least every 2 weeks for 1 month and then monthly thereafter. The plasma PTH should be measured monthly for at least 3 months and then every 3 months once target levels of PTH are achieved. (OPINION)**

**8B.3 For patients treated with peritoneal dialysis, oral doses of calcitriol (0.5 to 1.0 μg) or doxercalciferol (2.5 to 5.0 μg) can be given 2 or 3 times weekly. Alternatively, a lower dose of calcitriol (0.25 μg) can be administered daily. (OPINION)**

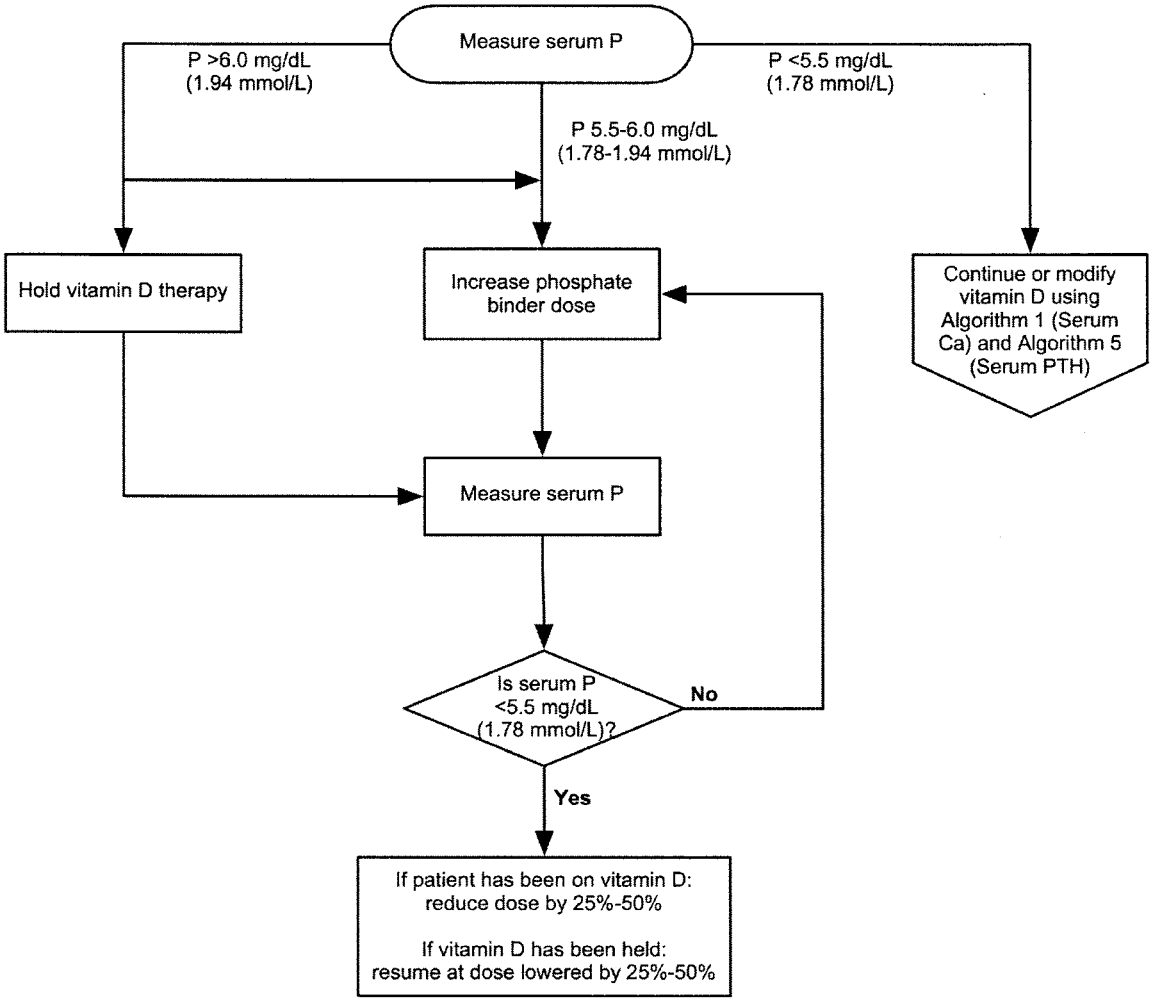



**Algorithm 3. Managing Vitamin D sterols based on serum calcium levels.**

**8B.4 When either hemodialysis or peritoneal dialysis patients are treated with active vitamin D sterols, management should integrate the changes in serum calcium, serum phosphorus, and plasma PTH. Each of these 3 variables is considered separately with suggested interventions based on the various values obtained in Algorithm 3, Algorithm 4, and Algorithm 5. (OPINION)**

## GUIDELINE 9. DIALYSATE CALCIUM CONCENTRATIONS (p S99)

**9.1 The dialysate calcium concentration in hemodialysis or peritoneal dialysis should be 2.5 mEq/L (1.25 mmol/L). (OPINION)**




**Algorithm 4. Managing Vitamin D sterols based on serum phosphorus levels.**

**9.2 Higher or lower dialysate calcium levels are indicated in selected patients. (See Clinical Applications.) (OPINION)**

## GUIDELINE 10. $\beta_2$-MICROGLOBULIN AMYLOIDOSIS (p S102)

**10.1 Screening for $\beta_2$-microglobulin amyloidosis, including measurement of serum levels of $\beta_2$-microglobulin, is not recommended. (OPINION)**

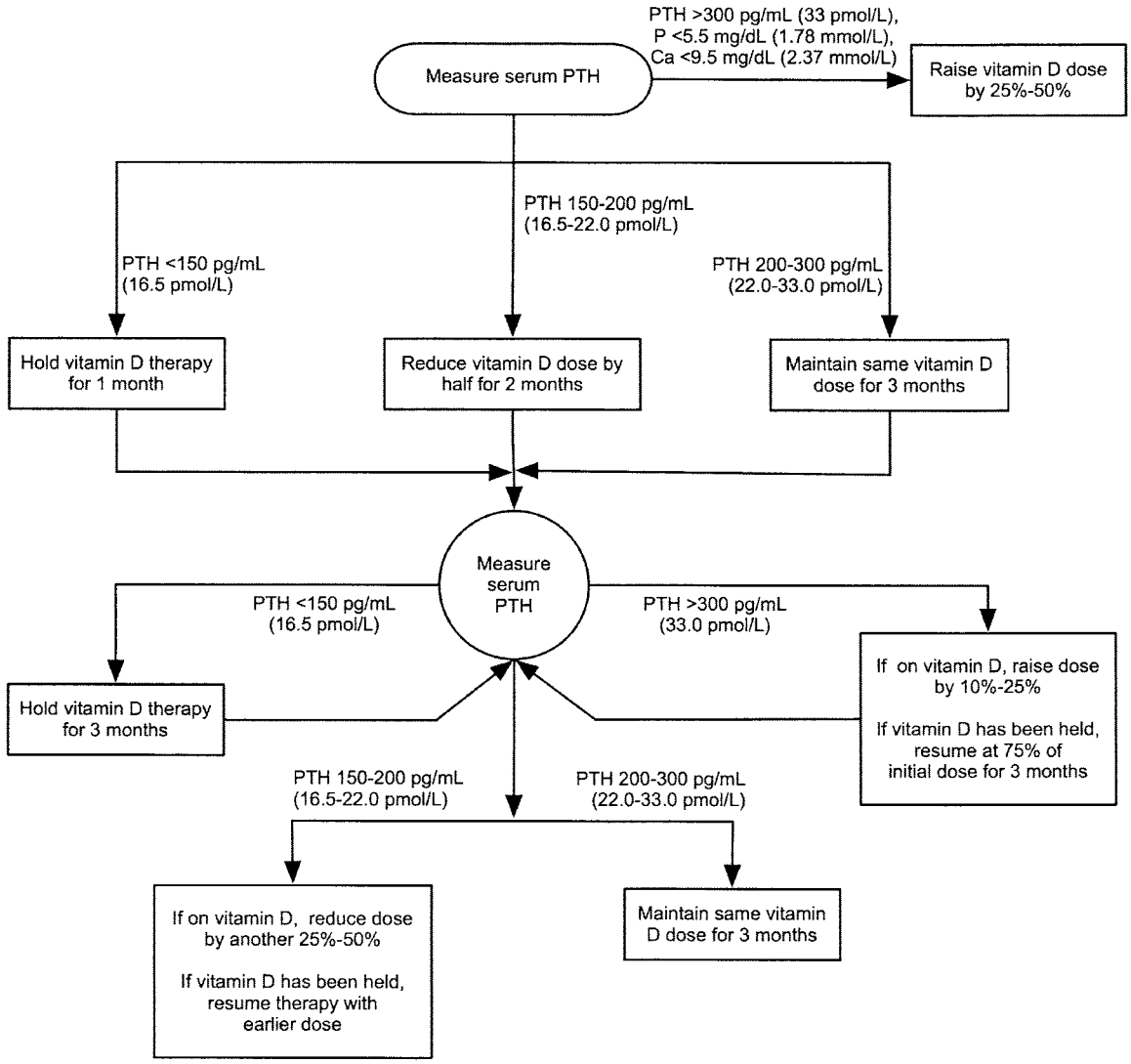
**10.1a No currently available therapy (except kidney transplantation) can stop disease progression of $\beta_2$-microglobulin amyloidosis or provide symptomatic relief. (EVIDENCE)**

**10.1b Kidney transplant should be considered to stop disease progression or provide symptomatic relief in patients with $\beta_2$-microglobulin amyloidosis. (EVIDENCE)**

**10.1c In patients with evidence of, or at risk for, $\beta_2$-microglobulin amyloidosis noncuprophane (EVIDENCE), high-flux dialyzers (OPINION) should be used.**

## GUIDELINE 11. ALUMINUM OVERLOAD AND TOXICITY IN CKD (p S108)

**11.1 To prevent aluminum toxicity, the regular administration of aluminum should be avoided and the dialysate concentration of aluminum should be maintained at $<10$ $\mu$g/L. (EVIDENCE)**




When intact serum PTH is between 300-500 pg/mL (33.0-55.0 pmol/L) and changes on two successive determinations are small (<25%), there is no need to modify vitamin D dose as long as P and Ca are within the desired limits (see Algorithms 3 and 4).

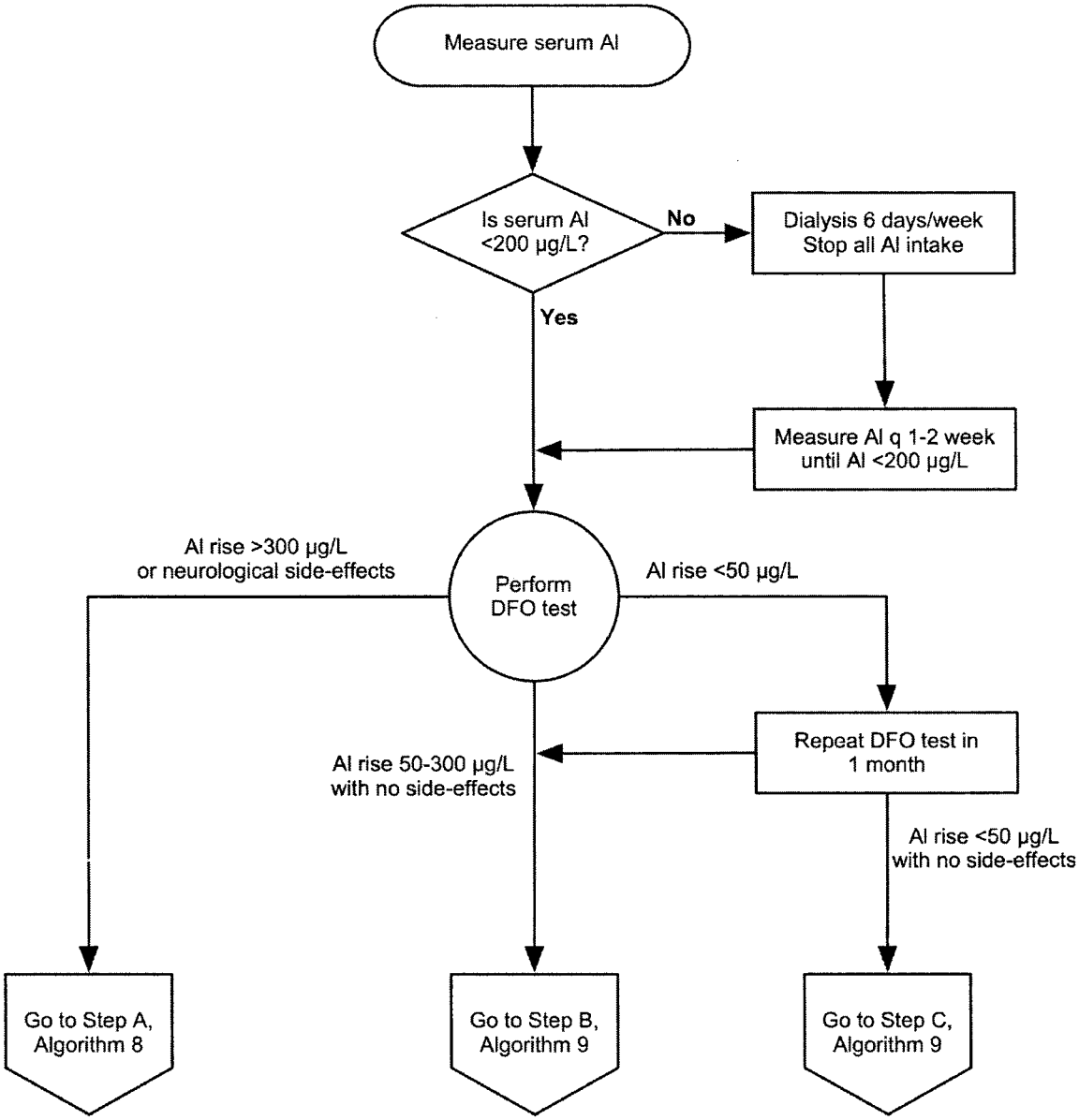
When intact PTH is persistently >500-800 pg/mL (55.0-88.0 pmol ng/L) and P is 5.5-6.5 mg/dL (1.78-1.94 mmol/L) and/or Ca is 10.2-10.5 mg/dL (2.54-2.62 mmol/L), a trial with a "less calcemic" analog may be warranted for 3-5 months; if such a patient fails to respond, parathyroidectomy may be required.

**Algorithm 5. Managing Vitamin D sterols based on intact PTH levels.**

**11.1a CKD patients ingesting aluminum should not receive citrate salts simultaneously. (EVIDENCE)**

**11.2 To assess aluminum exposure and the risk of aluminum toxicity, serum aluminum levels should be measured at least yearly and every 3 months in those receiving aluminum-containing medications. (OPINION)**

**11.2a Baseline levels of serum aluminum should be <20 $\mu$g/L. (OPINION)**

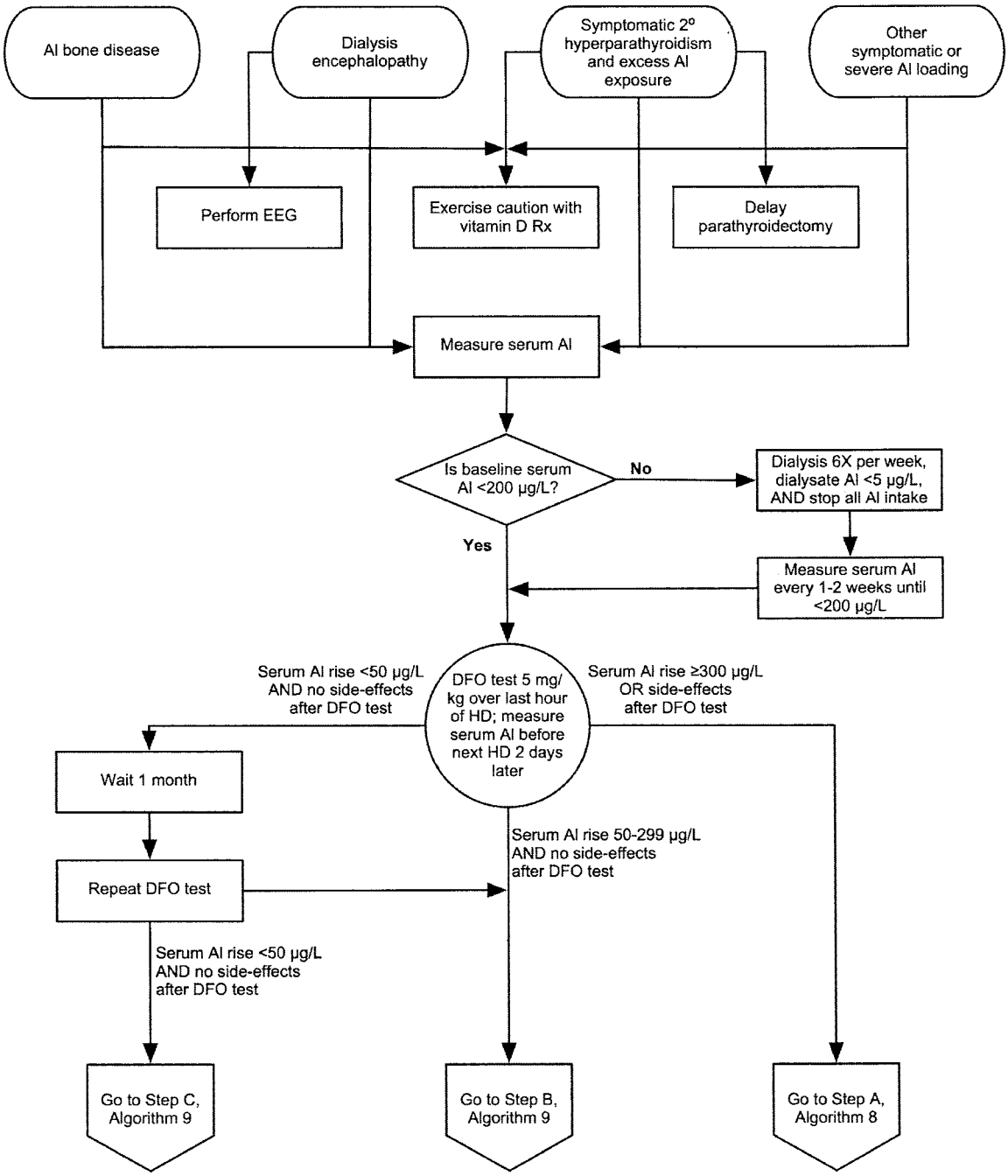



**Algorithm 6. Evaluation of aluminum neurotoxicity.**

**11.3 A deferoxamine (DFO) test should be performed if there are elevated serum aluminum levels (60 to 200 $\mu$g/L); clinical signs and symptoms of aluminum toxicity (Table 31, p S109), or prior to parathyroid surgery if the patient has had aluminum exposure. (EVIDENCE) (Algorithms 6 and 7)**

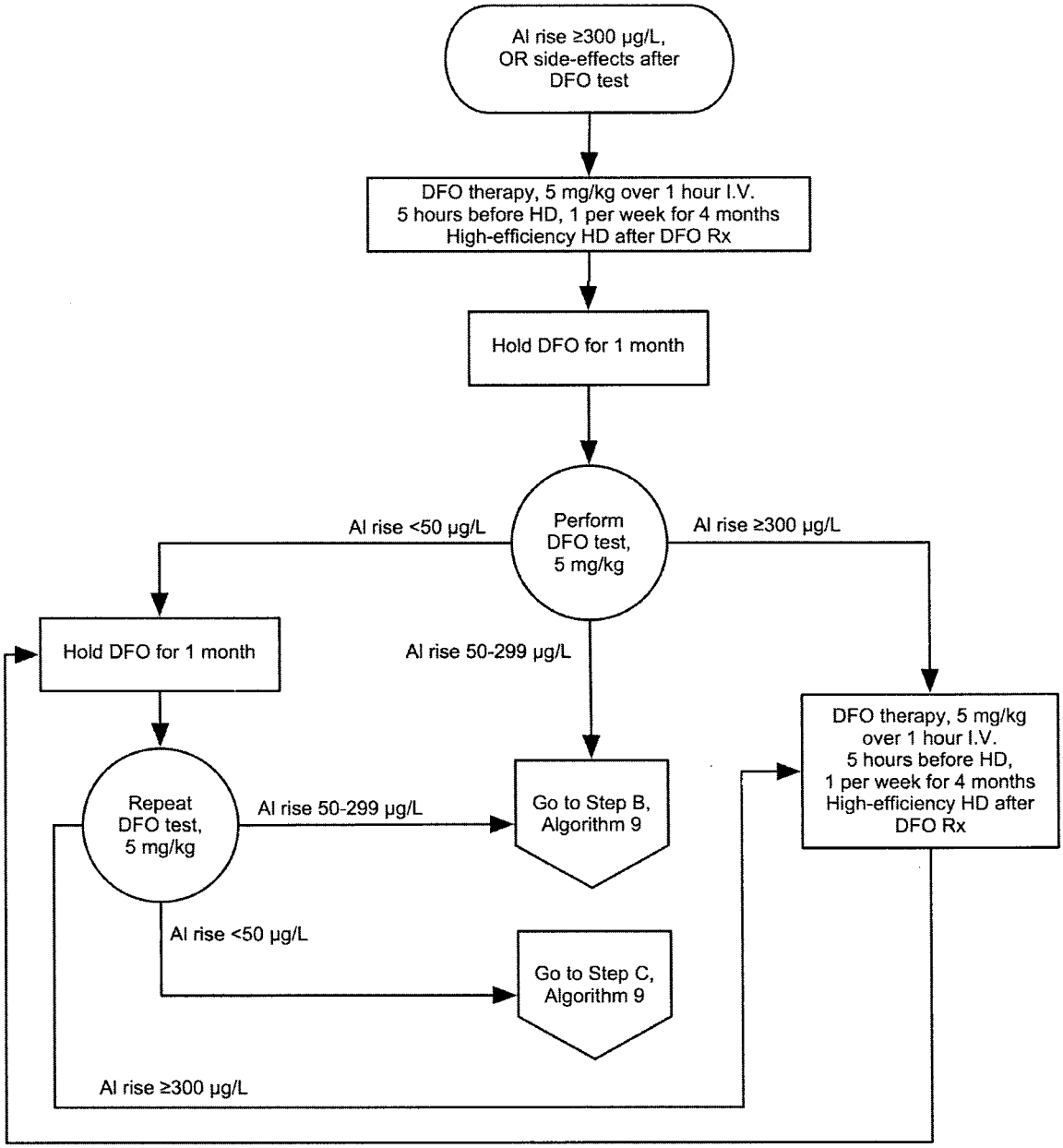
**11.3a The test is done by infusing 5 mg/kg of DFO during the last hour of the dialysis session with a serum aluminum measured before DFO infusion and 2 days later, before the next dialysis session. (OPINION)**

**11.3b The test is considered positive if the increment of serum aluminum is ≥50 $\mu$g/L. (OPINION)**




This algorithm is exclusive of acute Al neurotoxicity

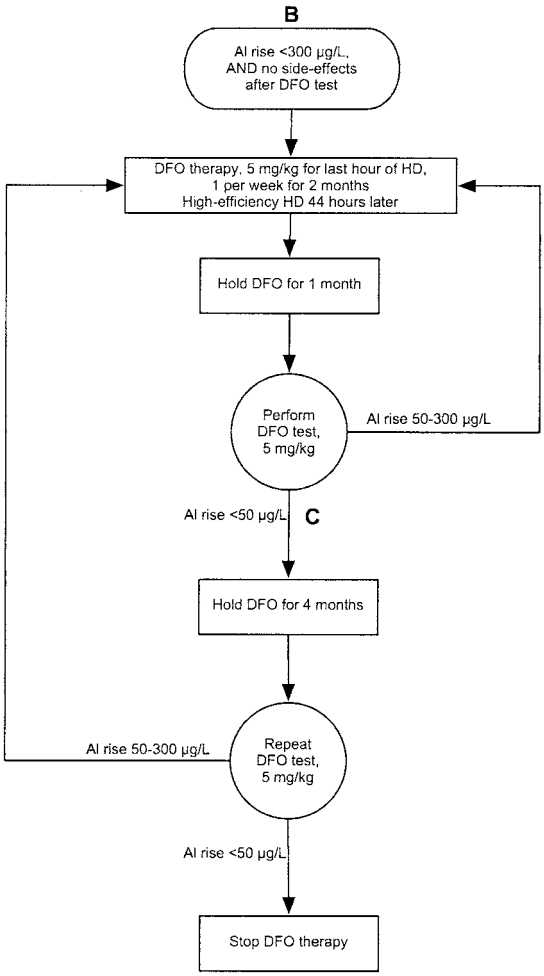
**Algorithm 7. Evaluation of aluminum-related disorders: considerations for DFO test and subsequent DFO treatment.**




**Algorithm 8. DFO treatment after $P_{Al}$ rise ≥300 $\mu$g/L.**

**11.3c A DFO test should not be performed if the serum levels of aluminum are >200 $\mu$g/L to avoid DFO-induced neurotoxicity. (OPINION)**

**11.4 The presence of aluminum bone disease can be predicted by a rise in serum aluminum of ≥50 $\mu$g/L following DFO challenge combined with plasma levels of intact PTH of <150 pg/mL (16.5 pmol/L). (OPINION) However, the gold standard for the diagnosis of aluminum bone disease is a bone biopsy showing increased aluminum staining of the bone surface (≥15% to 25%) using aluminum stain and often adynamic bone or osteomalacia. (EVIDENCE)**




**Algorithm 9. DFO treatment after $P_{Al}$ rise between 50 and 300 $\mu$g/L.**

## GUIDELINE 12. TREATMENT OF ALUMINUM TOXICITY (Algorithm 8 and Algorithm 9) (p S116)

**12.1 In all patients with baseline serum aluminum levels >60 $\mu$g/L, a positive DFO test, or clinical symptoms consistent with aluminum toxicity (Guideline 11, Table 31) the source of aluminum should be identified and eliminated. (OPINION)**

**12.2 In symptomatic patients with serum aluminum levels >60 $\mu$g/L but <200 $\mu$g/L or a rise in aluminum after DFO >50 $\mu$g/L, DFO should be given to treat the aluminum overload. (See Algorithm 8 and Algorithm 9). (OPINION)**

**12.3 To avoid DFO-induced neurotoxicity in patients with serum aluminum >200 $\mu$g/L, DFO should not be given until intensive dialysis (6 days per week) with high-flux dialysis membrane and a dialysate aluminum level of <5 $\mu$g/L and until the pre-dialysis serum aluminum level has been reduced to <200 $\mu$g/L. (OPINION)**

## GUIDELINE 13. TREATMENT OF BONE DISEASE IN CKD (p S122)

**The therapeutic approach to bone disease in CKD is based on its specific type. As such, this Guideline encompasses 3 parts: Guideline 13A deals with high-turnover and mixed bone disease, Guideline 13B with osteomalacia, and Guideline 13C with adynamic bone disease.**

## GUIDELINE 13A. HYPERPARATHYROID (HIGH-TURNOVER) AND MIXED (HIGH-TURNOVER WITH MINERALIZATION DEFECT) BONE DISEASE (p S123)

**13A.1** In CKD patients (Stages 3 and 4) who have plasma levels of intact PTH >70 pg/mL (7.7 pmol/L) (Stage 3) or >110 pg/mL (12.1 pmol/L) (Stage 4) on more than 2 consecutive measurements, dietary phosphate intake should be restricted. If this is ineffective in lowering plasma PTH levels, calcitriol (EVIDENCE) or one of its analogs [alfacalcidol (EVIDENCE) or doxercalciferol (OPINION)] should be given to prevent or ameliorate bone disease. (See Guideline 8A.)

**13A.2** In CKD patients (Stage 5) who have elevated plasma levels of intact PTH (>300 pg/mL [33.0 pmol/L]), calcitriol (EVIDENCE) or one of its analogs (doxercalciferol, alfacalcidol, or paricalcitol) (OPINION) should be used to reverse the bone features of PTH overactivity (ie, high-turnover bone disease) and to treat defective mineralization. (See Guideline 8B.)

## GUIDELINE 13B. OSTEOMALACIA (p S124)

**13B.1** Osteomalacia due to aluminum toxicity should be prevented in dialysis patients by maintaining aluminum concentration in dialysate fluid at <10 $\mu$g/L and avoiding the use of aluminum-containing compounds (including sucralfate). (OPINION)

**13B.2** Aluminum overload leading to aluminum bone disease should be treated with deferoxamine (DFO). (See Guidelines 11 and 12.) (OPINION)

**13B.3** Osteomalacia due to vitamin $D_2$ or $D_3$ deficiency or phosphate depletion, though uncommon, should be treated with vitamin $D_2$ or $D_3$ supplementation (see Guideline 7) and/or phosphate administration, respectively. (OPINION)

**13B.3a** If osteomalacia due to vitamin D deficiency fails to respond to ergocalciferol or cholecalciferol, particularly in patients with kidney failure (Stage 5), treatment with an active vitamin D sterol may be given. (OPINION) (See Guideline 8B.)

**13B.3b** Doses of phosphate supplementation should be adjusted upwards until normal serum levels of phosphorus are achieved. (OPINION)

## GUIDELINE 13C. ADYNAMIC BONE DISEASE (p S125)

**13C.1** Adynamic bone disease in Stage 5 CKD (as determined either by bone biopsy or intact PTH <100 pg/mL [11.0 pmol/L]) should be treated by allowing plasma levels of intact PTH to rise in order to increase bone turnover. (OPINION)

**13C.1a** This can be accomplished by decreasing doses of calcium-based phosphate binders and vitamin D or eliminating such therapy. (OPINION)

## GUIDELINE 14. PARATHYROIDECTOMY IN PATIENTS WITH CKD (p S127)

**14.1** Parathyroidectomy should be recommended in patients with severe hyperparathyroidism (persistent serum levels of intact PTH >800 pg/mL [88.0 pmol/L]), associated with hypercalcemia and/or hyperphosphatemia that are refractory to medical therapy. (OPINION)

**14.2** Effective surgical therapy of severe hyperparathyroidism can be accomplished by subtotal parathyroidectomy or total parathyroidectomy with parathyroid tissue autotransplantation. (EVIDENCE)

**14.3** In patients who undergo parathyroidectomy the following should be done:

**14.3a** The blood level of ionized calcium should be measured every 4 to 6 hours for the first 48 top 72 hours after surgery, and then twice daily until stable. (OPINION)

**14.3b** If the blood levels of ionized or corrected total calcium fall below normal (<0.9 mmol/L or <3.6 mg/dL corresponding to corrected total calcium of 7.2 mg/dL [1.80 mmol/L]), a calcium gluconate infusion should be initiated at a rate of 1 to 2 mg elemental calcium per kilogram body weight per hour and adjusted to maintain an ionized calcium in the normal range (1.15 to 1.36 mmol/L or 4.6 to 5.4 mg/dL). (OPINION) ***A 10-mL ampule of 10% calcium gluconate contains 90 mg of elemental calcium.***

**Table 32. Frequency for Measurement of Serum Levels of Total $CO_2$**

| CKD Stage | GFR Range (mL/min/1.73 m²) | Frequency of Measurement |
|---|---|---|
| 3 | 30-59 | At least every 12 months |
| 4 | 15-29 | At least every 3 months |
| 5 | <15 | At least every 3 months |
| | Dialysis | At least every month |

**14.3c The calcium infusion should be gradually reduced when the level of ionized calcium attains the normal range and remains stable. (OPINION)**

**14.3d When oral intake is possible, the patient should receive calcium carbonate 1 to 2 g 3 times a day, as well as calcitriol of up to 2 $\mu$g/day, and these therapies should be adjusted as necessary to maintain the level of ionized calcium in the normal range. (OPINION)**

**14.3e If the patient was receiving phosphate binders prior to surgery, this therapy may need to be discontinued or reduced as dictated by the levels of serum phosphorus. (OPINION)**

**14.4 Imaging of parathyroid glands with $^{99}$Tc-Sestamibi scan, ultrasound, CT scan, or MRI should be done prior to re-exploration parathyroid surgery. (OPINION)**

## GUIDELINE 15. METABOLIC ACIDOSIS (p S129)

**15.1 In CKD Stages 3, 4, and 5, the serum level of total $CO_2$ should be measured.**

**15.1a The frequency of these measurements should be based on the stage of CKD as shown in Table 32. (OPINION)**

**15.2 In these patients, serum levels of total $CO_2$ should be maintained at ≥22 mEq/L (22 mmol/L). (EVIDENCE) If necessary, supplemental alkali salts should be given to achieve this goal. (OPINION)**

## GUIDELINE 16. BONE DISEASE IN THE KIDNEY TRANSPLANT RECIPIENT (p S130)

**16.1 Serum levels of calcium, phosphorus, total $CO_2$ and plasma intact PTH should be monitored following kidney transplantation. (OPINION)**

**16.1a The frequency of these measurements should be based on the time following transplantation, as shown in Table 33. (OPINION)**

**16.2 During the first week after kidney transplantation, serum levels of phosphorus should be measured daily. Kidney transplant recipients who develop persistently low levels of serum phosphate (<2.5 mg/dL [0.81 mmol/L]) should be treated with phosphate supplementation. (OPINION)**

**16.3 To minimize bone mass loss and osteonecrosis, the immunosuppressive regimen should be adjusted to the lowest effective dose of glucocorticoids. (EVIDENCE)**

**Table 33. Frequency of Measurement of Calcium, Phosphorus, PTH and Total $CO_2$ after Kidney Transplantation**

| Parameter | First 3 Months | 3 Months to 1 year |
|---|---|---|
| Calcium | Every 2 weeks | Monthly |
| Phosphorus | Every 2 weeks | Monthly |
| PTH | Monthly | Every 3 months |
| Total $CO_2$ | Every 2 weeks | Monthly |

One year after transplantation, the frequency of measurements should follow the recommendations of Table 14,15, Guideline 1, depending on the level of kidney function.

**16.4 Kidney transplant recipients should have bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DEXA) to assess the presence or development of osteoporosis. (OPINION)**

**16.4a DEXA scans should be obtained at time of transplant and 1 year and 2 years post-transplant. (OPINION)**

**16.4b If BMD t-score is equal to or less than −2 at the time of the transplant, or at subsequent evaluations, therapy with parenteral amino-bisphosphonates should be considered. (OPINION)**

**16.5 Treatment of disturbances in bone and mineral metabolism is determined by the level of kidney function in the transplant recipient as provided in Guidelines 1 through 15 for CKD patients. (OPINION)**

# BACKGROUND

DISTURBANCES in mineral and bone metabolism are common in patients with chronic kidney disease (CKD). Table 2 lists the major features of these abnormalities.[4-15] The processes causing disordered mineral metabolism and bone disease have their onset in the early stages of CKD, continue throughout the course of progressive loss of kidney function, and may be influenced beneficially or adversely by various therapeutic approaches used.

In this section and those that follow, the stage of CKD is defined according to the Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification (Table 1).

## PATHOGENESIS OF BONE DISEASE IN CKD

### *Hypocalcemia and Secondary Hyperparathyroidism*

Patients with CKD almost always develop secondary hyperplasia of the parathyroid glands, resulting in elevated blood levels of parathyroid hormone (PTH). This abnormality is due to the *hypocalcemia* that develops during the course of kidney disease and/or to a deficiency of 1,25-dihydroxycholecalciferol [l,25$(OH)_2D_3$] that may directly affect the function of the parathyroid glands. With progressive loss of kidney function, a decrease in the number of vitamin D receptors (VDR) and calcium-sensing receptors (CaR) in the parathyroid glands occurs, rendering them more resistant to the action of vitamin D and calcium. In addition, the development of hyperphosphatemia directly affects the function and the growth of the parathyroid glands. These events will allow secondary hyperparathyroidism to worsen.

At least 3 hypotheses have been proposed to explain the pathogenesis of the hypocalcemia: (a) phosphate retention, (b) skeletal resistance to the calcemic action of PTH, and (c) altered vitamin D metabolism. The zeal and vigor with which the proponents of these hypotheses have defended these concepts have created the impression that a major controversy exists in the pathogenesis of hypocalcemia and secondary hyperparathyroidism. However, these possibilities are not mutually exclusive but rather interrelated. Together, these factors form a unified and integrated explanation for the hypocalcemia of CKD, and provide a framework for the management of altered mineral and bone metabolism of CKD.

***Role of phosphate retention.*** Several lines of evidence suggest that phosphate retention can provoke secondary hyperparathyroidism. First is a disorder called *sneezing disease* described in piglets ingesting high-phosphate diets. This disease is characterized by labored respiration and sneezing and is due to deformities of turbinate nasal bones caused by generalized osteitis fibrosa. This disease was reproduced in horses fed high-phosphate, low-calcium diets. The animals developed lameness and a "big head" secondary to swelling of facial bones; both abnormalities were due to osteoclastic bone resorption. Initially, these animals developed hyperphosphatemia and hypocalcemia followed by hypophosphatemia and hypercalcemia. Their parathyroid glands were diffusely hyperplastic. These observations demonstrate that the ingestion of an excessive amount of phosphate is associated with secondary hyperparathyroidism, even in the absence of CKD.

Second, the acute ingestion of inorganic phosphate by normal subjects has been shown to cause a transient rise in the levels of serum phosphorus, a fall in the concentration of ionized calcium, and a significant elevation in the blood levels of PTH even in the presence of normal kidney function.

Third, the development of secondary hyperparathyroidism in dogs with experimentally-induced reduction in kidney function is influenced by the magnitude of dietary phosphate intake; and the secondary hyperparathyroidism was prevented when dietary intake of phosphate was reduced in proportion to the experimentally induced reduction in the glomerular filtration rate (GFR).

It is evident, therefore, that phosphate retention and hyperphosphatemia can provoke secondary hyperparathyroidism in the absence or presence of impaired kidney function. Consequently, because secondary hyperparathyroidism occurs


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**Table 1. Stages of Chronic Kidney Disease**

| Stage | Description | GFR (mL/min/1.73 m²) |
|---|---|---|
| 1 | Kidney damage with normal or ↑ GFR | ≥90 |
| 2 | Kidney damage with mild ↓ GFR | 60-89 |
| 3 | Moderate ↓ GFR | 30-59 |
| 4 | Severe ↓ GFR | 15-29 |
| 5 | Kidney failure | <15 (or dialysis) |

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m² for ≥3 months. Kidney damage is defined as pathological abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

early in the course of CKD, hyperphosphatemia would be expected to develop at an early stage of reduced kidney function. However, the available data indicate that patients with moderate loss of kidney function (Stage 3) are not hyperphosphatemic but are either normophosphatemic or mildly hypophosphatemic. To explain this discrepancy, it was postulated that a transient and possibly undetectable increase in serum phosphorus occurs early in CKD with each decrement in kidney function. Such a transient hyperphosphatemia would directly decrease the blood levels of ionized calcium, which then stimulates the parathyroid glands to release more hormone (PTH). The elevation in the blood levels of PTH would decrease the tubular reabsorption of phosphate in the kidney and increase the excretion of phosphate in the urine, with the return of serum phosphorus and calcium levels to normal, but at the expense of a new steady state characterized by elevated blood levels of PTH.

This postulate implies that the adaptive changes occurring in patients with incipient loss of kidney function, and leading to secondary hyperparathyroidism, are geared to maintain normal phosphate homeostasis. However, ample evidence exists indicating that phosphate homeostasis in CKD can be maintained without secondary hyperparathyroidism. First, in thyroparathyroidectomized dogs with experimentally induced reduction in kidney function in which the serum calcium was maintained at a normal level by vitamin D supplementation, the fraction of filtered phosphate excreted by the kidney increased and the serum concentration of phosphorus remained normal despite the loss of kidney function. Second, rats immunized against tubular basement membrane developed interstitial nephritis and reduced kidney function, and the kidneys lost the ability to generate cyclic AMP in response to PTH. Despite these changes, the fraction of filtered phosphate excreted in the urine increased markedly. Third, studies in rats with reduced kidney function have clearly demonstrated that PTH is not the main regulator of the handling of phosphate by the kidney. Fourth, a very high fractional excretion of phosphate is present in patients with CKD, even after total parathyroidectomy.

If the sequence of events described by the phosphate retention hypothesis does occur, the basal serum levels of phosphorus and calcium should display one of the following combinations: hyperphosphatemia and hypocalcemia, normophosphatemia and normocalcemia, or hy-

**Table 2. Major Features of Abnormalities in Mineral Metabolism in Kidney Failure[4-15]**

- Hypocalcemia
- Secondary hyperparathyroidism
- Hyperphosphatemia
- Defective intestinal absorption of calcium
- Altered vitamin D metabolism
- Bone disease
- Soft-tissue calcification including coronary arteries and cardiac valves calcification
- Altered handling of phosphate, calcium, and magnesium by the kidney
- Pruritus
- Proximal myopathy
- Skin ulceration and soft-tissue necrosis

pophosphatemia and hypercalcemia. The latter may occur if the adaptive response of the parathyroid glands is exaggerated, as in the case of nutritionally induced secondary hyperparathyroidism in horses. However, available data show that the mean levels of both serum phosphorus and calcium in most patients with moderate loss of kidney function are actually lower than the values in normal subjects. These observations cannot be explained by the phosphate retention theory alone. Thus, other factors must also be operative and contribute to the genesis of the hypocalcemia in the early course of CKD.

These considerations do not necessarily mean that phosphate retention is not an important factor in the pathogenesis of the hypocalcemia and secondary hyperparathyroidism of CKD. Rather, they suggest that phosphate retention in the course of CKD may contribute to the hypocalcemia by mechanisms other than a direct effect of hyperphosphatemia on serum calcium.

It should be mentioned that with more advanced loss of kidney function (Stages 4 and 5) when hyperphosphatemia develops, the elevated blood levels of phosphorus may suppress blood levels of calcium and contribute to the hypocalcemia. In addition, experimental evidence indicates that the very high levels of serum phosphorus may directly affect the function of the parathyroid glands; such high serum phosphorus levels may induce hyperplasia of the parathyroid glands independent of hypocalcemia and/or reduced blood levels of $1,25(OH)_2D_3$. Hyperphosphatemia has a direct effect on post-transcriptional mechanisms that increase PTH synthesis and secretion.

***Role of skeletal resistance to the calcemic action of PTH.*** The calcemic response to the infusion of PTH or to an acute rise in the blood levels of endogenous PTH is markedly blunted in patients with mild to moderate loss of kidney function (creatinine clearance 25 to 85 mL/min/1.73 $m^2$ [0.42 to 1.42 mL/s/1.73 $m^2$]), indicating that this skeletal resistance occurs early in the course of loss of kidney function. This abnormality has also been documented in patients with severe loss of kidney function (creatinine clearance of less than 20 mL/min/1.73 $m^2$ [0.33 mL/s/1.73 $m^2$]) and in those treated with hemodialysis and in many kidney transplant recipients whose kidney function is usually below normal (creatinine clearance 71 $\pm$ 6.7 mL/min/1.73 $m^2$ [1.18 $\pm$ 0.11 mL/s/1.73 $m^2$]).

Skeletal resistance to the calcemic action of PTH occurs in patients with acute kidney failure as well. Hypocalcemia is almost always observed in these patients. The degree of hypocalcemia is moderate to marked (range, 7.5 to 8.0 mg/dL) and lower levels have also been reported. The hypocalcemia occurs early in the course of the oliguric phase of the disease and persists through the diuretic period. This hypocalcemia is observed in patients with low, normal, or elevated serum concentrations of phosphorus, indicating that the hyperphosphatemia of acute kidney failure is not the major determinant of the hypocalcemia. Also, the hypocalcemia cannot be attributed to a failure in the function of the parathyroid glands because the blood levels of PTH are elevated and display an inverse correlation to the concentrations of serum calcium. Further, the infusion of PTH fails to elicit a normal rise in serum calcium. All these derangements are reversed after the return of kidney function to normal.

These observations indicate that there is a skeletal resistance to the calcium-mobilizing action of PTH, an abnormality that occurs early in the course of both acute and chronic kidney disease and is not reversed by hemodialysis. This derangement is an important factor contributing to the hypocalcemia in kidney disease and to the pathogenesis of secondary hyperparathyroidism in these patients.

A series of studies in thyroparathyroidectomized dogs with diverse models of acute kidney failure (bilateral ureteral ligation, bilateral nephrectomy, or diversion of both ureters into the jugular veins) has demonstrated that the skeletal resistance to the calcemic action of PTH is partially due to a deficiency of $1,25(OH)_2D_3$ and its complete correction requires adequate amounts of both $1,25(OH)_2D_3$ and $24,25(OH)_2D_3$. Other studies suggest that the skeletal resistance to the calcemic action of PTH is, at least in part, due to downregulation of PTH receptors. Indeed, several studies have shown that the PTH-PTHrP receptors are downregulated in many organs in uremia; these include the kidney, liver, and heart. This downregulation of the PTH-PTHrP receptors is not due to the high blood levels of PTH but rather to the PTH-induced elevation in the

basal levels of intracellular concentrations of calcium (cytosolic calcium) in those organs. Indeed, in kidney failure the basal levels of cytosolic calcium is elevated in all organs, and the correction of this abnormality by treatment with calcium channel blockers is associated with reversal of the downregulation of the PTH-PTHrP receptors.

***Role of altered vitamin D metabolism.*** The experimental data cited previously suggest that alterations in vitamin D metabolism and/or a deficiency of 1 or more of the vitamin D metabolites are present in patients with early CKD (Stage 2 and 3) because these patients display skeletal resistance to the calcemic action of PTH. Indeed, disturbances in the functional integrity of the target organs for vitamin D (impaired intestinal absorption of calcium and/or defective mineralization of osteoid) have been found in patients with mild CKD (Stage 2 and 3), indicating that a state of relative or absolute vitamin D deficiency exists in these patients.

The blood levels of l,25$(OH)_2D_3$ are usually normal or modestly elevated in patients with moderate CKD (creatinine clearance >50 mL/min/1.73 $m^2$ [0.83 mL/s/1.73 $m^2$]), although low levels have also been noted in both adults and children with these levels of kidney function. Therefore, it appears that absolute deficiency of and/or resistance to vitamin D [normal blood levels of 1,25$(OH)_2D_3$] develop early in the course of CKD. As mentioned earlier, the number of VDRs decreases as the loss of kidney function progresses, resulting in resistance to vitamin D action. The blood levels of 1,25$(OH)_2D_3$ in Stage 4 of CKD are definitely low and are usually undetectable in the dialysis patients.

It is intriguing that, despite the presence of adequate functioning kidney mass in patients with moderate reduction in kidney function (Stage 2), the production of l,25$(OH)_2D_3$ does not increase adequately to meet the needs of the target organs for vitamin D. Because the regulation of the kidney l$\alpha$-hydroxylase, the enzyme responsible for 1,25$(OH)_2D_3$ production, is influenced by alterations in phosphate homeostasis, it is possible that phosphate retention, which may develop with declining kidney function, plays a role in the disturbances in 1,25$(OH)_2D_3$ production. Indeed, dietary phosphate restriction in proportion to the reduction in GFR in adults with Stage 2 CKD has been associated with a significant increase in the blood levels of l,25$(OH)_2D_3$ and with biological evidence for the normalization of the target organ response to vitamin D.

The mechanisms through which dietary phosphate restriction in patients with Stage 2 CKD is associated with increased production of l,25$(OH)_2D_3$ are not evident. This effect does not seem to be mediated by changes in the serum levels of phosphorus because no significant changes in this parameter were found in adults. The effect of dietary phosphate on kidney production of l,25$(OH)_2D_3$ could be mediated through changes in transcellular flux of phosphate and/or in the concentration of inorganic phosphorus in kidney cortical cells. Indeed, studies in rats have shown that the level of inorganic phosphorus in the kidney cell is reduced during the feeding of a phosphate-restricted diet.

***Interaction between 1,25$(OH)_2D_3$ and parathyroid glands.*** Available data indicate that l,25$(OH)_2D_3$ may have a direct effect on the parathyroid glands. First, exposure to 1,25$(OH)_2D_3$ both in vivo and in vitro may directly suppress the activity of the parathyroid glands. Second, l,25$(OH)_2D_3$ renders the parathyroid glands more susceptible to the suppressive action of calcium. Such an effect of l,25$(OH)_2D_3$ may correct the abnormal shift in set point for calcium of the parathyroid glands in patients with CKD. Third, 1,25$(OH)_2D_3$ decreases prepro-PTH messenger RNA in a dose-dependent manner. Thus, it is possible that deficiency of 1,25$(OH)_2D_3$ may initiate secondary hyperparathyroidism even in the absence of overt hypocalcemia; this has been demonstrated in dogs with reduced kidney function.

***Regulation of the parathyroid hormone gene by vitamin D, calcium, and phosphorus.*** Secondary hyperparathyroidism in CKD is due to increased synthesis and secretion of PTH secondary to an increase in PTH gene expression and parathyroid cell proliferation. 1,25$(OH)_2D_3$ acts directly on the PTH gene, causing a decrease in its transcription and hence in the synthesis of PTH. Hypocalcemia increases and hypophosphatemia decreases PTH gene expression by an effect on the stability of the PTH mRNA. Thus, there is an increase in the stability PTH mRNA associated with hypocalcemia, resulting in increased synthesis of the PTH protein. In contrast,

the stability of PTH mRNA is decreased during hypophosphatemia, leading to increased degradation of the PTH mRNA and hence decreased production of PTH. Thus, the effects of hypercalcemia and hypophosphatemia on PTH synthesis is post-transcriptional.

## INTEGRATION OF THE VARIOUS PATHOGENETIC FACTORS IN THE GENESIS OF SECONDARY HYPERPARATHYROIDISM (FIG 1)

The clinical and experimental evidence considered thus far allow an integrated formulation for the mechanisms of secondary hyperparathyroidism in CKD. It appears that phosphate retention, which may develop with loss of kidney function, interferes with the ability of patients with CKD to augment the production of $1,25(OH)_2D_3$ by the kidneys to meet the increased need for this metabolite. Thus, a state of absolute or relative vitamin D deficiency develops, leading to defective intestinal absorption of calcium and impaired calcemic response to PTH. These 2 abnormalities produce hypocalcemia which in turn causes secondary hyperparathyroidism. Although this formulation still assigns an important role to phosphate retention in the genesis of secondary hyperparathyroidism in CKD, the pathway through which such phosphate retention mediates its effect is different from that originally proposed. The original theory maintained that phosphate retention in the early course of CKD is associated with a rise in levels of serum phosphorus and a consequent fall in the levels of serum ionized calcium, which in turn stimulates the parathyroid gland activity. However, it must be emphasized that if marked hyperphosphatemia does develop in a patient with CKD, it could directly lower the level of serum calcium and contribute to the severity of the hypocalcemia and the secondary hyperparathyroidism. In addition, hyperphosphatemia per se may stimulate parathyroid hormone synthesis by a post-transcriptional effect on PTH gene expression. An Na-P cotransporter is present in the parathyroid gland, and this transporter may play a role in the process that allows the parathyroid gland to sense the level of extracellular phosphorus.

An additional pathway through which an absolute or relative deficiency of $1,25(OH)_2D_3$, independent of hypocalcemia, may mediate secondary hyperparathyroidism is related to its direct effect on the parathyroid glands, as discussed earlier.

This integrated formulation for the pathogenesis of secondary hyperparathyroidism has important clinical implications. It is consistent with the hypothesis that dietary phosphate restriction in proportion to the fall in GFR in patients with CKD is adequate to reverse and correct secondary hyperparathyroidism and other abnormalities in mineral metabolism. However, achieving the proper and adequate dietary phosphate restriction and successful patient compliance with the dietary regimen may prove difficult. Because the available data indicate that dietary phosphate restriction exerts its effect through the increased production of $1,25(OH)_2D_3$ and because this vitamin D metabolite also exerts a direct effect on the parathyroid glands, an alternative therapeutic approach would be supplementation of $1,25(OH)_2D_3$. Indeed, treatment of patients with Stage 3 CKD with $1,25(OH)_2D_3$ for 12 months was associated with improvement or normalization of the disturbances in mineral metabolism, including secondary hyperparathyroidism and bone disease.

### *Structure and Function of the Parathyroid Glands*

Hyperplasia of the parathyroid glands is almost always present in patients with CKD, but the increase in volume and mass of the glands varies among patients and among the 4 glands in the same patient. The size of the glands may reach 10 to 50 times normal. Occasionally, the parathyroid glands may be of normal size in patients with CKD. Histologically, the glands show chief cell hyperplasia with or without oxyphil cell hyperplasia. The usual cell is the vacuolated or chronically stimulated chief cell, 6 to 8 $\mu$m wide, with a sharply defined plasma membrane. Nodular or adenomatous-like masses may be found within the hyperplastic glands. These nodules are well circumscribed and surrounded by a fibrous capsule. The cells in the nodular hyperplasia have less VDR and calcium-sensing receptor (CaR) density and a higher proliferative potential than the cells of diffuse hyperplasia. The change in the structure of the parathyroid glands begins as polyclonal diffuse hyperplasia. The cells with the lower density of VDR and

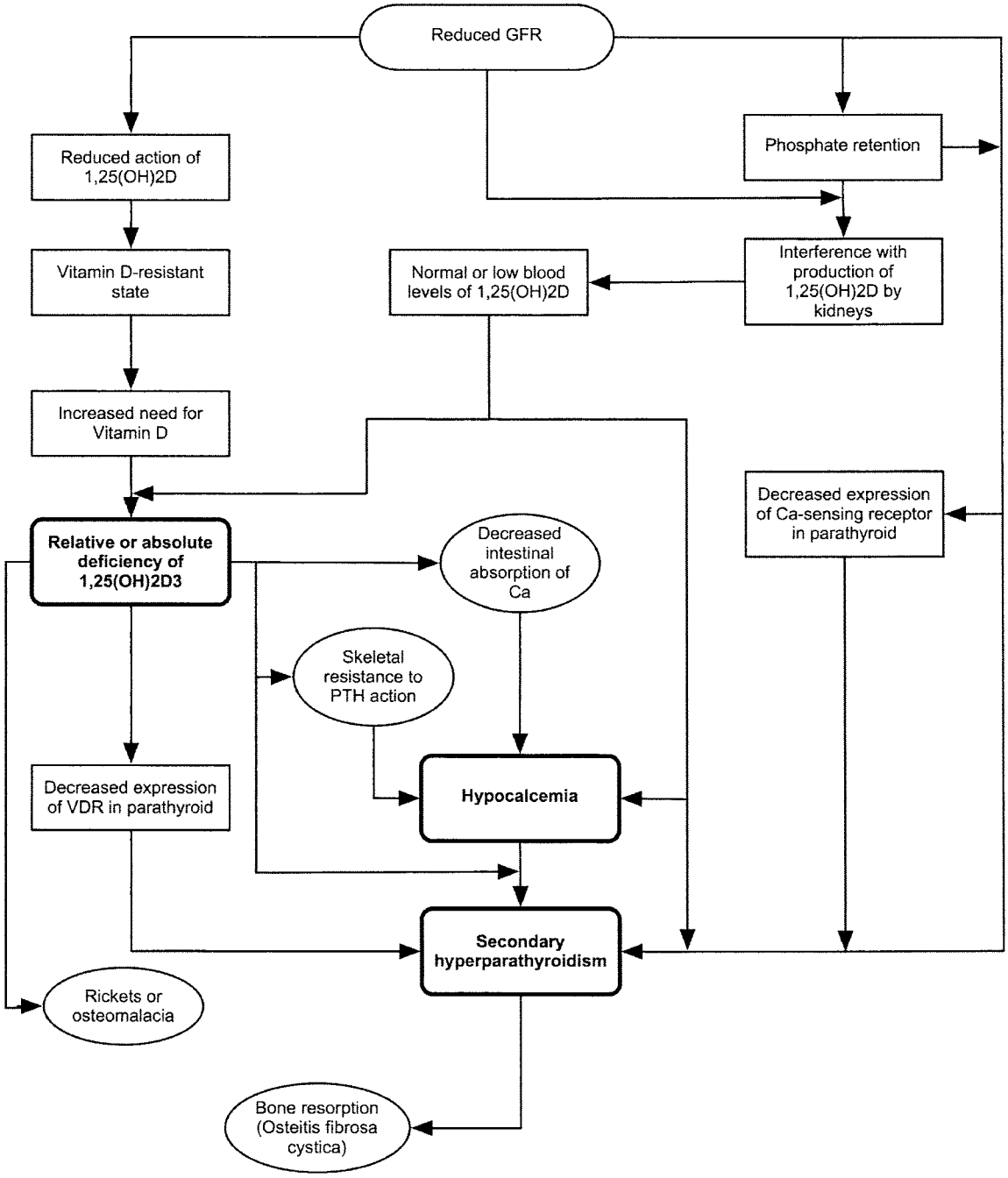



**Fig 1. Pathogenesis of abnormalities in mineral metabolism and bone disease in CKD.**

CaR start to proliferate monoclonally (early nodularity in diffuse hyperplasia) and form nodules. Several monoclonal nodules of different size may develop resulting in multinodular hyperplasia. Alternatively, the cells of 1 of the nodules may proliferate faster and more vigorously giving rise to a very large nodule that almost occupies the entire gland (single nodular gland). Molecular changes are implicated in the tumorigenesis of the parathyroid gland in CKD. However, the exact abnormalities underlying the monoclonal cell proliferation and the biochemi-

cal and molecular processes responsible for the differences in the proliferative potentials of these nodules are, as yet, not elucidated.

Hypocalcemia, relative or absolute deficiency of $1,25(OH)_2D_3$, and phosphate retention or hyperphosphatemia are the most important factors responsible for the hyperplasia of the parathyroid glands. Because hypocalcemia and relative or absolute deficiency of $1,25(OH)_2D_3$ (vitamin D resistance) may develop early in the course of CKD, hyperactivity of the parathyroid glands is also encountered in the early stages of kidney disease. Indeed, elevated blood levels of PTH may be noted when the GFR falls below 60 mL/min/1.73 $m^2$.

The appearance of spontaneous and persistent hypercalcemia in some uremic patients (Stage 4 and 5 CKD) has led to the suggestion that the parathyroid glands in these patients may ultimately become autonomous. However, after calcium infusion, the blood levels of PTH of these patients invariably fall, but not to normal levels. Thus, the parathyroid glands in these patients are suppressible at higher levels of serum calcium. The appearance of spontaneous hypercalcemia and the failure of the blood levels of PTH to fall to normal values after calcium infusion in uremic patients (Stage 4 and 5 CKD) are most likely due to the large mass of the parathyroid glands in these individuals. Malregulation of PTH release at the cellular level may also be present. Indeed, in vitro studies of dispersed cells from the parathyroid glands of such patients show that a higher concentration of calcium is required to achieve a suppression of PTH secretion. This has been interpreted to indicate a shift in the set point for calcium; this abnormality is at least in part due to deficiency in $1,25(OH)_2D_3$. True adenomas may develop and function autonomously in certain cases of secondary hyperparathyroidism, but such cases are not common. The use of the term tertiary hyperparathyroidism should be limited to those cases in which it is documented that a true adenoma has developed in a previously hyperplastic gland.

Multiple factors control the release of PTH from the glands, and they do so by inducing changes in the cellular function of the parathyroid glands. Calcium is the most important regulator of PTH secretion, and its effect is mediated by changes in intracellular concentration of calcium. An increase in the latter influences PTH secretion through several cellular mechanisms such as inhibition of cAMP accumulation or its action, and/or the stimulation of intracellular degradation of preformed PTH.

The CaR is located in the membrane of the cells of the parathyroid glands. This receptor protein plays an important role in the ability of parathyroid glands to recognize changes in the concentration of calcium ion in the blood and as such, CaR mediates the effect of calcium on the secretion of PTH from the parathyroid glands. In the course of CKD, there is a reduction in the density of CaR in the parathyroid gland cells. The levels of serum calcium and $l,25(OH)_2D_3$ as well as dietary phosphate do not appear to regulate the synthesis of CaR.

The relationship between the serum levels of calcium and the parathyroid gland in the modulation of PTH secretion is altered in CKD patients. In normal subjects, this relationship is sigmoidal over a narrow range of calcium concentration, but in patients with CKD, higher levels of serum calcium are needed to suppress the secretion of PTH compared to normal subjects. Also, in CKD patients, the susceptibility of parathyroid adenyl cyclase to the inhibitory effect of calcium is reduced. Such an effect would impair the ability of calcium to inhibit PTH secretion. These abnormalities in calcium and PTH secretion could be evaluated by the changes in set-point for calcium. The latter is defined as the calcium concentration that produces half the maximal inhibition of PTH and that is the midpoint between the maximal and minimal PTH secretions. Indeed, alterations in set-point for calcium with a shift to right (eg, 50% inhibition of PTH secretion occurs at higher calcium concentration) were observed in parathyroid glands of patients with primary or secondary hyperparathyroidism. Administration of $1,25(OH)_2D_3$ to dialysis patients was associated with suppression of PTH secretion and with a shift of the set-point to the left, supporting the hypothesis that deficiency of this vitamin D metabolite plays an important role in the genesis of secondary hyperparathyroidism in CKD.

Thus, the available evidence suggests that in patients with CKD, the structural changes in the parathyroid glands (increase in their mass due to diffuse and nodular hyperplasia) and its func-

**Table 3. Factors Affecting the Level of Serum Phosphorus in CKD**

- Level of residual kidney function
- Dietary intake of phosphate
- Ingestion of phosphate-binding compounds
- Degree of secondary hyperparathyroidism and the responsiveness of the skeleton to parathyroid hormone
- Magnitude of vitamin D deficiency and treatment with vitamin D or its metabolites
- Balance between degradation and synthesis of tissue protein
- Frequency, duration, and adequacy of dialysis
- Parenteral alimentation
- Intake of large supplements of calcium

tional abnormality (shift in set point of calcium to the right) are responsible to the increase production and release of PTH. Because the changes in the structure and function of the parathyroid glands occur early in the course of CKD, the blood levels of PTH are elevated when the GFR falls below 60 mL/min/1.73 $m^2$.

After its secretion from the parathyroid gland, intact PTH is cleaved by the liver into an N- and a C-terminal fragment. The half-life of both the intact hormone and its N-terminal fragment is short (about 5 minutes), whereas that of the C-terminal fragment is much longer. Stages 4 and 5 of CKD are associated with alterations in PTH metabolism. Both the hepatic removal of the intact hormone and the kidney clearance of the C-terminal fragment are impaired. Thus, the elevated blood levels of PTH in CKD are due to both increased secretion and impaired degradation. The major component of the elevated blood levels of the immunoreactive PTH in these patients is the C-terminal fragments and particularly the midmolecule or midregion of C-terminal fragments.

Hyperplasia of the parathyroid glands in patients with CKD is not easily reversed, even after the correction of its causes. Some investigators found that parathyroid gland hyperplasia regresses in all patients in whom PTH secretion was successfully suppressed. The mechanisms underlying this regression are not well understood. Apoptosis has been proposed, and certain in vitro studies indicate that very high concentrations of $1,25(OH)_2D_3$ induce apoptosis of parathyroid gland cells. Such an effect may occur in vivo as well. This phenomenon has been utilized to achieve medical parathyroidectomy by injecting $1,25(OH)_2D_3$ directly into the hyperplastic parathyroid glands. In some patients, spontaneous hemorrhage in the hyperplastic glands occurs and may be responsible for the regression of the hyperplastic glands in occasional cases.

### *Hyperphosphatemia*

Although phosphate retention occurs early in the course of CKD (Stage 2), hyperphosphatemia becomes evident in patients with marked loss of kidney function (Stage 4). Several factors may affect the level of serum phosphorus in patients with CKD (Table 3).

As mentioned earlier, elevation in serum levels of phosphorus occurs when GFR falls below 30 mL/min/1.73 $m^2$ and the severity of hyperphosphatemia becomes greater with further declines in GFR. The dietary intake of phosphate and the fraction of the ingested phosphate absorbed by the intestine have an important effect on the serum levels of phosphorus in patients with CKD. These patients have only mild impairment in intestinal absorption of phosphate, but their kidneys are unable to adequately handle phosphate loads. Thus, an increase in phosphate intake can cause a marked rise in serum phosphorus levels when GFR falls below 30 mL/min/1.73 $m^2$.

Intestinal absorption of phosphate is enhanced by $1,25(OH)_2D_3$, and its administration to patients in Stages 4 and 5 of CKD may produce or worsen hyperphosphatemia. In patients who have substantial osteomalacia, the levels of serum phosphorus may remain unchanged or even fall during therapy with $1,25(OH)_2D_3$. This is due to the deposition of calcium and phosphorus into

bone as $1,25(OH)_2D_3$ improves mineralization of osteoid and heals osteomalacia.

Phosphate-binding compounds render dietary phosphate and phosphate contained in swallowed saliva and intestinal secretions unabsorbable. Thus, patients receiving these compounds may have normal levels of serum phosphorus or develop modest hypophosphatemia. It should be emphasized that these compounds are most effective when dietary intake of phosphate is below 1.0 g/day. With higher phosphate intake (more than 2.0 g/day), their effectiveness is reduced and hyperphosphatemia may persist despite their use.

An important factor determining the level of serum phosphorus in Stage 4 and 5 CKD is the degree of hypersecretion of PTH and the response of the skeleton to the high levels of this hormone. Normally, PTH decreases the tubular reabsorption of phosphate by the kidney, increases urinary phosphate excretion, and consequently maintains serum phosphorus levels. This effect becomes progressively limited as loss of kidney function advances (GFR $<$20 mL/min/1.73 $m^2$). In such patients, the severely damaged kidneys cannot respond to further increments in PTH with additional augmentation in phosphate excretion. The enhanced bone resorption, which is induced by the high levels of PTH, liberates calcium and phosphorus from the skeleton into the extracellular fluid. This phosphorus cannot be excreted by the kidney and hence serum phosphorus concentration rises. The same phenomenon occurs in dialysis patients. Several clinical observations support this view. First, the levels of serum calcium and phosphorus are higher in patients with advanced kidney failure (Stage 5) and severe secondary hyperparathyroidism than in other patients with comparable kidney failure but without severe hyperparathyroidism. Second, following total or subtotal parathyroidectomy in patients with kidney failure and severe secondary hyperparathyroidism, the serum concentrations of calcium and phosphorus fall (Fig 2). Third, when patients with chronic kidney disease and overt secondary hyperparathyroidism are treated with hemodialysis, the serum phosphorus levels not only may remain above normal but may rebound rapidly after dialysis to predialysis levels.

A shift in the balance between protein synthesis and breakdown toward catabolism, as occurs

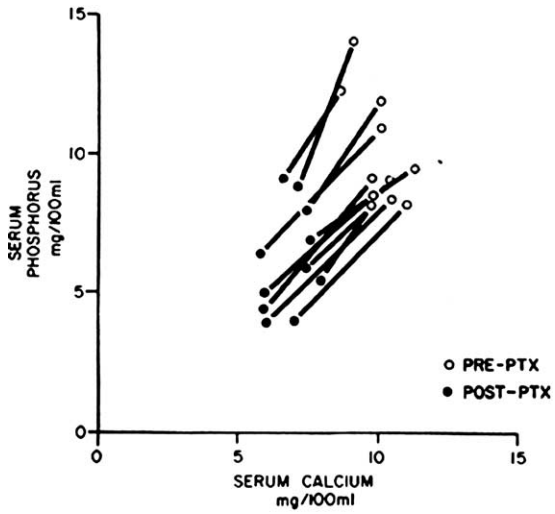



**Fig 2. Changes in total serum calcium and inorganic phosphorus observed in 11 uremic patients before and after subtotal parathyroidectomy. Reproduced with permission.[16]**

with infection, trauma, starvation, and the administration of glucocorticoids or tetracycline, can cause an increase in serum phosphorus concentration. The parenteral administration of solutions containing large quantities of glucose and amino acids to such patients cause an abrupt reduction in serum phosphorus levels. Also, the concentration of serum phosphorus may fall during refeeding after a period of calorie or protein malnutrition.

The use of calcium compounds in patients with Stage 4 and 5 CKD results in the reduction in the serum levels of phosphorus due to the ability of these compounds to bind phosphate in the intestine. In addition, these calcium compounds cause a rise in serum calcium levels which would inhibit the parathyroid gland and results in a fall in blood PTH levels. This would be followed by a reduction in serum levels of serum phosphorus as discussed above.

### *Altered Vitamin D Metabolism*

Patients with Stage 2 and 3 CKD may have a vitamin D-resistant state and/or a relative vitamin D-deficient state. As kidney function deteriorates further, an absolute vitamin D-deficient state develops, with the blood levels of $1,25(OH)_2D_3$ being reduced when GFR falls below 50 mL/min/1.73 $m^2$ (Stage 3) in children and below 30 mL/min/1.73 $m^2$ (Stage 4) in adults. In

**Table 4. Biological Consequences of Vitamin D Deficiency and its Metabolite**

- Shift in set-point of calcium for the parathyroid gland
- Secondary hyperparathyroidism
- Skeletal resistance to the calcemic action of parathyroid hormone
- Impaired mineralization of osteoid
- Abnormalities in formation and maturation of collagen
- Retarded growth in uremic children
- Defective intestinal absorption of calcium and phosphorus
- Abnormalities in the structural integrity of the intestinal mucosa
- Proximal myopathy

anephric patients and in those treated with dialysis, the blood levels of $1,25(OH)_2D_3$ are usually undetectable. In advanced CKD (Stages 4 and 5), the number of VDRs is reduced, leading to vitamin D resistance. Thus, in such patients, there is vitamin D deficiency and vitamin D resistance as well.

The blood levels of 25-hydroxyvitamin D [$25(OH)D_3$] in patients with CKD may be low. Low levels of $25(OH)D_3$ may be encountered in patients who have nephrotic-range proteinuria due to loss of $25(OH)D_3$ in urine, those who are treated with peritoneal dialysis due to loss of $25(OH)D_3$in peritoneal fluid, or those who have nutritional vitamin D deficiency.

The biological consequences of vitamin D deficiency are multiple and are manifested by disturbances in the function of its target organs: parathyroid glands, bone, intestine, and skeletal muscle (Table 4). Because other organs such as testes, myocardium, and pancreas have receptors for $1,25(OH)_2D_3$, it is possible that a deficiency of this vitamin D metabolite plays a role in the dysfunction of these organs in kidney failure.

The factors responsible for the decrease in the number of VDRs in kidney failure are not fully elucidated, but may include (a) reduced levels of $1,25(OH)_2D_3$ because this metabolite affects the production of VDRs (low levels of $1,25(OH)_2D_3$, downregulates the mRNA of VDR); (b) hyperparathyroidism of CKD (high levels of PTH interfere with the $1,25(OH)_2D_3$-induced upregulation of VDR); and (c) uremic toxins, which may decrease the stability of the mRNA of VDRs, resulting in reduced expression of VDR protein.

The action of vitamin D is mediated by its binding to its cytosolic receptor, VDR. The DNA binding site for VDR is a nuclear receptor that contains 2 "zinc fingers" that mediate the binding of VDR to a regulatory promoter in regions of DNA upstream of the vitamin D-responsive genes. This domain is the VDR element (VDRE). Thus, the binding of the vitamin D-VDR complex to the VDRE results in the transcription of specific mRNAs. In advanced CKD, there are impairments in the binding of vitamin D to VDR as well as in the binding of the vitamin D-VDR complex to the VDRE. Both of these events, in addition to the reduced number of VDR, are responsible for the vitamin D-resistant state of severe kidney dysfunction (Stages 4 and 5).

### *Bone Disease*

The nature and type of bone disease that develops in CKD may vary from one patient to another. Multiple reasons may account for these variations (Table 5). The 2 major types of bone disease that are commonly encountered in patients with CKD are enhanced bone resorption (osteitis fibrosa) and adynamic bone disease. Some patients may have 1 of these types predominantly, whereas others may have a mixed type of bone disease. Mild forms of these derangements in bone metabolism may be observed in the early stages of CKD (Stage 2) and they become more severe as kidney function deteriorates. Osteosclerosis may also occur, and osteoporosis may be encountered.

***Bone lesion of excess PTH (high-turnover bone disease).*** The elevated blood levels of PTH are responsible for the enhanced number and activity of osteoclasts leading to increased bone resorption. As this process increases in severity, marked fibrosis involving the marrow space develops, with the histological picture of osteitis fibrosa becoming evident. The marrow fibrosis is caused by activation of marrow mesenchymal cells, which differentiate into fibroblast-

**Table 5. Possible Reasons for Variations in Bone Disease Among Patients with Chronic Kidney Disease**

| |
|---|
| ▪ Age of the patient |
| ▪ Genetic effects |
| ▪ Type of underlying kidney disease |
| ▪ Duration of kidney failure |
| ▪ Relative severity of the pathogenetic processes underlying the derangement in bone metabolism |
| ▪ Differences in dietary habits |
| ▪ Type of therapy used |
| ▪ Treatment with dialysis and its duration |
| ▪ Aluminum burden |
| ▪ Diabetes |

like cells, which form fibrous tissue. In this condition, there is also increased bone formation as evidenced by increased amounts of osteoid. This osteitis fibrosa is a high-turnover bone disease. The manifestations of excess PTH in the bone of uremic patients include increased numbers of osteoclasts and osteoblasts, osteoclastic bone resorption, enlarged haversian lacunae, endosteal fibrosis, and accumulation of woven osteoid and woven bone.

***Bone lesion of defective mineralization.*** Defective mineralization of osteoid leads to rickets in children and osteomalacia in adults. Histologically, osteomalacia can be accurately diagnosed only by the evaluation of undecalcified bone specimens. Osteomalacia is due to a delay in the rate of bone mineralization resulting in accumulation of excess unmineralized osteoid. However, it must be emphasized that the presence of excess osteoid does not necessarily mean osteomalacia. Excess osteoid may be (a) secondary to abnormalities in normal mineralization (osteomalacia); or (b) caused by an increased rate of synthesis of bone collagen, which exceeds normal mineralization. The use of double tetracycline labeling can differentiate between these 2 possibilities and is thus critical for the diagnosis of osteomalacia. The skeleton in osteomalacia is weakened, and patients with this bone disease have skeletal deformities, bone pain, fractures, and musculoskeletal disabilities.

Several mechanisms may underlie the defective mineralization of osteoid and hence the development of osteomalacia in CKD patients. The most important factor in the development of osteomalacia is aluminum overload. Also, relative or absolute deficiency of vitamin D or its active metabolites and/or resistance to their action are factors responsible for the osteomalacia. Vitamin D may affect mineralization through several pathways; it may affect collagen synthesis and maturation, directly stimulate bone mineralization, and/or increase the levels of calcium and phosphorus in the extracellular fluid surrounding the bone. This latter effect is the result of the action of vitamin D on intestinal absorption of these minerals. It is not evident whether a deficiency in one or more of the vitamin D metabolites is critical. For example, few anephric patients with undetectable blood levels of $1,25(OH)_2D_3$ did not show histological evidence of osteomalacia. On the other hand, long-term therapy with $1,25(OH)_2D_3$ improved or healed osteomalacia in many patients with advanced CKD. Osteomalacia may be more frequently encountered in uremic patients with low blood levels of $25(OH)D_3$.

Second, abnormalities in the formation and maturation of collagen have been found in rats with experimental uremia and in patients with advanced CKD. These derangements result in a defect in collagen cross-linking and may affect bone mineralization. These abnormalities in collagen metabolism are most likely due to vitamin D deficiency. Indeed, treatment with $25(OH)D_3$ reversed these defects.

Third, inhibition of maturation of amorphous calcium phosphate to its crystalline phase is another defect participating in the genesis of the osteomalacia. The magnesium content of the bones of these patients is increased, and this may interfere with the process of normal mineraliza-

tion. Magnesium stabilizes the amorphous calcium phosphate and inhibits its transformation into hydroxyapatite. The bone content of pyrophosphate is also increased in these patients, and pyrophosphate may inhibit mineralization.

Fourth, aluminum toxicity may be responsible for a certain type of mineralization defect that is resistant to vitamin D therapy. This type of bone disease has been called low-turnover bone disease or low-turnover osteomalacia. This is mainly seen in dialysis patients who have a large content of aluminum in bone and in whom the aluminum is localized in the mineralization front (ie, the limit between osteoid and calcified tissue). With a decrease in the use of aluminum-containing compounds for the control of hyperphosphatemia, the incidence and prevalence of osteomalacia have been decreasing. Increased burden of iron, alone or in combination with aluminum, can cause osteomalacia in kidney failure patients.

***Adynamic bone disease.*** The exact mechanisms underlying adynamic bone disease (ABD) are not fully elucidated. It is seen in kidney failure patients before and after treatment with peritoneal dialysis or hemodialysis. The prevalence of ABD varies between 15% and 60% in dialysis patients. In 1 study, 30% of bone biopsies from patients with Stage 4 CKD displayed findings consistent with ADB. This entity is characterized by a defect in bone matrix formation and mineralization, increased osteoid thickness, and a decrease in the number of both osteoblast and osteoclast on bone surfaces. There are no excessive amounts of aluminum in the mineralization front. Patients with ABD have lower blood levels of PTH than those with other forms of bone disease. The oversuppression of the parathyroid gland activity with high calcium intake and/or administration of $1,25(OH)_2D_3$ resulting in normal blood levels of PTH may be a factor in the genesis of ABD. ABD is also encountered after parathyroidectomy, in CKD patients with diabetes, and in those with increased aluminum burden; in all these clinical settings, the blood levels of PTH are low. This relationship between the PTH level and ABD is understandable because hypersecretion of PTH in patients with CKD is needed to maintain normal rates of bone formation. It is generally accepted that the blood levels of PTH in the range of 2 to 3 times normal are necessary to maintain normal rates of bone formation and prevent the emergence of ABD.

Patients with ABD have increased rates of overt fractures and microfractures. The latter causes bone pain. Calcium uptake by the adynamic bone is reduced, and therefore patients with ABD may develop hypercalcemia if calcium intake is increased or if dialysate calcium is high.

***Osteosclerosis and osteoporosis.*** Osteosclerosis appears as increased bone density in roentgenographic studies. Histologically, osteosclerosis is most likely due to accumulation of unmineralized trabecular bone with an increase in total bone mass. Because osteosclerosis affects trabecular bone, it is most evident in the vertebrae, pelvis, ribs, clavicles, and metaphyses of long bones, which are made predominantly of cancellous (trabecular) bone. In patients with osteosclerosis, no correlation is found between the bone lesion and any specific pattern of change in serum levels of calcium, phosphorus, or alkaline phosphatase. Certain experimental and clinical evidence suggests that osteosclerosis could be induced by excess PTH. Indeed, patients with primary hyperparathyroidism may display radiographic evidence of osteosclerosis.

Osteoporosis is defined as a decrease in the mass of normally mineralized bone. Immobilization, calcium deficiency per se, and chronic protein depletion may be causes of the osteoporotic component of kidney osteodystrophy. In patients older than 50 years, factors that cause postmenopausal, idiopathic, or senile osteoporosis may contribute to the skeletal abnormalities of CKD.

### *Role of Acidosis in Bone Disease*

Acute acidosis produces a significant loss of the acid-soluble calcium carbonate from bone and is usually associated with negative calcium balance. Rats fed a diet rendering them permanently acidotic were found to have less calcified bone than control animals, despite adequate intake of calcium. Patients with CKD show a persistent positive retention of hydrogen ion which is partially buffered by bone. Indeed, evaluation of the composition of bone in CKD reveals a loss of calcium carbonate. These observations imply that acidosis may contribute to negative calcium balance and the development of skeletal demineralization. However, there is

**Table 6. Factors That May Predispose to Soft-Tissue Calcification in Stages 4 and 5 CKD**

| |
|---|
| ▪ Hyperphosphatemia |
| ▪ An increase in serum calcium-phosphorus product |
| ▪ Secondary hyperparathyroidism |
| ▪ Local tissue injury |
| ▪ A rise in local pH of tissue |
| ▪ Removal of calcification inhibitors by dialysis |
| ▪ Excessive calcium intake |

no evidence that the chronic acidosis observed in CKD can produce continued loss of bone minerals once the labile calcium carbonate component of bone is lost. Although there may be a slight improvement in negative calcium balance following treatment of the chronic acidosis with alkali, a positive balance for calcium usually does not occur, and hypocalcemia, bone pain, and radiographic abnormalities are not corrected. Moreover, there is no convincing evidence suggesting that chronic acidosis can cause defective mineralization. It appears that the chronic acidosis of CKD may not play a major role in the pathogenesis of bone disease in adult patients with CKD.

### *Soft-Tissue Calcification*

Various factors present in Stage 4 and 5 of CKD may predispose to soft-tissue calcification (Table 6). An increase in the calcium-phosphorus product in the extracellular fluid is probably the most important pathogenetic factor. The incidence of soft-tissue calcification is high when the calcium-phosphorus product (each in mg/dL) exceeds 70, while soft-tissue calcification is infrequently noted when the calcium-phosphorus product is below 50. These breakpoints not withstanding, and because of the biological variations in range of calcium-phosphorus product over which calcification may occur and because of other contributing factors including age, it is recommended that the product be maintained below 55. Alkalemia, which often occurs after hemodialysis, may persist during the interdialytic period and may predispose to precipitation of calcium salts in soft tissues. An increase in local pH due to loss of $CO_2$ from the exposed part of the eye may bring about the observed conjunctival and corneal calcification. PTH enhances movement of calcium into cells, and the state of secondary hyperparathyroidism may play an important part in the genesis of soft-tissue calcification in kidney failure. Certain factor(s) that may act locally to inhibit calcification and are present in the blood of these patients may possibly be removed during hemodialysis. Local tissue injury may also predispose to calcification when the calcium-phosphorus product is normal or only slightly elevated. The expression of genes coding for certain proteins involved in prevention of calcification has been demonstrated in macrophages and smooth muscle cells of blood vessel walls. One of these proteins is matrix gla protein (MGP). Its deficiency permits medial calcification of blood vessels. Indeed, MGP knockout homozygous mice displayed extensive and severe vascular calcification. It is possible that downregulation of the production of this protein occurs in uremia and participates in the genesis of the vascular calcification seen in patients with kidney failure.

The chemical nature of soft-tissue calcification may vary in different tissues. Thus, the calcification found in nonvisceral tissue (periarticular and vascular calcification) consists of hydroxyapatite, with a molar Ca:Mg:P ratio similar to that of bone. In contrast, the calcification found in visceral organs (skeletal and myocardial muscle) is made of amorphous $(CaMg)_3(PO_4)_2$ which has a much higher magnesium content. These observations suggest that the mechanisms responsible for the calcification of various tissues in uremic patients may be different.

Soft-tissue calcification constitutes a serious problem in CKD patients. These extraskeletal calcification may be localized in the arteries (vascular calcification), in the eyes (ocular calcification), in the visceral organs (visceral calcification), around the joints (periarticular calcification), and in the skin (cutaneous calcification).

***Vascular calcification.*** Vascular calcification is detected radiographically. The calcification appears as a fine, granular density outlining a portion of the entire artery, giving a radiographic appearance of a pipestem due to deposition of calcium within the media and the internal elastic membrane of the artery. The lumen of the vessel is usually not involved. This medial calcification may first be seen in the dorsalis pedis as a ring or a tube as it descends between the first and second metatarsals. Calcification can also occur in atherosclerotic plaques in the intima of large vessels whose radiographic appearance is that of discrete, irregular densities. It is possible that uremic patients are more prone to this type of calcification because of the presence of hypertension and a propensity to accelerated atherosclerosis.

Arterial calcification is rare in children, uncommon between 15 and 30 years of age, and common in those older than 40. Vascular calcifications are seen in kidney failure patients and in those treated with hemodialysis, and they persist after kidney transplantation. The reported incidence of arterial calcification in dialysis patients has varied from 3% to 83%. In general, the reported incidence of arterial calcification increases with duration of dialysis treatment. In a series of 135 patients published in 1977, the incidence of vascular calcification increased from 27% in those treated for less than 1 year to 83% in patients treated for more than 8 years.

Vascular calcification may involve almost every artery and has been seen in arteries of the forearm, wrist, hands, eyes, feet, abdominal cavity, breasts, pelvis, and brain. The calcification may be very extensive, rendering the artery so rigid that the pulse is not palpable and the Korotkoff sounds may be difficult to hear during the measurement of the blood pressure. Such calcification may also present difficulties during surgery for the creation of arteriovenous shunts or fistulas for maintenance hemodialysis or during renal transplantation.

Arterial calcification shows little tendency to regress; in some patients, improvement or disappearance of arterial calcification occurs within months to years after subtotal parathyroidectomy or renal transplantation.

***Ocular calcification.*** Ocular calcification are the most common types of soft-tissue calcification seen in Stage 4 and 5 CKD. Calcium deposition in the eye may produce visible inflammation and local irritation, resulting in the *red eye* of uremia. This is a transient phenomenon and may last only a few days. Recurrence of the red eye phenomenon is not infrequent, and it becomes apparent each time a new calcium deposition occurs in the conjunctiva. More commonly, conjunctival calcium deposits are asymptomatic and are seen as white plaques or as small punctate deposits on the lateral or medial segment of the bulbar conjunctiva. Also, calcium deposits may occur within the cornea at the lateral or medial segments of the limbus, the so-called band keratopathy. Slit-lamp examination permits easier recognition of these lesions. The loss of $CO_2$ through the conjunctival surface into the air increases the local pH of the ocular tissue, and this rise in pH predisposes to calcium deposition.

***Visceral calcification.*** Deposits of calcium may be found in the lungs, stomach, myocardium, skeletal muscles, and kidney. These calcification are usually not evident radiographically, but can be detected by $^{99m}$Tc-pyrophosphate scan.

Visceral calcification may cause serious clinical complications. Congestive heart failure, cardiac arrhythmias, and heart block may occur in patients with calcium deposition in the myocardium or in and around the conduction system of the heart or the mitral annulus. Calcification of cardiac valves are not infrequent. Abnormal pulmonary function may be noted in patients with pulmonary calcification. Such patients may have reduced vital capacity and reduced carbon monoxide diffusion. Improvement in pulmonary function has been noted after subtotal parathyroidectomy in these patients. Extensive pulmonary calcification may lead to severe pulmonary fibrosis, pulmonary hypertension, and right ventricular hypertrophy. Calcification of the heart and lung constitute a major risk factor for increased morbidity and mortality in dialysis patients.

Increased oxalate burden may occur in Stage 5 CKD patients, especially if they receive large amounts of ascorbic acid. This may be associated with marked deposition of calcium oxalate in soft tissues. Such deposition in the myocardium, or mitral and aortic valves, can cause cardiomyopathy and congestive heart failure, eventually leading to death. Since vitamin C is metabolized to oxalic acid, it is recommended that vitamin C

intake in Stage 5 CKD patients be limited to the daily recommended dose.

***Periarticular calcification.*** Periarticular calcification, with or without symptoms, may develop in patients with Stage 5 CKD. The incidence of periarticular calcification varies widely among dialysis patients. These calcification were absent in 1 report but were encountered in up to 52% of the patients in other series of dialysis patients. The incidence of periarticular calcification may increase with the duration of dialysis. In a study of 135 patients, the incidence of these calcification increased from 9% to 42% from the first to the eighth year of dialysis. With better control of serum levels of phosphorus, this type of calcification is not encountered frequently.

Periarticular calcification may be detected because of the pain induced by the deposition of calcium or may be noted by routine X-ray examination. Most frequently, the calcification appear as small discrete radiodensities around the shoulders, wrists, phalangeal joints, hips, or ankles. Tendosynovitis or tendonitis with abrupt pain may develop, presumably caused by deposition of microcrystals of hydroxyapatite. The synovial fluid of the involved joints is clear with normal viscosity and number of cells. This acute periarticular illness is called *calcific periarthritis*.

Occasionally, large tumoral masses consisting of encapsulated chalky fluid or pastelike material develop adjacent to joints of dialysis patients. The lesions are usually painless, but they may restrict movement of the joint by virtue of their size. The intake of food with high phosphorus content may enhance the development of tumoral calcification. These lesions often regress with the control of serum phosphorus levels by phosphate-binding antacids or following subtotal parathyroidectomy.

***Cutaneous calcification.*** These lesions may appear as small macules or papules composed of firm calcium deposits which are best detected by the chemical analysis of small skin biopsy specimens. Calcium content of skin is increased in most uremic patients and such increments are more commonly seen in patients with severe secondary hyperparathyroidism. Subtotal parathyroidectomy is followed by a decrease in the calcium content of skin, underscoring the role of secondary hyperparathyroidism in the genesis of the cutaneous calcification. Children exhibit soft-tissue calcification far less frequently than adults, and the calcium content of skin is significantly lower than that observed in adults.

***Skin ulcerations and tissue necrosis.*** A syndrome characterized by the development of progressive ischemic skin ulcerations involving the fingers, toes, thighs, legs, and ankles has been observed in a small number of patients with advanced kidney failure. This syndrome occurs in patients after successful kidney transplantation, in those treated with hemodialysis, and less frequently in patients with Stage 5 CKD who are not on dialysis. It appears that this entity is less common among patients treated with continuous ambulatory peritoneal dialysis.

The patients almost always have vascular calcification involving the media of the arteries, and they usually exhibit X-ray evidence of subperiosteal bone resorption. Serum calcium is usually normal and occasionally elevated. A period of hyperphosphatemia has been present for some time before the appearance of the syndrome. The lesions may be preceded or accompanied by severe pain. Before the appearance of ulcerations or tissue necrosis, tender, slightly erythematous, subcutaneous nodules may develop, or there may be blotchy, bluish discoloration. Raynaud's phenomenon may also precede the lesions of the fingers or toes. The ulcers may develop slowly over several months, or may appear and progress rapidly over a few weeks. Infection may supervene, leading to sepsis and death. The original reports of this entity termed it *calciphylaxis* because of an apparent similarity to the calciphylaxis described by Seyle in 1962. Others have argued that the name should be changed to *calcific uremic arteriopathy*.

This syndrome could be life-threatening and requires aggressive therapeutic attention. The lesions do not respond to treatment with local measures but have healed following subtotal parathyroidectomy in most patients. However, in some patients, the lesions did not heal after parathyroidectomy, and in others, the lesions seem to be aggravated.

Although disturbances in mineral metabolism, secondary hyperparathyroidism, and vascular calcification appear to play an important role in the genesis of this entity, other factors may also contribute to its emergence and progression. Acquired protein C deficiency has been reported in

patients with CKD, and such a derangement may lead to a hypercoagulability state and consequently to vascular occlusion and tissue necrosis. Therefore, it is important that the blood levels and the activity of protein C be measured in patients with calciphylaxis. It is interesting that obesity, especially in white women, predisposes to calciphylaxis, and the relative risk for calciphylaxis rises with weight increase. Local trauma may be a contributory factor as to site where the lesion may appear; indeed, in some patients, the necrotic lesions began in areas where insulin, heparin, or iron dextran were injected. Warfarin prescription is a possible risk factor as well.

### WHY THESE GUIDELINES ARE NEEDED

Disturbances in mineral and bone metabolism are common in patients with CKD. The processes causing disordered mineral metabolism and bone disease have their onset in the early stages of CKD, continue throughout the course of progressive loss of kidney function, and may be influenced beneficially or adversely by various therapeutic approaches used. The pathogenesis of abnormalities in bone mineral metabolism and disease in CKD are shown in Fig 1.

A large body of evidence has accumulated indicating that the derangements in mineral and bone metabolism in CKD are associated with increased morbidity and mortality. These patients have bone pain, increased incidence of fractures, bone deformity, myopathy, muscle pain, and ruptures of tendons, and children with chronic kidney failure suffer from retarded growth.

The long-term effects of soft tissue calcifications have become an area of growing concern for CKD patients and those who treat them. Calcification of the lung leads to impaired pulmonary function, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, and right-side congestive heart failure. Calcification of the myocardium, coronary arteries, and cardiac valves result in congestive heart failure, cardiac arrhythmias, ischemic heart disease, and death. Vascular calcification leads to ischemic lesions, soft-tissue necrosis, and difficulties for kidney transplantation.

Hyperphosphatemia also appears to be associated with increased mortality, and elevated blood levels of PTH exert significant adverse effects on the function of almost every organ. Thus, prevention of the disturbances in mineral and bone metabolism and their management early in the course of chronic kidney disease are extremely important in improving patients' quality of life and longevity.

Although much remains to be learned about these conditions, the recommendations made in these guidelines are intended to aid clinicians in developing an integrated approach to their diagnosis and management of this complicated area, based on the best available evidence. It is clear that the kidney community has many opportunities to develop strategic alliances in order to add to the existing body of knowledge. Ongoing research in this exciting area will lead to improvements in care and, thus, to updating of guidelines when such information is available.

Throughout the guidelines, the stages of CKD are defined according to the K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification (Table 2).

# METHODS FOR ANALYSIS OF LITERATURE

## AIMS

THE OVERALL AIMS of the project were to develop a set of clinical practice guidelines that would improve diagnoses and treatment of bone disease in CKD and serve as a clinical action plan for the health care practitioner.

Fundamental to this effort was the development of an evidence base upon which the guidelines are founded. This base was derived through a systematic summary of the available scientific literature on the clinical assessment and treatment of bone disease and derangement in mineral metabolism in CKD, and the inter-relationship of disorders of mineral and bone with the various stages of CKD.

Two products resulted from this process: (a) an evidence report which consists of the summary of the literature (portions of the evidence report are contained in this document; the entire evidence report remains on file with the National Kidney Foundation) and (b) a set of clinical practice guidelines regarding the clinical action plan which are contained in this report.

## ASSIGNMENT OF DOMAINS

The Co-Chairs of the K/DOQI Advisory Board selected the Work Group Chair and Vice Chair, who selected the Work Group and assigned "domain experts" to be responsible for the development of guideline statements in different areas. These were individuals from North America with expertise in nephrology, pediatrics, laboratory medicine, bone disease, and nutrition. ECRI was selected by the National Kidney Foundation as the Evidence Review Team that would review and analyze the published evidence and produce an evidence report, collaborating integrally with the Work Group. The Evidence Review Team and the Work Group collaborated closely throughout the project.

## OVERVIEW OF PROCESS

Three Work Group meetings and a series of conference calls were carried out to develop an evidence model, assess the literature, evaluate the evidence base, review the evidence report, and draft guideline statements. Prior to the development of the evidence base, a set of hypothetical guideline statements (leaving a blank where values from the evidence were to be inserted following development of the final evidence report) were developed by the Work Group in order to define the parameters of the literature review. This evidence base consisted of an evidence report prepared by the Evidence Review Team that included 26 meta-analyses of the available scientific literature and numerous summaries of data.

The steps used to develop the guidelines and evidence base are listed in Table 7.

Final voting was used to arrive at a Work Group consensus on final guideline statements and supporting rationale, graded according the level of evidence on which it was based. The overall guidelines were then graded according to the strength of evidence supporting the line of logic of the rationale statements.

## DEVELOPMENT OF TOPICS

The goals of the Work Group spanned a diverse group of topics. The Work Group Chair and Vice Chair initially formulated a working list of "key questions" that should be addressed in the evidence report and then converted into hypothetical guideline statements. At an initial Work Group meeting in April 2000, these questions and resulting statements were refined through discussions between the Work Group and the Evidence Review Team. Work Group members were given two additional opportunities to refine the key questions, which were finalized in May 2000. Each key question typically had several outcomes of interest, from long-term, patient-oriented outcomes such as quality of life and mortality, to short-term intermediate outcomes such as serum calcium and phosphate levels. The key questions were divided into 9 sections:

1. Phosphate
2. Calcium
3. PTH
4. Vitamin D
5. Bone Diseases
6. Dialysis


*0272-6386/03/4204-0301$30.00/0*
*doi:10.1053/S0272-6386(03)00905-3*

**Table 7. Steps Used to Develop the Bone Disease Guidelines**

| |
|---|
| ▪ Develop a set of key questions addressed by the literature, serving as an underpinning to the hypothetical guideline statements |
| ▪ Meet to discuss process, methods, and results |
| ▪ Develop and refine topics via conference calls and correspondence, and finalize that development at the face-to-face meetings |
| ▪ Define populations of interest |
| ▪ Develop literature search strategies |
| ▪ Define *a priori* inclusion and exclusion criteria of the literature |
| ▪ Create and standardize quality assessment metrics |
| ▪ Perform literature searches |
| ▪ Create data abstraction forms |
| ▪ Screen abstracts and retrieve full articles |
| ▪ Review literature |
| ▪ Create draft evidence tables |
| ▪ Quantitatively analyze literature (when appropriate) |
| ▪ Create draft guideline statements and rationales |
| ▪ Tabulate standardized data from articles into summaries and create summary graphics |
| ▪ Write guideline statements and rationales based on literature |

7. Amyloidosis
8. Aluminum
9. Acid-Base

Hypothetical guideline statements were then prepared from the key questions, and these statements were used to formulate and refine the final guideline statements. The Work Group voted on the final wording of each guideline statement in relationship to the final evidence report presented. As the hypothetical guideline statements were formulated, these questions were redivided into 16 different Guideline areas corresponding to the guidelines set forth in this document.

### LITERATURE SEARCHES

The Work Group and Evidence Review Team agreed on a systematic process to be followed to review literature pertaining to the key questions and hypothetical guideline statements. Based on these key questions, information specialists at the Evidence Review Team performed database literature searches to identify the relevant published medical literature to address the key questions. A list of terms pertaining to specific kidney and bone diseases was forwarded to the Work Group members for review. Terms were excluded from the strategies only if all members of the Work Group agreed that they were not essential. The strategies were modified following the first Work Group meeting in April 2000, and were further modified following the second meeting in July 2000. Major databases searched included: Medline, Embase, PsychLit, Cochrane Library, and CINAHL. In total, 10 major databases were searched.

### ARTICLE RETRIEVAL CRITERIA

A priori criteria were established for determining whether an article identified by the literature searches should be retrieved before the searches were performed to reduce the possibility of bias in selecting articles. The criteria served to establish minimum standards of relevance and quality of the retrieved articles. The agreed-upon inclusion criteria were:

- Articles must be published as letters or full-length articles. Meeting abstracts were not included. Abstracts were not included because the space limitations of abstracts do not allow evaluation of the quality of the study. Further, it is likely that not all abstracts are submitted as full articles for publication, which calls the authors' confidence in their data into question.
- Multi-arm crossover studies must contain 5

or more patients in each arm. Trials of all other designs must contain 10 or more patients in each arm.
- The study must address a key question as developed by the Work Group.
- The study must be written in English, due to prohibitive translation costs of articles written in other languages.
- The study must include chronic kidney disease patients and not mix results with other types of patients or individuals without disease.
- Literature was searched back to the earliest date of articles available on the database being used, eg, Medline coverage began in 1966, while EMBASE coverage began in 1972. The cutoff date for all literature considered as evidence was *January 1, 2001*.

### ARTICLE RETRIEVAL METHODOLOGY

Abstracts of each article identified in the electronic searches were downloaded into the Evidence Review Team's database. These abstracts were then reviewed by research analysts trained in the assessment and analysis of medical data. Articles were requested if they appeared to meet the criteria outlined above. If there was any uncertainty as to whether an article met the criteria, the article was requested.

### ARTICLE INCLUSION CRITERIA

The resulting articles were then evaluated to determine whether they met criteria for inclusion in this evidence report. There were both general and question-specific inclusion criteria, in order to include only the most appropriate and highest-quality evidence. Studies were included only if:
- The article provided sufficient detail about diagnostic or treatment protocols to determine that it addressed a question from the K/DOQI Bone Guideline List of Questions;
- The article provided sufficient detail about important study protocols to allow one to evaluate study quality;
- Results from Stage 5 CKD patients both prior to dialysis and on dialysis, and/or post-transplant patients were not combined (except in diagnostic studies);
- The diagnostic or treatment of interest was applied to the patient population in the way it was intended or designed to be used in clinical practice;
- The study was not confounded by concurrent administration of other therapies applied inconsistently (ie, all groups in the study received similar concurrent therapies);
- Single-arm studies provided baseline measurements.

In the consideration of any treatment-related question, the following hierarchy, an adaptation of that proposed by the US Preventative Health Task Force, was used to identify the highest quality studies:

Highest quality
- Randomized controlled trials
- Matched controlled trials
- Prospective nonrandomized/nonmatched controlled trials
- Retrospective nonrandomized/nonmatched controlled trials

Low quality
- Uncontrolled pre- or post-cross-sectional studies

**Table 8. Summary of Article Retrievals**

| No. of Articles | Status |
|---|---|
| 4,223 | Requested |
| 4,161 | Received |
| 892 | Cited in the final evidence report (including excluded articles) |
| 467 | Serve as the evidence base for these Guidelines |

### RETRIEVAL AND INCLUSION OF PUBLISHED TRIALS

There were 22,353 citations identified for this project through electronic and hand searches. Some of these citations represent entire database searches rather than a single document. Any studies deemed relevant to the topic were retrieved. Article retrieval requests made for this project are summarized in Table 8.

Table 9 outlines the number of studies included in each of the 15 evidence reports, as well as the number of patients represented by these studies.

**Table 9. Evidence Base for Evidence Reports**

| Evidence Report | No. of Studies Considered* | No. of Studies in Evidence Base | No. of Patients in Evidence Base |
|---|---|---|---|
| Risk Factors for Bone Diseases | 88 | 49 | 13,229 |
| Evaluating Bone Diseases | 76 | 26 | 1,868 |
| Treatment of Bone Disease | 6 | 1 | 120 |
| Dietary Phosphorus Restriction | 71 | 41 | 4,214 |
| Phosphate Binders | 38 | 28 | 3,157 |
| Treatment of Hypocalcemia | 22 | 15 | 3,339 |
| Vitamin D Supplementation | 92 | 78 | 2,809 |
| Monitoring During Calcium and Vitamin D Treatment | 48 | 11 | 850 |
| Calcium in Dialysis | 35 | 11 | 541 |
| $\beta_2$ Microglobulin Amyloidosis | 103 | 61 | 4,815 |
| Diagnosis and Treatment of Aluminum Bone Toxicity | 55 | 31 | 4,852 |
| Assessing Hyperparathyroidism | 51 | 9 | 729 |
| Hyperparathyroidism | 142 | 65 | 1,817 |
| Acid-Base Status | 33 | 22 | 2,809 |
| Kidney Transplant | 26 | 18 | 1,872 |

* Includes studies that met the general inclusion criteria but were later excluded because they did not meet the question specific inclusion criteria.

### *Format for Evidence Tables*

Five types of evidence tables were prepared during the course of this project and were included in the Evidence Reports prepared by the Evidence Review Team.

Detailed tables contain data from each field of the components of the data abstraction forms. These tables were initially distributed to the Work Group in September 2000, so that they could evaluate the evidence and determine whether any important articles were missed or inappropriate articles were included. These tables are contained in the Appendix of each Evidence Report.

In-text study detail tables summarized the most salient aspects of study design, in particular those aspects that were used to determine the methodology quality rating. These tables were constructed for each key question and included in the body of each evidence report.

In-text patient characteristics tables summarized the most salient aspects of the patients included in each study. The tables were produced for each key question. In particular, these tables pointed out the number of patients, number of women, number of patients with diabetes, number of children, and mean age of the patients (with standard deviation), among other characteristics.

In-text evidence tables were produced for each outcome measure within each key question. The evidence tables reported the evidence as it was used by the Evidence Review Team to perform quantitative analyses, not the evidence as it was reported by the authors of a study. Whenever possible, the results from each study were recalculated and standardized into a common, metric, Hedges' d. This is a standardized metric that converts results comparing 2 independent groups into standard deviation units. In this way, results from different studies that were reported in different metrics could be combined for analysis. *P* values were not reported in these tables, as they are strongly affected by the study size and therefore can be misleading about the true size of the effect found.

Study Quality Overview tables, also included in the body of the evidence reports, were produced for those key questions that addressed a treatment issue for which controlled trials were available. The rating scheme used was applied *only* to controlled trials. No rating scheme was developed for diagnostic studies, as there is no widely accepted hierarchy of evidence in the

technology assessment community. These tables described the strength of evidence according to 3 dimensions: size of the study, applicability, and methodological quality.

### *Rating Scheme to Evaluate the Quality of Controlled Trials*

Rating schemes are an essential part of the clinical guideline development process. To the reader of a guideline, the use of these rating scales provides an easy indicator of the quality of the evidence on which the guideline was formulated. As a result, any clinician reading the guideline knows how confidently to believe the recommendations of the guideline.

The rating scheme used in this evidence report is multidimensional and takes into account the following study attributes:

- study design and methodology;
- patient generalizability ("applicability"); and
- the statistical significance of the study findings ("association").

The exact rating method used for each of these dimensions is outlined briefly below.

### *Study Design and Methodology*

The quality of the study design, or "internal validity" was the focal point of the rating scale. The methodology of a single study was rated using a 0 to 7 scale as shown in Table 10.

This 0 to 7 rating scale was developed by extracting the following data from each study, and assigning various point values:

- prospective or retrospective design;
- patients randomized to treatment and control groups;
- randomization method (if randomization method was described);
- control method and group; and
- blinding.

All points were then added together for a final score in the range of 0 to 7. The final score was

**Table 10. Rating of Methodological Quality**

| Rating | Description | Symbol |
|---|---|---|
| 0-2 | High quality studies | ● |
| 3-4 | Studies with some limitations in quality that may limit interpretability of results | ◘ |
| 5-7 | Low quality studies that may be substantially affected by bias | ○ |

**Table 11. Rating of Applicability**

| Points Given | Description | Symbol |
|---|---|---|
| 1 | Low applicability | 🧍 |
| 2 | Applicable, but with limitations | 🧍🧍 |
| 3 | Very applicable | 🧍🧍🧍 |

represented using the graphics shown above in the Overview of Study Quality table included for each key question answered in the evidence reports.

### *Patient Applicability*

Patient applicability refers to whether a patient group included in any given trial is relevant to the issue being addressed. This is a measure of external validity or generalizability of a study's results.

The rating of patient applicability was done on a 3 point scale as shown in Table 11.

The entries on patient applicability for each study required the input of the Work Group. They were instructed to enter the point rating for each study as they reviewed draft copies of the evidence reports for these Guidelines, produced by the Evidence Review Team.

An example of the quality overview of a study is shown in Table 12. A filled-in circle represents the highest quality and an empty circle the lowest quality. Applicability indicates whether the patients included in this study were appropriate for answering the question; 3 figures is most appropriate, while 1 figure is least appropriate. (Adults and children were indicated separately, as shown.) We stress that rating systems such as this are highly subjective.

### *Reporting of Results*

The results for most controlled and pre-/post-treatment trials were reported in terms of Hedges' d, a standardized effect size. Because Hedges' d is in standard deviation units, its value generally can range from $-3$ to $+3$. Thus, the graphical representation used was as follows:

⇧ Hedges' d significantly greater than zero

⇔ Hedges' d not significantly greater than zero

⇩ Hedges' d significantly less than zero

**Table 12. Example of a Study Quality Overview Table**

| Author | Year | N | Methodology Quality | Applicability |
|---|---|---|---|---|
| Author A (1) | 2000 | 27 | ◎ | Pediatrics |
| Author B (2) | 1999 | 53 | ○ | |
| Author C (3) | 1995 | 223 | ● | |

If Hedges' d could not be calculated for a particular study (because not enough information was available), the reported study results were tabled instead, and the above graphics were used to represent whether the results were statistically significant or not (as indicated by the *P* value reported by the study).

### *Quantitative Analysis of Studies*

To analyze diagnostic trials, ECRI used a method called the "summary receiver operating characteristics (ROC) curve." This is the most widely accepted analytical method for combining results from different diagnostic trials. It combines and plots the sensitivity (true positive rate) against specificity (inverse of the false positive rate) of a particular diagnostic test from several trials. The summary ROC includes 95% confidence intervals for complete evaluation of the statistical significance of the efficacy of the test compared to flipping a coin (chance). In this way, all the available evidence about a test's tradeoffs between false positives and false negatives can be considered.

In ROC space, sensitivity is plotted against specificity. The more effective the diagnostic test, the closer it falls to the upper left corner of the grid (sensitivity and specificity 100%). The summary ROC curve (Fig 3) represents a diagnostic meta-analysis, combining the results from all 4 studies on X-ray erosions. This curve reflects

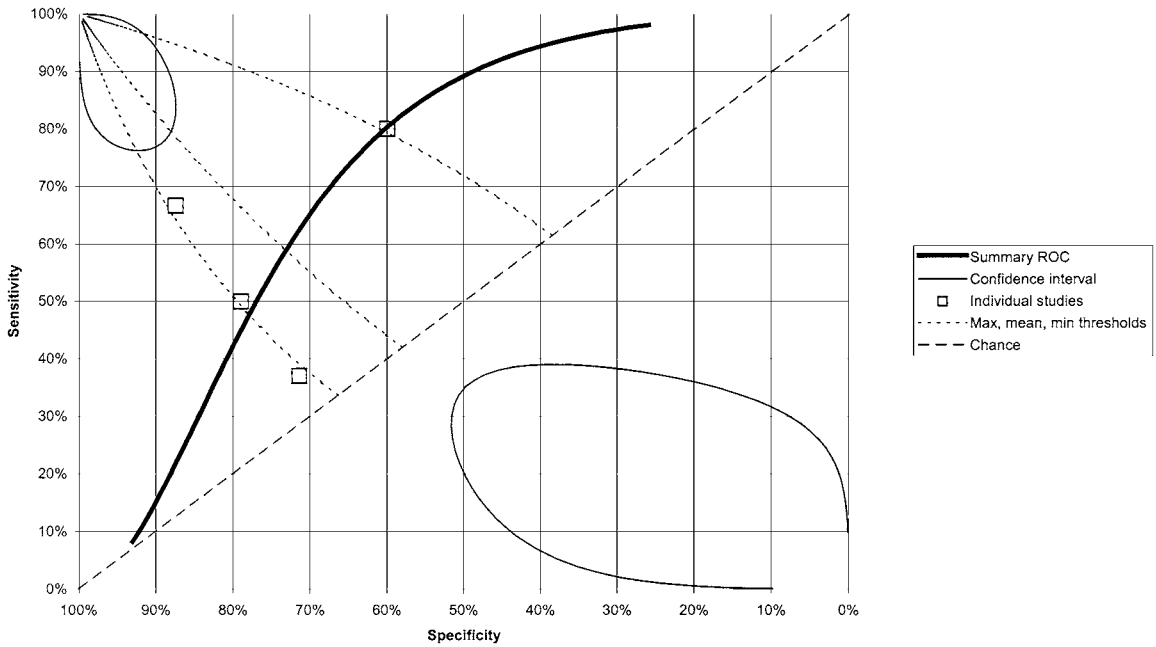



**Fig 3. Example of Summary ROC analysis.**

the necessary tradeoff between sensitivity (1 − false negative rate) and specificity (1 − false positive rate) inherent in any diagnostic test. By changing the diagnostic threshold between results called positive and results called negative, the test can theoretically operate at any point along the ROC curve. The summary ROC is superior to averaging study results for meta-analysis of diagnostic test results because averaging systematically underestimates sensitivity and specificity.

The mean threshold point is the best single point estimate of the sensitivity and specificity of the diagnostic test in question. The 95% confidence intervals (CIs) for the ROC curve are also important to consider. If the lower 95% CI line were to fall below the chance line (a 45° line), it would suggest that the diagnostic test does not have a statistically significantly probability greater than chance of detecting the disease.

### *Voting Procedures on Final Guideline Statements*

The following voting method was used:

A tally was taken to determine whether consensus among Work Group members exists for each Guideline statement. Consensus among Work Group members was defined by at least a 75% majority approval of a Guideline statement (eg, with 12 Work Group members present, a vote of 9 was necessary to consider the statement approved). Guidelines that did not receive approval were re-drafted and re-submitted to Work Group members for final voting.

**Table 13. Grading Rationale Statements**

| | Rationale Statements |
|---|---|
| 1. | Analysis of controlled trials, generalizable studies of high methodological quality |
| 2. | Analysis of lower quality studies |
| 3. | Vote count analysis of evidence tables |
| 4. | Review of reviews and selected original articles |
| 5. | Opinion |

## STRENGTH OF EVIDENCE

Each rationale statement has been graded according to the level of evidence on which it is based (Table 13). The overall guideline is then graded according to the strength of evidence supporting the rationale statements.

# CLINICAL PRACTICE GUIDELINES

## GUIDELINE 1. EVALUATION OF CALCIUM AND PHOSPHORUS METABOLISM

**1.1 Serum levels of calcium, phosphorus, and intact plasma parathyroid hormone (PTH) should be measured in all patients with CKD and GFR <60 mL/min/1.73 m$^2$. (EVIDENCE) The frequency of these measurements should be based on the stage of chronic kidney disease (Table 14). (OPINION)**

**1.2 These measurements should be made more frequently if the patient is receiving concomitant therapy for the abnormalities in the serum levels of calcium, phosphorus or PTH, as detailed in Guidelines 4, 5, 7, and 8 and in transplant recipient, Guideline 16.**

**1.3 Measurement of plasma PTH levels may be done less frequently for those with levels within the low end of the target levels (Table 15). (OPINION)**

**1.4 The target range of plasma levels of intact PTH in the various stages of CKD are denoted in Table 15.**

### Background

A disorder of bone remodeling, the osteodystrophy of CKD, is a common complication. By the time patients require dialysis replacement therapy, nearly all are affected. The onset of the disorder is detectable about the time 50% of kidney function is lost.[17,18] There are multiple histological types of bone pathology in patients with CKD. At the present time, the ability to diagnose the exact type of osteodystrophy of CKD without the pathological description enabled by bone biopsy does not exist. Since high-turnover osteodystrophy can be prevented,[19,20] patients with CKD should be monitored for imbalances in calcium and phosphate homeostasis, and for secondary hyperparathyroidism, by determination of serum calcium, phosphorus, and intact PTH levels.

Levels of intact parathyroid hormone as determined by immunoradiometric assay (IRMA) or immunochemiluminometric assay (ICMA) are an adequate screening tool to separate high-turnover bone disease (osteitis fibrosa) from low-turnover bone disorders (adynamic bone disorder).[21-26] While the ability to discriminate between the histological types of osteodystrophy of CKD has been demonstrated with determination of blood levels of intact parathyroid hormone, the optimal target level for PTH in CKD is not known due to limitations in the available data, and the emerging consensus that those target levels may be lower than currently thought.[27] Recent studies demonstrate that intact PTH assays overestimate the levels of biologically active PTH by detecting C-terminal fragments missing amino acids from the N-terminus of the molecule, which may have an inhibitory activity. Newer PTH assays have been developed to overcome this problem by using an antibody that detects the first several amino acids in a 2-site assay, but sufficient research has not accumulated to establish the predictive power of these newer assays, and whether they will overcome the shortfalls in the intact hormone assays. Furthermore, the newer assays have not as yet replaced the intact hormone assays as standard clinical tools.

The predictive power of parathyroid hormone levels is increased by concomitant consideration of alkaline phosphatase levels,[28] although insufficient data exist to determine the sensitivity and specificity of alkaline phosphatase in osteodystrophy of CKD, or its concomitant use with parathyroid hormone levels. These studies were performed in the era of high osteomalacia prevalence, and it remains to be determined whether alkaline phosphatase determinations are additive to the

**Table 14. Frequency of Measurement of PTH and Calcium/Phosphorus by Stage of CKD**

| CKD Stage | GFR Range (mL/min/1.73 m$^2$) | Measurement of PTH | Measurement of Calcium/Phosphorus |
|---|---|---|---|
| 3 | 30-59 | Every 12 months | Every 12 months |
| 4 | 15-29 | Every 3 months | Every 3 months |
| 5 | <15 or dialysis | Every 3 months | Every month |

**Table 15. Target Range of Intact Plasma PTH by Stage of CKD**

| CKD Stage | GFR Range (mL/min/1.73 m$^2$) | Target "intact" PTH (pg/mL [pmol/L]) |
|---|---|---|
| 3 | 30-59 | 35-70 [3.85-7.7 pmol/L] (OPINION) |
| 4 | 15-29 | 70-110 [7.7-12.1 pmol/L] (OPINION) |
| 5 | <15 or dialysis | 150-300 [16.5-33.0 pmol/L] (EVIDENCE) |

newer PTH assays. Several other biochemical markers of bone turnover have been developed (osteocalcin, hydroxyproline) and are possibly useful in the evaluation and management of osteoporosis, but CKD affects each of these determinations, and no evidence of their usefulness in this population exists.[28] No bone imaging methods exist for measuring bone disease that can be used diagnostically in place of bone biopsy for osteodystrophy of CKD.

### Rationale

Blood levels of PTH begin to rise when GFR falls below 60 mL/min/1.73 m$^2$, and evidence of bone disease due to hyperparathyroidism may be present at Stage 3 of CKD (Fig 4). This secondary hyperparathyroidism progresses as kidney function worsens. During this process, changes in blood levels of serum phosphorus (hyperphosphatemia) and calcium (hypocalcemia) occur and contribute to the worsening of hyperparathyroidism and bone disease. Therefore, measurements of serum levels of phosphorus, calcium, and PTH should be made when GFR falls below 60 mL/min/1.73 m$^2$ and these parameters should be monitored thereafter in patients with CKD (Table 14).

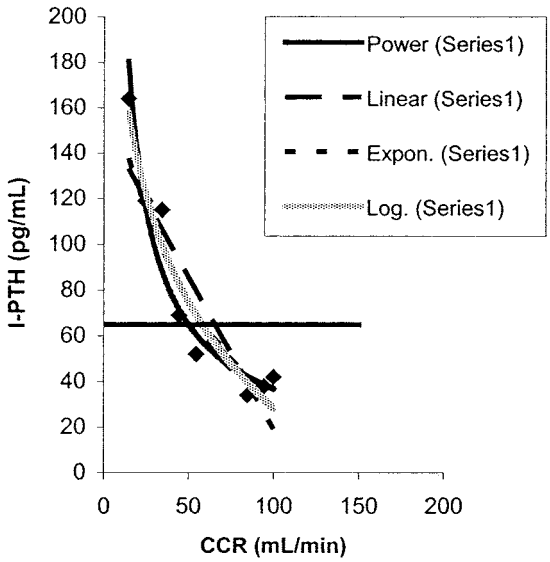



**Fig 4. Graph showing relationship between serum I-PTH levels and CCR based on data extracted from Martinez et al (1997). Values on the y-axis are serum I-PTH levels (pg/mL). Values on the x-axis are CCR in mL/min. The lines fitted to the data set are based on 4 different mathematical functions (power, linear, exponential, and logarithmic), rather than on any assumptions about an underlying physiological mechanism. The horizontal line represents the upper limit of the normal range of serum I-PTH levels.**

Most patients with kidney failure or those on maintenance dialysis have some form of osteodystrophy of CKD. Despite considerable advances in understanding the pathophysiology, prevention, and treatment of osteodystrophy of CKD, an adequate substitute for bone biopsy in establishing the histological type of osteodystrophy has not been developed. Standard bone radiography can reliably detect bone erosions, but has a sensitivity of approximately 60% and a specificity of 75% for the identification of osteitis fibrosa using such erosions (Fig 5). Skeletal radiography is therefore an *inadequate test*. Sufficient data to assess the sensitivity and specificity of other imaging methods in the diagnosis of osteodystrophy of CKD do not exist. Data on the assessment of the usefulness of quantitative computed tomography in the diagnosis of osteodystrophy of CKD are also insufficient. Standard radiography is more useful in the detection of vascular calcification than it is for osteodystrophy. Studies determining the sensitivity and specificity for detection of vascular calcification in CKD have not been performed, but the sensitivity is expected to be low. Recently, newer imaging techniques such as electron beam computed tomography (EBCT) and spiral CT have been developed to detect vascular calcification.[29,30] These studies demonstrate an alarming and progressive vascular calcium burden during CKD

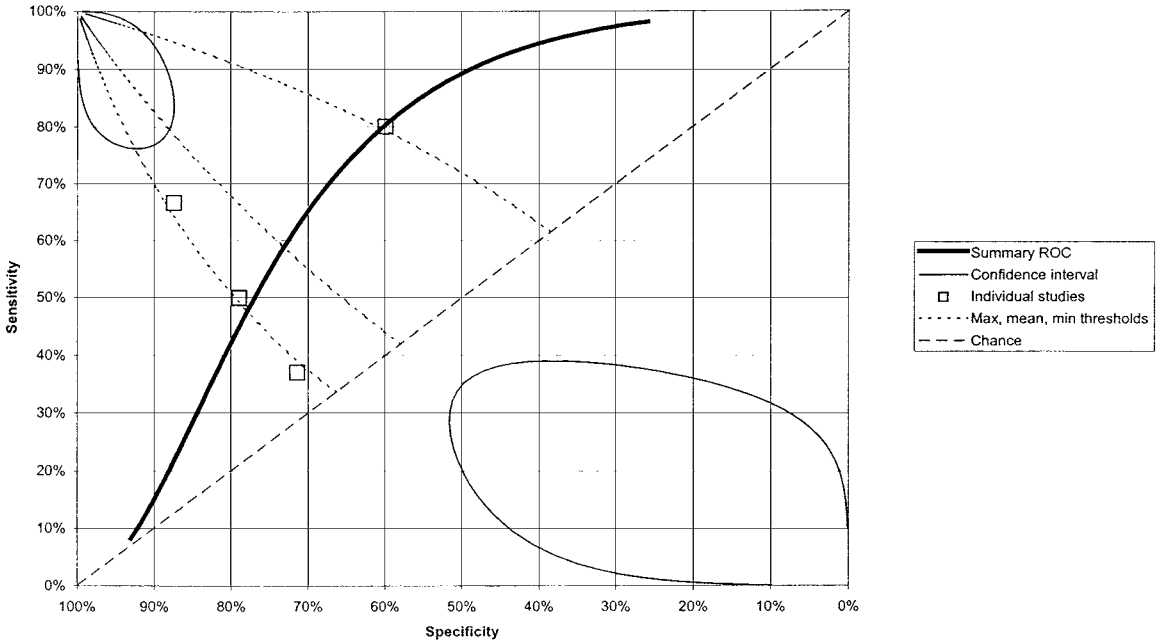



**Fig 5. Summary ROC derived from 4 individual studies assessing the diagnostic characteristics of erosions on X-ray for diagnosis of osteitis fibrosa. Values on the y-axis are the diagnostics sensitivity and values on the x-axis are the diagnostics specificity. The more effective the test is as a diagnostic, the closer it falls to the upper left hand corner of the graph. The summary ROC curve and its 95% confidence interval provides a summary estimate of the performance of the test based on the meta-analytically combined results from all 4 studies. The mean threshold (indicated on the graph by a diamond icon) is the best point estimate of the sensitivity and specificity of erosions on X-ray for diagnosis of osteitis fibrosa.**

and the treatment of kidney failure with replacement therapies. These techniques will likely become standard tools to monitor vascular calcification and its therapy.

There are very few studies with sufficient detail about diagnostic protocols to assess the usefulness of dual energy X-ray absorptiometry (DEXA) in the diagnosis of osteodystrophy of CKD. However, whole-body DEXA is a reliable, noninvasive method of assessing bone mineral density (BMD). Since BMD is helpful in the diagnosis of osteopenia and/or osteoporosis, and may assist in predicting risk for fractures, DEXA is a useful tool in assessing these abnormalities in CKD patients. Indeed, available data indicate that BMD decreases as CKD progresses (Fig 6).

DEXA should be employed in CKD to monitor patients with fractures or those with known risk factors of osteoporosis. These include, but are not limited to: menopause, other causes of gonadal hormone deficiency, smoking, Caucasian race, age greater than 65, and medications such as glucocorticosteroids. Guidelines to treat osteoporosis in the general population are available at www.nof.org. Whether these Guidelines are applicable for the treatment of osteoporosis in CKD patients has not been established.

Multiple studies have been performed using intact PTH assays to diagnose high-turnover bone disorders and distinguish them from low-turnover disorders. A receiver operating characteristics (ROC) analysis (in essence, a diagnostic meta-analysis) of using PTH to diagnose high-turnover disorders revealed an estimate of the sensitivity 93% (95% CI, 87% to 97%) and a specificity of 77% (95% CI, 62% to 87%), using threshold PTH levels between 150 and 200 pg/mL. Thus, PTH is a useful test in detecting high-turnover bone disorders (Fig 7). Studies performed using PTH to diagnose low-turnover bone disorders use levels of 60 pg/mL as the threshold. In this case, the estimated sensitivity and specificity from the ROC analysis were 70% and 87%, respectively. Thus, PTH is also useful in diagnosing low bone turnover (Fig 8). Newer assays specific for 1-84 PTH have recently become available and will likely refine and update this information. In the diagnosis and manage-

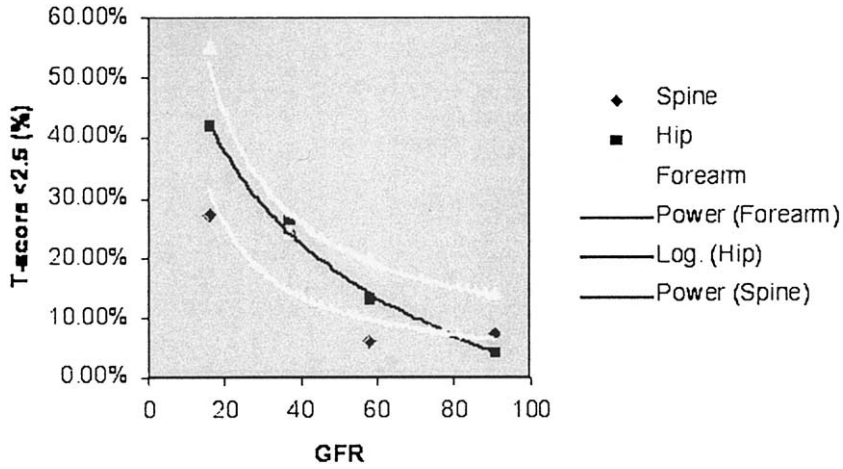



**Fig 6. Graph showing relationship between prevalence of osteoporosis as a function of GFR based on data extracted from Rix et al (1999). Values on the y-axis are the prevalence of osteoporosis as defined by a T-Score less than −2.5. Values on the x-axis are midpoint values of GFR in mL/min. The lines fitted to each data set are empirical fits and are not based on any assumptions about an underlying physiological mechanism. Reproduced with permission.[31]**

ment of osteodystrophy of CKD, the usefulness of these newer assays for parathyroid hormone are being examined. The normal range for the new assay for 1-84 PTH is 7 to 36 pg/mL (0.77 to 3.96 pmol/L) compared to 16 to 65 pg/mL (1.76 to 7.15 pmol/L) for intact PTH. Thus, the relationship between the 2 assays is about 1:2 (1-84 PTH to intact PTH). The differences in the levels between the 2 types of assays are a reflection of the levels of circulating PTH fragments that are detected by the intact PTH assay but not by the new 1-84 PTH assay.

Current data are insufficient to assess the diagnostic utility of bone markers such as osteocalcin and serum pyridinoline.

*Strength of Evidence*

Extensive review of the literature revealed numerous gaps in the available database, necessitating that some aspects of this Guideline be based upon opinion. For instance, there were no data indicating the appropriate frequency with which parameters of osteodystrophy of CKD should be followed.

Four studies that provided GFR data showed an inverse relationship between serum PTH levels and GFR (Fig 7). The 2 studies that presented creatinine clearance data showed that serum PTH increases as creatinine clearance decreases (Fig 4). It was not possible to find a function that best described the relationship between GFR and PTH or the relationship between serum creatinine or creatinine clearance and PTH. Despite this difficulty, these data still permit one to make clinically relevant decisions about when to begin screening for high serum levels of PTH. Based on these studies, it is the opinion of the Work Group that measurements of serum PTH levels in CKD patients should be initiated when GFR falls below 60 mL/min/1.73 $m^2$ (ie, Stage 3 CKD).

The most robust available data were related to the use of intact PTH levels as a marker of osteodystrophy of CKD. In this instance, there were seven studies that met the defined criteria selected for meta-analysis and derivation of an ROC curve.[23,26,32-34] These data demonstrated the usefulness of intact PTH for predicting both high- and low-turnover bone disease (Figs 7 and 8, respectively). The ability of bone imaging methods to substitute for bone biopsy in the diagnosis of osteodystrophy of CKD has only been adequately studied in the case of erosions demonstrated in standard X-rays as a diagnosis of osteitis fibrosa. A meta-analysis of 5 studies met the criteria to perform an ROC curve.[23,35-38] The best single-point estimates of the sensitivity and specificity of erosions as a tool to diagnose osteitis fibrosa were 60% sensitivity and 76% specificity. Thus, standard X-rays were not con-

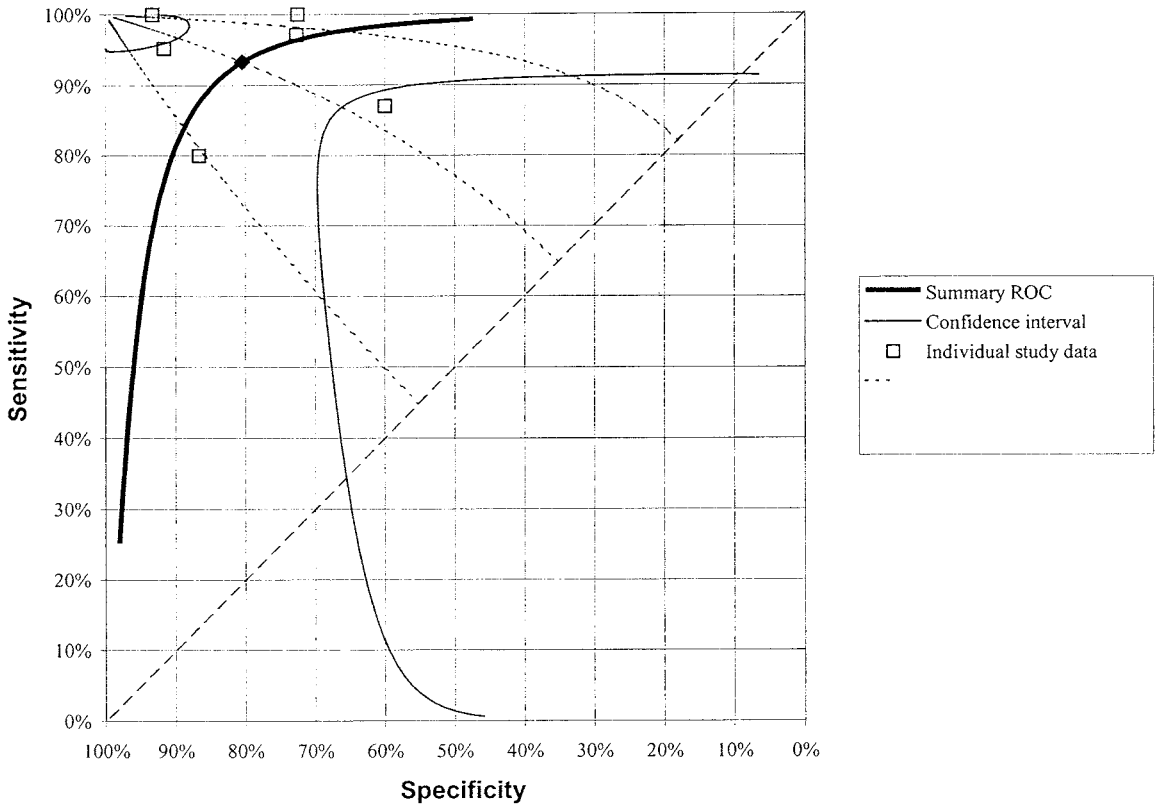



**Fig 7. Summary ROC derived from 5 individual studies assessing the diagnostic characteristics of iPTH levels for the diagnosis of high-turnover bone disease. Values on the y-axis are the diagnostic sensitivity and values on the x-axis are the diagnostic specificity. The more effective the test is as a diagnostic tool, the closer it falls to the upper left hand corner of the graph. The summary ROC curve and its 95% CI provide a summary estimate of the performance of the test based on the meta-analytically combined results from all 5 studies. The mean threshold (indicated in the graph by a diamond icon) is the best point estimate of the sensitivity and specificity of iPTH levels for the diagnosis of high-turnover bone disease.**

sidered an adequate diagnostic tool. There were no adequate studies evaluating the usefulness of quantitative computed tomography (QCT), dual photon absorptiometry, or DEXA in the diagnosis of osteodystrophy in CKD patients. However, a study using DEXA showed that BMD decreases as GFR declines in CKD patients (Fig 6).

### Limitations

The application of modern techniques for assessing bone turnover from biochemical markers or imaging is severely limited in osteodystrophy of CKD by the effects of CKD on the tests themselves and by the lack of sufficient studies. As a result, accurate diagnosis and management are difficult. The most robust currently available data, using intact PTH, permit a general distinction to be made between high- and low-turnover osteodystrophy, but recent studies suggest the need for more accurate assays of PTH levels.

### Clinical Applications

These Guidelines promote the use of PTH in the diagnosis and management of osteodystrophy in patients with CKD. They indicate the limited usefulness of other biochemical markers related—in large part—to lack of information. They demonstrate that standard X-rays are not useful and that inadequate data exist in the utilization of other imaging techniques.

### Research Recommendations

Much work is needed to relate biochemical markers of bone turnover to osteodystrophy in CKD. The role of new PTH assays must be further defined. The usefulness of DEXA re-

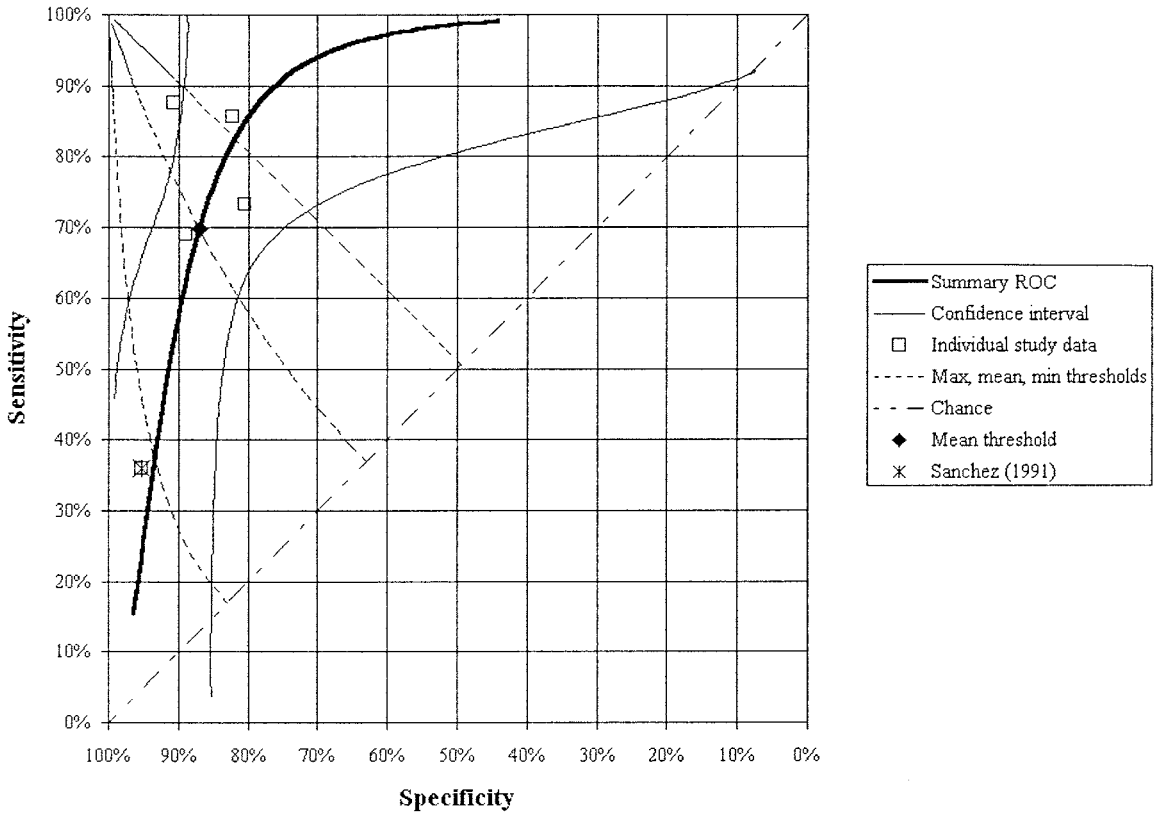



**Fig 8. Summary ROC derived from 5 individual studies assesing the diagnostic characteristics of iPTH levels for the diagnosis of low-turnover bone disease. Values on the y-axis are the diagnostic sensitivity and values on the x-axis are the diagnostic specificity. The more effective the test is as a diagnostic, the closer it falls to the upper left hand corner of the graph. The summary ROC curve and its 95% CI provides a summary estimate of the performance of the test based on the meta-analytically combined results from all 5 studies. The mean threshold (indicated in the graph by a diamond icon) is the best point estimate of the sensitivity and specificity of iPTH levels for the diagnosis of low-turnover bone disease.**

quires demonstration. Optimal clinical practice guidelines await outcome studies on the monitoring of osteodystrophy of CKD, and validating outcome data of the recommendations made in these guidelines.

## GUIDELINE 2. ASSESSMENT OF BONE DISEASE ASSOCIATED WITH CKD

**2.1 The most accurate diagnostic test for determining the type of bone disease associated with CKD is iliac crest bone biopsy with double tetracycline labeling and bone histomorphometric analysis. (EVIDENCE)**

**2.2 It is not necessary to perform bone biopsy for most situations in clinical practice. However, a bone biopsy should be considered in patients with kidney failure (Stage 5) who have:**

**2.2a Fractures with minimal or no trauma (pathological fractures); (OPINION)**

**2.2b Intact plasma PTH levels between 100 and 500 pg/mL (11.0 to 55.0 pmol/L) (in CKD Stage 5) with coexisting conditions such as unexplained hypercalcemia, severe bone pain, or unexplained increases in bone alkaline phosphatase activity; (OPINION)**

**2.2c Suspected aluminum bone disease, based upon clinical symptoms or history of aluminum exposure. (OPINION) (See Guideline 11.)**

**Table 16. Factors Prevalent in CKD Patients Which May Influence the Type of Osteodystrophy Lesion**

| |
|---|
| ▪ Prolonged aluminum exposure |
| ▪ Glucocorticoid therapy as in patients with parenchymatous kidney diseases and in kidney transplant recipients |
| ▪ Previous parathyroidectomy |
| ▪ Vitamin D treatment |
| ▪ Diabetes mellitus[a] |
| ▪ $\beta_2$-microglobulinemia amyloidosis |
| ▪ Metabolic acidosis |
| ▪ Hypophosphatemia secondary to aggressive dietary phosphate restriction or excessive use of phosphate binders |

[a] Diabetes mellitus is a common cause of CKD and is responsible for 30%-40% of patients reaching dialysis.

**2.3 Bone radiographs are not indicated for the assessment of bone disease of CKD, (EVIDENCE) but they are useful in detecting severe peripheral vascular calcification (OPINION) and bone disease due to $\beta_2$-microglobulin amyloidosis. (See Guideline 10.) (EVIDENCE)**

**2.4 Bone mineral density (BMD) should be measured by dual energy X-ray absorptiometry (DEXA) in patients with fractures and in those with known risk factors for osteoporosis. (OPINION)**

### Background

Bone disease may occur early in the course of CKD, and worsens as the decline in kidney function progresses. In Stage 5 CKD, bone disease is common and, by the time dialysis is initiated, nearly all patients are affected. In addition, patients with CKD (especially those at Stage 5) have an above-average risk for bone fractures.[39,40]

Beginning at Stage 3, patients with CKD almost always have secondary hyperparathyroidism and elevated blood levels of PTH.[31,41-46] In these patients, the classical lesion that is seen in bone biopsy is osteitis fibrosa cystica due to hyperparathyroidism,[14,23,26,47-54] although recent studies have shown increasing prevalence of other bone lesions such as low-turnover bone disease.[14,23,33,47-51,53,55-62]

In addition to secondary hyperparathyroidism, there are other factors that are common in CKD patients and may have a major impact on bone- and mineral metabolism. A partial list of some of these factors is shown in Table 16.

Current therapy with biologically active 1$\alpha$-hydroxyvitamin D metabolites, as well as the use of various phosphate-binding agents, adjustments of dialysate calcium, and introduction of other drugs (such as anti-bone resorptive agents), have led to the emergence of bone disorders associated with low or nearly normal levels of parathyroid hormone. Many of these latter lesions are associated with below-normal rates of bone formation (adynamic or low-turnover bone disease).

CKD patients with prolonged exposure to aluminum-based phosphate binders (see Guidelines 11 and 12) and those with diabetes mellitus[14,23,47,55-59,62] have lower blood levels of PTH than other patients with comparable levels of kidney function. Aluminum deposition in bone, secondary to aluminum overload, interferes with bone mineralization (see Guidelines 11 and 12). Therefore, low-turnover and/or adynamic bone disease may be more prevalent in these patients.

Patients with CKD may also have other factors that are not related to their CKD, but may impact bone and mineral metabolism (Table 17). Advanced age and deficiency in sex hormones (estrogen and androgens) are associated with osteoporosis and loss of bone mass. Nutritional vitamin D deficiency, medications that affect vitamin D metabolism such as anticonvulsants, and/or hypophosphatemia would cause defective

**Table 17. Non-CKD-Related Factors Which May Affect Bone Metabolism in CKD Patients**

- Old age
- Postmenopausal status
- Race
- Nutritional vitamin D deficiency
- Medications that interfere with Vitamin D metabolism (e.g., anticonvulsants)
- Malignancy with or without bone metastasis
- Prolonged immobilization

mineralization of osteoid leading to osteomalacia.

### *Bone Histomorphometric Diagnoses*

In general, bone histomorphometric examinations can help classify bone diseases into one of the following general diagnostic categories: mild hyperparathyroid bone disease; moderate-to-severe hyperparathyroid bone disease; mixed bone disease; osteomalacia; or adynamic bone disease (Table 18). Histochemical aluminum staining may show deposition of aluminum in any of these conditions, and suggest coexisting aluminum-related bone disease, coexistent with the basic type of osteodystrophy of CKD. Osteoporosis and osteopenia are characterized by decreased in trabecular or cortical bone volume on bone biopsy. Osteopenia may also be diagnosed by alternate means, such as DEXA, permitting selective determination of bone mineral density in the entire skeleton or in specific regions (eg, lumbar spine, hip, femoral neck).

#### Rationale

In deciding when it is appropriate to perform a bone biopsy in patients with chronic kidney disease, 2 questions should be considered:

- At what level of kidney function does bone disease begin?
- Why should bone biopsies be performed in patients with chronic kidney disease?

Regarding the first question, it has been established that blood levels of PTH begin to rise when GFR falls below 60 mL/min/1.73 $m^2$,[31,41-46] and levels of Vitamin D [$1,25(OH)_2D_3$] fall at this level of GFR.[45,63-67] Since these developments are considered central to the development of bone disease in CKD patients, it is reasonable to assume that bone disease begins at Stage 3 of CKD (when GFR declines below 60 mL/min/1.73 $m^2$) and that it progresses as GFR continues to decline.

Despite considerable advances in the understanding of the pathophysiology, prevention, and

**Table 18. Frequently Used Histomorphometric Parameters**

| Three-Dimensional Parameters | Normal Values |
|---|---|
| 1. Bone volume/tissue volume | 16 - 23% |
| 2. Osteoid thickness | 4 - 20 µm |
| 3. Osteoid surface/bone surface | 1 - 39% |
| 4. Osteoblast surface/bone surface | 0.2 - 10% |
| 5. Osteoclast surface/bone surface | 0.15 – 1.2% |
| 6. Activation frequency | 0.49 – 0.72 $Year^{-1}$ |
| 7. Fibrosis volume/tissue volume | 0 |
| 8. Mineralization lag time | < 50 Days |

Lower values in parameter 1 indicate osteoporosis, higher values in 2-7 indicate hyperparathyroid bone disease or osteitis fibrosa, higher values in 2&8 and lower values in 6 indicate osteomalacia, lower values in 2-6 and absence of fibrosis indicate adynamic bone disease.

treatment of osteodystrophy of CKD, there is no adequate substitute for bone biopsy in establishing the histological type of osteodystrophy in these patients.[23,24,26,47-51,53] Over the past 50 years, bone biopsy has provided the most accurate diagnosis of the type of bone disease in both CKD and non-CKD patients. Over the last 3 decades, quantitative bone histomorphometry with double tetracycline labeling has become the "gold standard" for the diagnosis of metabolic bone disease in CKD patients.[14,23,33,48-53,55,57,68-75]

There have been many reports of bone biopsy findings in patients with CKD that have documented abnormalities in bone histology with increasing prevalence, when the GFR has declined below 50 to 60 mL/min/1.73 $m^2$.[14,23,26,47-54]

Several studies have demonstrated a direct correlation between elevated blood levels of intact PTH and bone biopsy findings of increased bone turnover, the main feature of bone disease due to hyperparathyroidism (Fig 6).[23,24,26,32-34,58] Evidence of increased bone resorption has been detected in bone biopsies obtained from CKD patients with a GFR below 60 mL/min/1.73 $m^2$ when blood levels of PTH begin to rise.[31,41-46]

The prevalence of osteopenia and/or osteoporosis also increases with decreasing levels of GFR.[31] In a study of patients with CKD, the highest levels of BMD in the lumbar spine, hip and distal forearm were found in those with GFR between 70 and 110 mL/min/1.73 $m^2$ (Stage 1 and 2 CKD), while those with GFR between 6 and 26 mL/min/1.73 $m^2$ (Stage 4 CKD) had the lowest BMD levels (Fig 6).[31] The abnormalities in bone metabolism that might be responsible for the decreased BMD were not characterized in these studies. The presence of osteoporosis is a strong predictor of increased risk for fractures in the general population. Therefore, the measurement of BMD by DEXA is an important diagnostic procedure for the identification of CKD patients who are more prone to fractures. Three recent studies have noted an increased risk of fracture in CKD patients.[39,40,76] However, there are limited data on the correlation of BMD with fractures in CKD.[77]

### Limitations

There were very few studies of bone biopsies that met all of the inclusion criteria as described in the Method of Analysis of the Literature. This was due to differences in patient populations, various definitions of bone disease, and incomplete information regarding the level of kidney function. Many studies were retrospective in nature, and therefore subject to potential bias. None of the studies met the criteria for highest quality (ie, double-blind, placebo-controlled, randomized), but sufficient information was available to permit some conclusions. Overall, a relatively small amount of moderate- to high-quality studies and a small amount of data were relevant to the issues in this Guideline. Effect size could be calculated for individual studies in many instances, but it was not possible to combine multiple studies into an overall statistical analysis. Therefore, certain biases may occur in this interpretation due to the fact that most studies had to be evaluated individually.

### Clinical Applications

The use of bone biopsy as a diagnostic tool requires trained personnel for the preparation of a decalcified section of the biopsy and for performing the morphometric analysis. At present, these personnel are not available in most medical institutions. Reimbursement for obtaining and interpreting bone biopsies should be made available, and will require education of payors as to the importance of bone biopsy in the diagnosis and management of patients with CKD.

The Work Group recognized that, in most circumstances, clinicians will have to depend upon indirect methods, rather than bone biopsy, to diagnose the type of bone disease associated with CKD. The reasons for lack of more frequent use of bone biopsy include: patient refusal; a mistaken perception that bone biopsy is painful and overly invasive; the lack of local resources to properly procure, process, and reliably interpret the bone biopsy; and difficulty in obtaining appropriate reimbursement for bone biopsy performance.

Recognizing these limitations, the Work Group agreed that in the following circumstances, a bone biopsy will often yield essential information and should be strongly considered:

- In the absence of other known causes of a bone fracture (eg, malignancy), a bone biopsy should probably be undertaken in CKD patients with a pathological fracture. Bone biopsy is useful to assess the net effect of

various factors (known or unsuspected) upon bone formation rate, bone mineralization rate, and bone architecture (eg, hyperparathyroidism, osteomalacia, aluminum intoxication, osteoporosis).

- There is insufficient sensitivity and specificity of serum levels of PTH to reliably predict the presence of adynamic bone disease (PTH <100 pg/mL [11.0 pmol/L]) or hyperparathyroidism (PTH >500 pg/mL [55.0 pmol/L]) (see Guideline 1) when the serum levels of intact PTH levels are between 100 and 500 pg/mL (11.0 to 55.0 pmol/L). If a CKD patient with serum levels of intact PTH between 100 and 500 pg/mL (11.0 to 55.0 pmol/L) develops unexplained hypercalcemia, bone pain, or an increase in bone alkaline phosphatase activity, a bone biopsy can be useful. The bone biopsy will allow more accurate assessment of the rate of bone formation and bone mineralization and will help guide therapy.
- If a patient is suspected of having aluminum toxicity (see Guidelines 11 and 12), then the Work Group recommends that in certain situations a bone biopsy be performed to ascertain the diagnosis before starting deferoxamine therapy. The Work Group made this recommendation because of the potential toxicity and side effects of deferoxamine (see Guidelines 11 and 12).

The Work Group agreed that bone biopsy should also be considered in some patients prior to parathyroid ablation therapy. If the clinical history includes oral or parenteral aluminum exposure, then a bone biopsy may be helpful to exclude the coexistence of hyperparathyroidism and aluminum bone disease (see Guidelines 11 and 12). In these circumstances, parathyroid ablation therapy may worsen aluminum toxicity of bone; therefore, aluminum toxicity must be excluded prior to parathyroidectomy. In other patients, the levels of PTH may not be excessively elevated, yet there may be other suggestions of excessive effects of PTH (hypercalcemia, hyperphosphatemia, elevated bone alkaline phosphatase activity, bone resorption on X-ray, etc). In such patients, inappropriate parathyroid ablation can induce hypoparathyroidism and adynamic bone disease. For this reason, any patient with PTH levels less than 800 to 1,000 pg/mL (88.0 to 110.0 pmol/L) may require bone biopsy prior to parathyroid ablative therapy, to clearly document the increased bone formation rate and histological findings of hyperparathyroidism prior to an ablative procedure.

Several conditions should be satisfied to ensure that the bone biopsy provides reliable information:

- The bone biopsies should be performed after tetracycline labeling and be obtained from the anterior iliac crest using an instrument designed to obtain a core of bone of at least 4 to 5 mm diameter. The bone specimen should be processed and analyzed in accordance with accepted standard techniques.
- Data on normal bone histomorphometry should be obtained and the results reported in accordance with the standard nomenclature suggested by the American Society of Bone and Mineral Research (www.asbmr.org).[78] Normal ranges, with appropriate confidence intervals, for all histomorphometric parameters must be developed for each laboratory performing diagnostic bone biopsy.
- The most commonly used histochemical stain for aluminum uses the "aluminon" method.[14,54,55,69,79,80] The results for aluminum stain should be quantitative or semiquantitative and the location for aluminum staining (at the osteoid-mineralized bone interface or in cement lines) should be reported. Aluminum-positive surfaces <5% are usually not considered to be significant, while those >25% are considered to be strongly positive.

#### Research Recommendations

Considering the invasive nature of bone biopsy, there is a need to investigate whether other markers of bone disease could be developed to replace bone biopsy for the accurate diagnosis of bone disease in patients with chronic kidney disease.

At the present time, there are not any noninvasive tests that have sufficient accuracy for the diagnosis of bone disease in CKD patients. The Work Group recommends that bone biopsy be used to accurately establish the diagnosis in CKD patients enrolled in clinical research protocols studying bone disease. These protocols may

be designed to assess the sensitivity or specificity of other diagnostic tests, or to assess the effectiveness of various therapies. In either instance, accurate diagnosis of the bone disease is pivotal to the quality and utility of such studies.

Most of the currently used PTH assays are purported to measure only the "intact" PTH molecule, consisting of 84 amino acids. Most of the biological activity of the PTH molecule resides in the N-terminal, and, in large part, in the amino acid residues in positions 1 to 7. It appears that many "intact PTH" assays also detect biologically inactive fragments of PTH formed from the amino acids in the 7 to 84 positions.[81-83] This phenomenon leads to spurious elevations in the levels of intact PTH in CKD patients, in that these patients do not have significant hyperparathyroid bone disease even though the PTH level is above normal. If clinicians attempt to maintain intact PTH levels of CKD patients in the "normal" range below 65 pg/mL (7.15 pmol/L), then some CKD patients have low levels of bone formation and adynamic bone disease.[81-83] Hence, our current recommendations distinguish between the "desired target range" for intact PTH in CKD patients and the "normal range" that has been determined for patients with normal kidney function.

## GUIDELINE 3. EVALUATION OF SERUM PHOSPHORUS LEVELS

**3.1 In CKD patients (Stages 3 and 4), the serum level of phosphorus should be maintained at or above 2.7 mg/dL (0.87 mmol/L) (EVIDENCE) and no higher than 4.6 mg/dL (1.48 mmol/L). (OPINION)**

**3.2 In CKD patients with kidney failure (Stage 5) and those treated with hemodialysis or peritoneal dialysis, the serum levels of phosphorus should be maintained between 3.5 and 5.5 mg/dL (1.13 and 1.78 mmol/L). (EVIDENCE)**

### Background

Hyperphosphatemia leads to secondary hyperparathyroidism and elevated blood levels of PTH by: (a) lowering the levels of ionized calcium; (b) interfering with the production of $1,25(OH)_2D_3$; and (c) by directly affecting PTH secretion.[84,85]

These processes lead to high-turnover bone disease and other adverse consequences of excess PTH (see Background).

Prolonged hyperphosphatemia causes soft-tissue and vascular calcification due at least in part to an increase in calcium-phosphate product[86-89] and is associated with increased morbidity[90,91] and mortality.[92-95] In the case of vascular calcification, hyperphosphatemia exerts a direct calcifying effect on vascular smooth muscle cells.[96] Calcification of coronary arteries, cardiac valves, and pulmonary tissues produces cardiac disease, the leading cause of death in patients with CKD.[90,97-99] It is therefore imperative to prevent hyperphosphatemia and maintain serum phosphorus levels within the normal range.

### Rationale

Among the factors that contribute to secondary hyperparathyroidism in CKD patients are phosphate retention and/or elevated levels of serum phosphorus. Hyperphosphatemia is associated with increased morbidity and mortality in CKD patients.[86-93] Therefore, the maintenance of normal serum levels of phosphorus in CKD patients is critical for the prevention of abnormalities in parathyroid hormone metabolism and for the reduction of morbidity and mortality.

#### *Strength of Evidence*

The influence of phosphorus levels on PTH secretion has not been conclusively demonstrated in humans. While available experimental data support a direct role of phosphorus on PTH secretion,[84,85] the data in humans are less straightforward. One study has shown elevated PTH levels in patients with serum phosphorus levels $>$6.2 mg/dL (2.0 mmol/L).[90] On the other hand, other studies have failed to demonstrate consistent changes in PTH levels across a range of serum phosphorus levels,[100] and no direct correlation between the level of serum phosphorus and PTH has been established.[85] The lack of conclusive studies in humans is to be expected, given that many studies measuring serum PTH levels are confounded by the use of phosphate binders and vitamin D therapy. Such a study design precludes the evaluation of a direct association between serum phosphorus and PTH levels. Based on available evidence and upon clinical experience, it is the opinion of the Work

Group that elevated phosphorus levels in CKD and dialysis patients contribute to the development of hyperparathyroidism.

In order to eliminate the potentially confounding influence on outcomes of aluminum-containing phosphate binders, only studies of dialysis patients, and only those published after 1990, were included in the data analysis. Four studies meet these criteria, and all are observational or cross-sectional in design.[90,92,93,100] These studies correlate serum phosphorus levels with multiple end-points in patients treated with hemodialysis.

The 4 cross-sectional studies[90,92,93,100] that met the inclusion criteria evaluated the association of serum phosphorus levels with extraskeletal outcomes. Two studies evaluated the relative risk of mortality associated with serum phosphorus levels in patients treated with hemodialysis. In 1 study, a reference serum phosphorus range of 4.6 to 5.5 mg/dL (1.49 to 1.78 mmol/L) was used[92]; the relative risk of mortality increased with serum phosphorus levels >6.5 mg/dL (2.10 mmol/L). In the other study, a reference range of 5 to 7 mg/dL (1.61 to 2.26 mmol/L) was used[93]; the relative risk of mortality increased with serum phosphorus levels less than or greater than this range. The increase in mortality was particularly significant for levels of phosphorus >7 mg/dL (2.26 mmol/L) or <3 mg/dL (0.97 mmol/L). Serum phosphorus levels <2.5 mg/dL (0.81 mmol/L) may be associated with abnormalities in bone mineralization such as osteomalacia.[100]

In another study, serum phosphorus levels >6.2 mg/dL (2.00 mmol/L) were associated with increased blood pressure, hyperkinetic circulation, increased cardiac work, and high arterial tensile stress.[90] One study failed to find an association between serum phosphorus levels and quality of life.[100]

The available evidence supports an association between serum phosphorus levels both above and below the normal range with poor outcomes, including mortality. Given that the major goal of phosphorus control in patients with CKD is to prevent morbidity and mortality, it was the opinion of the Work Group that serum phosphorus should be maintained between 2.7 and 4.6 mg/dL (0.87 and 1.49 mmol/L) in CKD patients Stages 3 and 4, and between 3.5 and 5.5 mg/dL (1.13 and 1.78 mmol/L) in CKD patients Stage 5.

#### Limitations

Cross-sectional studies have established a correlation between serum phosphorus levels and various extraskeletal outcomes, but this correlation does not rise to the level of causality. Further, the studies of higher methodological quality[92,93] relied on data from 1990 or earlier, indicating that their results may have been confounded by the use of aluminum hydroxide and/or by less aggressive vitamin D therapy. To date, studies performed in dialysis patients have failed to conclusively demonstrate a reduction in morbidity or mortality through dietary intervention or the use of phosphate binders to lower serum phosphorus levels to the suggested target range.

#### Clinical Applications

This Guideline supports intensive control of serum phosphorus in patients with CKD. Most data indicate that fewer than 30% of dialysis patients are able to maintain phosphorus in the suggested target range. The goal should be to increase the percentage of patients in this target range. Successful implementation will require an increased dietitian-to-patient ratio, educational tools to increase patient compliance, as well as studies to further explore the feasibility of dialytic techniques that are better able to control serum phosphorus levels (such as nocturnal or daily hemodialysis), and the widespread availability and affordability of different phosphate binders, regardless of patient insurance.

#### Research Recommendations

Longitudinal studies of patients on dialysis are needed, evaluating the effects of controlling serum phosphorus in the target range on morbidity and mortality.

## GUIDELINE 4. RESTRICTION OF DIETARY PHOSPHORUS IN PATIENTS WITH CKD

**4.1 Dietary phosphorus should be restricted to 800 to 1,000 mg/day (adjusted for dietary protein needs) when the serum phosphorus levels are elevated (>4.6 mg/dL [1.49 mmol/L]) at Stages 3 and 4 of CKD, (OPINION) and >5.5 mg/dL (1.78 mmol/L) in those with kidney failure (Stage 5). (EVIDENCE)**

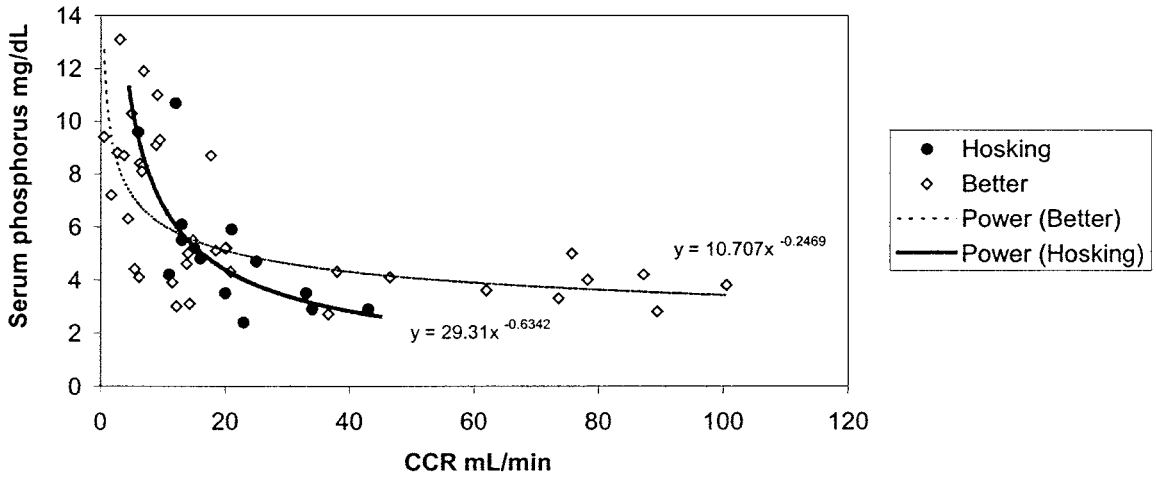



**Fig 9. Relationship between serum phosphorus and CCR.**

**4.2 Dietary phosphorus should be restricted to 800 to 1,000 mg/day (adjusted to dietary protein needs) when the plasma levels of intact PTH are elevated above target range of the CKD stage (see Table 15 in Guideline 1). (EVIDENCE)**

**4.3 The serum phosphorus levels should be monitored every month following the initiation of dietary phosphorus restriction. (OPINION)**

### Background

Levels of serum phosphorus in patients with CKD remain within the normal range or may even be modestly below the normal range until the GFR declines to 20 to 30 mL/min/1.73 $m^2$ (Stage 4 of CKD). At these latter levels of GFR, hyperphosphatemia becomes evident (Fig 9). Therefore, it may appear that dietary phosphate intervention is not necessary in patients with Stages 1, 2, and 3 of CKD. However, phosphate retention occurs very early in the course of CKD (probably at Stage 1, but definitely at Stage 2) and such phosphate retention participates in the genesis of secondary hyperparathyroidism. Indeed, the blood levels of PTH are elevated when GFR falls to 60 mL/min/1.73 $m^2$, even though serum phosphorus levels are not elevated. Studies in animals[85,101] and in human adult patients[102] and children showed that dietary phosphate restriction in proportion to the decrease in GFR in the early and moderate stages of CKD (Stages 2 and 3) when blood levels of PTH are elevated and serum phosphorus levels are normal, was effective in lowering blood PTH levels.

### Rationale

Since phosphate retention occurs early in the course of CKD (probably Stage 1, but certainly Stage 2) and contributes to the genesis of secondary hyperparathyroidism, and since PTH levels begin to rise when GFR falls below 60 mL/min/1.73 $m^2$ (Stage 3 of CKD), even when serum phosphorus levels are normal, the plasma level of PTH is a better marker in the early course of CKD for the need to begin dietary phosphate restriction than is serum phosphorus, calcium, or creatinine levels. Of course, at later stages of CKD (Stage 4 and 5), the levels of serum phosphorus are elevated and therefore dictate the need for the prescription of dietary phosphate restriction, as an essential approach to controlling serum phosphorus and plasma levels of intact PTH.

### *Strength of Evidence*

The efficacy of dietary phosphate restriction and the timing of its initiation were assessed through an evidence-based review of the literature. Because dietary phosphate restriction alone is most commonly used in CKD patients, the focus was on the following questions:

(1) What is the correlation between serum phosphate levels and outcomes?

(2) How effective is dietary phosphate restriction at different stages of CKD?

(3) What percentage of patients comply with dietary phosphate restriction and how does noncompliance affect patient outcomes?

(4) What side-effects are associated with a phosphorus-restricted diet?

Unfortunately, there were no studies in CKD patients that met the inclusion criteria and addressed the relationship between serum phosphate and multiple indices of morbidity and mortality such that an absolute level of serum phosphorus could be used to guide initiation of dietary phosphate restriction.

The relationship between kidney function and serum phosphorus was evaluated. The included studies evaluated the relationship between serum phosphorus and creatinine clearance or serum creatinine (Cr)[103-105]; they showed an inverse relationship between serum phosphorus levels and kidney function. Two studies[104,106] that could be used to determine the correlation between serum phosphorus levels and creatinine clearance reported data on 51 patients (Fig 9). These studies showed that serum phosphorus levels begin to rise when creatinine clearance falls below 20 to 30 mL/min/1.73 $m^2$ (0.33 to 0.50 mL/s/1.73 $m^2$). Other studies on 121 patients reporting a direct relationship between serum phosphorus and serum Cr showed no clear indication as to the absolute level of serum Cr that is associated with hyperphosphatemia.[103-108] *Taken together, the data support an association between the decline in kidney function and the rise in serum phosphorus, with increments in the latter becoming evident when creatinine clearance falls to 20 to 30 mL/min/1.73 $m^2$ (0.33 to 0.50 mL/s/1.73 $m^2$) (Stage 4).*

However, there are other confounding issues when utilizing the serum Cr or creatinine clearance as a guide for the initiation of dietary phosphorus restriction, since serum creatinine is influenced by existing muscle mass, which varies from patient to patient. There may be patients who have increased levels of serum phosphorus at a lower level of serum creatinine because of their lower muscle mass. Most importantly, a rise in the serum phosphorus level represents a failure of the normal compensatory response of elevated parathyroid hormone to adequately increase kidney excretion of phosphate. It appears that at creatinine clearances of 20 to 30 mL/min/1.73 $m^2$ (0.33 to 0.50 mL/s/1.73 $m^2$), the maximum decrement in kidney reabsorption of phosphate has been reached. With further deterioration in kidney function, there is no further increase in urinary excretion of phosphate, even in the presence of elevated parathyroid hormone; thus, serum phosphorus levels begin to rise. There are no reports that met the inclusion criteria to specifically identify the level of kidney function at which the decrement in reabsorption of phosphate by the kidney reaches its maximum and/or at what levels of serum phosphorus, in the course of CKD, blood PTH levels begin to rise.

*In summary, the available data and the opinion of the Work Group support the proposal that dietary phosphate restriction should be initiated when blood PTH levels begin to rise (Stage 2) and/or when serum phosphorus levels are elevated at any stage of CKD.*

The effectiveness of dietary phosphate restriction in controlling the hyperphosphatemia of CKD was analyzed in 19 studies examining 2,476 patients. Fifteen randomized controlled trials[110-124] and 4 nonrandomized controlled trials[125-128] met the inclusion criteria. The last 4 studies evaluated the side effects of dietary phosphate restriction (Table 19). The vast majority of studies evaluated restricted protein diets, which are usually (but not always) equivalent to low phosphorus diets. In many of these studies, calcium[100,103-108,129,130] and vitamin D supplements were used,[87,90,92,93,100,103-108,129-131] or phosphate binders were also administered to the patients in addition to the dietary intervention. Thus, the interpretation of these data should be done with caution. Various end-points were utilized:

- Quality of life. One study reported that low protein diet did not adversely affect employment,[127] but the results of the Modification of Diet in Renal Disease (MDRD) study indicated that patients with CKD (Stages 3 and 4) treated with very restricted protein diets were less able to socialize.[132]
- Mortality. Nearly all of the included studies evaluated the role of dietary restriction of protein/phosphorus on mortality. The reported results were variable. When these data were analyzed by meta-analysis, no effect on mortality was found.
- Kidney Function. Seven of nine studies in adult patients with CKD suggest that dietary phosphorus restriction may stabilize

kidney function.[110,111,113,116,117,121,123,125,128] Conclusions in this regard could not be drawn from studies in children or in adults with severe CKD.

- Bone and Mineral Metabolism. Several small studies reported that dietary phosphorus restriction in patients with CKD had no significant effect on serum alkaline phosphatase,[112,115,117,126] PTH levels[112,117,125,127] serum calcium levels,[112,115,117,125,126] serum phosphorus levels,[112,115,122, 125,126,133] and urinary phosphate excretion.[111,119,122] In contrast, in a careful and well-controlled study of 4 patients with Stages 1 and 2 of CKD conducted in a metabolic ward before and after 8 weeks of dietary phosphate restrictions in proportion to the decrement in GFR, there was a reduction in blood PTH levels to normal without significant changes in the serum levels of phosphorus, significant decrements in blood levels of alkaline phosphatase and in urinary excretion of phosphate, and significant increments in blood levels of $1,25(OH)_2D_3$ and intestinal absorption of calcium.[10] Also, the dietary phosphate restriction was associated with marked improvement in bone resorption and defects in bone mineralization as evidenced by studies of bone biopsy.[10]

Moderate dietary phosphate restriction is also appropriate for children, provided close monitoring of linear bone growth is exercised, as no study provided evidence for adverse effects.[116,120,134,135] In addition, studies in adults did not support any adverse effect on nutritional status as a result of dietary phosphate restriction.[110-112,115-117,119,123,126,128,136,137]

Compliance. Compliance with dietary restriction in the research setting of clinical studies may not reflect the situation in clinical practice. While compliance with dietary phosphorus restriction in clinical practice is commonly believed to be poor, there is a lack of data to support this supposition. Most studies have found compliance rates of 35% to 91% with low-protein diets.[102,116,122,132] One study reported 41% and 77% compliance at years 1 and 3, respectively.[138] The compliance rates with dietary phosphate restriction were similar to compliance rates for low-protein diets. It was not addressed whether the improvement at year 3 is related to continuous education and/or the realization by the patient of the adverse effects of noncompliance.

*Given the lack of evidence of adverse effects, and the evidence of positive benefit of dietary phosphate restriction, it is the consensus of the Work Group that dietary phosphate restriction be initiated in patients with CKD when PTH levels are elevated (GFR $<60$ mL/min/1.73 $m^2$, Stage 3) or with elevated blood levels of serum phosphorus (Stages 4 and 5).*

### Limitations

Despite the relatively large number of prospective randomized trials evaluating dietary phosphorus restriction, most of these studies specifically utilized protein-restricted diet and therefore indirectly restricted phosphate intake. While protein and phosphorus are closely related in foods, it is possible to restrict protein without fully restricting phosphorus. Much of the data is also difficult to interpret since most of the reports provided analysis for "prescribed diet" rather than "consumed diet." Furthermore, in many studies, the patients had concomitant therapy with Vitamin D and/or phosphate binders making interpretation of the results difficult.

While the available data do not support the common belief that dietary phosphate restriction negatively impacts nutritional status, it must be stressed that dietary phosphate restriction has the potential of adversely impacting nutritional status if done in a haphazard manner. The data that demonstrate the ability to maintain good or stable nutritional status during dietary phosphate restriction were obtained in studies in which dietitians provided careful instruction and regular counseling and monitoring. In the research setting, patients are monitored closely and have regular contact with their kidney-care providers. Those patients who have been "casually" instructed to watch their protein or phosphate intake, without regular follow-up, may be at risk for serious side-effects such as malnutrition. Unfortunately, there are no data on those patients who are not regularly and closely followed.

### Clinical Applications

It is critical to provide consistent instruction and regular follow-up during prescription of dietary phosphate restriction. In patients with early stages of CKD (Stages 2 and 3), compliance with

**Table 19. Side Effects Associated with a Phosphorus-Restricted Diet and Their Rate of Occurrence**

| Author | Year | N | Follow-up time | Diet | | | Serious medical problems | Nausea, hunger, anorexia | Malnutrition | Weight loss | Effect size d (95% CI)[a] | Effect size summary[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Protein g/kg/day | Phosphorus per day | Supplements | | | | | | |
| MDRD Group[109] | 1994 | 291 | 26.4 months mean | 0.58 | NR | none | 23.7% | NR | NR | 29% | Medical: 0.98 (-0.23 to 0.19) Weight loss: 1.40 (0.12 to 0.55) | ⇔ ⬆ |
| | | 294 | | 1.3 | NR | none | 24.5% | | NR | 18% | | |
| | | 126 | | 0.28 | NR | KA | 25.4% | | 0.79% | 30% | Medical: 0.95 (-0.36 to 0.26) Malnutrition: 1.0 (-1.5 to 1.5) Weight loss: 0.78 (-0.53 to 0.04) | ⇔ |
| | | 129 | | 0.58 | NR | none | 27.1% | | 0.78% | 40% | | |
| Zeller et al.[110] | 1991 | 24 | 34.7 months mean | 0.6 | 0.5-1.0 g | none | NR | NR | NS difference between groups | NR | ND | ⇔ |
| | | 23 | | Ad lib | Ad lib | none | | | | | | |
| Williams et al.[111] | 1991 | 33 | 19 months mean | 0.6 | 0.8 g | none | NR | NR | NR | NS difference between groups | ND | ⇔ |
| | | 30 | | Ad lib | 1 g | Phosphate binders | | | | | | |
| | | 32 | | Ad lib | Ad lib | none | | | | | | |
| Mahmoud et al.[112] | 1989 | 15 | 15 days | 0.4 | NR | 0.2 g/kg/day KA | NR | Nausea = 13.3% Hunger = 40% Anorexia = 6.7% | NR | NR | ND | ND |
| | | 15 | | 1.0 | NR | 0.2 g/kg/day KA | NR | | NR | NR | | |

***Abbreviations**: SD, standard deviation; CI, confidence interval; NR, not reported; KA , keto amino acids; ND, not determined.*

[a] calculated by ECRI. Effect sizes are reported in the standardized metric of Hedges' d, which indicates a greater effect the further away d is from zero. If the 95% confidence intervals cross zero, the effect size is non-significant.

[b] The effect size summary indicates whether effect sizes were significantly positive or negative. A horizontal arrow indicates that the result was non-significant.

dietary phosphate restriction is difficult and requires intensive dietitian support. In patients with advanced CKD (Stages 4 and 5), restriction of dietary phosphorus is more easily accomplished because of concomitant dietary protein modification. However, in CKD patients treated with dialysis (Stages 5), care must be taken to reduce phosphate intake while maintaining adequate protein intake as recommended by the K/DOQI Guidelines on Nutrition (www.kdoqi.org). In individuals >80 kg, it is impossible to plan a palatable diet with adequate protein while limiting the phosphate intake to <1,000 mg. In view of this limitation, the phosphate level of the diet should be as low as possible while ensuring an adequate protein intake. If one multiplies the recommended protein level times 10 to 12 mg phosphate per gram of protein, a reasonable phosphate level can be estimated. The average amount of phosphorus per gram of protein ranges from 12 to 16 mg. In order to limit phosphorus significantly, those protein sources with the least amount of phosphorus must be prescribed (Table 20). There is clear need for more active involvement and reimbursement for counseling from renal dietitians in the care of patients with CKD, beginning with Stage 2. This enhanced involvement has been hindered by inadequate reimbursement for the services of qualified renal dietitians. While the Medical Nutrition Act of 2002 funds nutrition services only to Medicare-eligible patients, it does not provide for all CKD patients who need ongoing nutrition services prior to the need for dialysis therapy.

### Recommendations for Research

There is a need for large, multi-center longitudinal studies evaluating the effects of dietary phosphate restriction (as opposed to only protein restriction) on nutritional status, growth in children, morbidity, mortality, bone disease, and progression of decline in kidney function. These studies should be conducted in patients with all stages of CKD beginning in Stage 2.

**Table 20. Phosphorus Content of Protein-Containing Foods**

| Food | Common Measure | Phosphorus (mg) | Protein (g) | mg P/ g protein |
|---|---|---|---|---|
| **Beans, Legumes, Tofu** | | | | |
| Beans, Kidney | 1 cup | 251 | 15 | 16.7 |
| Beans, Lima | 1 cup | 209 | 15 | 13.9 |
| Beans, Navy | 1 cup | 286 | 16 | 17.9 |
| Beans, Black | 1 cup | 241 | 15 | 16.1 |
| Beans, Refried | 1 cup | 217 | 14 | 15.5 |
| Soybeans, Boiled | 1 cup | 421 | 29 | 14.5 |
| Soybeans, Roasted | 1 cup | 624 | 61 | 10.2 |
| Sunflower Seeds | 1 oz | 322 | 6 | 53.7 |
| Tofu, Firm | 100 g | 76 | 6 | 12.7 |
| Tofu, Soft | 100 g | 52 | 4 | 13.0 |
| Tofu, Lite | 100 g | 68 | 5 | 13.6 |
| **Cheese/Cheese Products** | | | | |
| Cheese, Cheddar | 1 oz | 145 | 7 | 20.7 |
| Cheese, Swiss | 1 oz | 171 | 8 | 21.4 |
| Cottage Cheese, Reg | 1 cup | 297 | 28 | 10.6 |
| Cottage Cheese, 1% | 1 cup | 151 | 14 | 10.8 |
| Cottage Cheese, 2% | 1 cup | 340 | 31 | 11.0 |
| Cottage Cheese, Nonfat | 1 cup | 151 | 25 | 6.0 |
| Cheese, Cream | 2 Tb | 30 | 2 | 15.0 |
| **Combination Foods** | | | | |
| Bean/Cheese Burrito, FF | 2 small | 180 | 15 | 12.0 |
| Breakfast Biscuit, FF | 1 egg/cheese/bacon | 459 | 16.3 | 28.2 |
| Cheeseburger, FF | Single w/condiments | 310 | 28.2 | 11.0 |
| Chicken Sandwich, FF | 1 sandwich | 405 | 29.4 | 13.8 |
| Fried Shrimp, FF | 6 to 8 small | 344 | 18.9 | 18.2 |
| Hot Fudge Sundae | 1 small | 227 | 5.6 | 40.5 |
| Morningstar Breakfast Patty | 1 patty | 106 | 9.9 | 10.7 |
| Pepperoni Pizza, 1 sl | Froz Pepperoni | 222 | 16 | 13.9 |
| Roast Beef Sandwich | 1 sandwich | 239 | 21.5 | 11.1 |
| Sub Sandwich, FF | 1 cold cuts | 287 | 21.8 | 13.2 |
| Taco, FF | Large | 313 | 31 | 10.1 |
| **Dairy and Milk** | | | | |
| Buttermilk | 1 cup | 219 | 8 | 27.4 |
| Cream Light | 1 cup | 192 | 7 | 27.4 |
| Cream Sour | 1 Tb | 32 | 1.2 | 26.7 |
| Cream, Half and Half | 1 cup | 230 | 7 | 32.9 |
| Cream, Heavy | 1 cup | 149 | 5 | 29.8 |
| Milk, 2% | 1 cup | 232 | 8 | 29.0 |
| Milk, 1% | 1 cup | 235 | 8 | 29.4 |
| Milk, Low-Sodium | 1 cup | 209 | 8 | 26.1 |
| Milk, Nonfat | 1 cup | 247 | 8 | 30.9 |
| Milk, Whole | 1 cup | 227 | 8 | 28.4 |
| Yogurt, Lowfat | 4 oz | 162 | 6 | 27.0 |
| Yogurt, Nonfat | 4 oz | 177 | 6 | 29.5 |
| Yogurt, Reg | 4 oz | 107 | 4 | 26.8 |

**Table 20. Phosphorus Content of Protein-Containing Foods (cont'd)**

| Food | Common Measure | Phosphorus (mg) | Protein (g) | mg P/ g protein |
|---|---|---|---|---|
| **Fish and Seafood** | | | | |
| Crab, Blue | 3 oz. | 175 | 17 | 10.3 |
| Crab, Dungeness | 3.oz. | 149 | 19 | 7.8 |
| Halibut | 3 oz. | 214 | 23 | 9.3 |
| Oysters, Fried | 3 oz. | 196 | 13 | 15.1 |
| Salmon | 3 oz. | 282 | 21 | 13.4 |
| Shrimp | 3 oz. | 116 | 18 | 6.4 |
| **Meats/Poultry/Egg** | | | | |
| Beef Liver | 3 oz. | 392 | 23 | 17.0 |
| Beef, Top Sirloin | 3 oz. | 203 | 25 | 8.1 |
| Chicken, breast | 3 oz. | 196 | 27 | 7.3 |
| Chicken, thigh | 3 oz. | 148 | 22 | 6.7 |
| Egg, Large | 1 large | 86 | 6 | 14.3 |
| Ham | 3 oz. | 239 | 19 | 12.6 |
| Lamb Sirloin Chop | 3 oz. | 190 | 22 | 8.6 |
| Pork Loin | 3 oz. | 146 | 22 | 6.6 |
| Turkey | 3 oz. | 210 | 28 | 7.5 |
| Veal Loin | 3 oz. | 189 | 22 | 8.6 |
| **Nuts/Nut Butter** | | | | |
| Almonds | 1 oz. | 139 | 6 | 23.2 |
| Macadamia | 1 oz. | 56 | 2 | 28.0 |
| Peanut Butter, Chunky | 2 Tb | 101 | 8 | 12.6 |
| Peanut Butter, Smooth | 2 Tb | 118 | 8 | 14.8 |
| Peanuts, Roasted | 1 oz. | 147 | 8 | 18.4 |
| Walnuts | 1 oz. | 98 | 4 | 24.5 |
| **Other Sources of Phosphorus** | | | | |
| Beer | 12 oz | 43 | 1 | 43.0 |
| Chocolate, Milk | 1 miniature | 95 | 3 | 31.7 |
| Chocolate, Semi Sweet | 1 oz | 37 | 1 | 37.0 |
| Coffee, Brewed | 1 cup | 2.3 | 0 | |
| Coffee, Instant | 1 tsp. | 4.5 | 0 | |
| Cola | 12 oz | 44 | 0 | |
| Lemon Lime | 12 oz | 0 | 0 | |
| Lemonade | 1 cup | 5 | 0.3 | 16.7 |
| Root Beer | 12 oz | 0 | 0 | |
| Tea, Brewed | 1 cup | 2.4 | 0 | |

***Abbreviations:*** *FF, fast food; Tb, tablespoon*

**Reference:** U.S. Department of Agriculture, Agricultural Research Service. 2001. USDA Nutrient Database for Standard Reference, Release 14. Nutrient Data Laboratory Home Page, http://www.nal.usda.gov/fnic/foodcomp

Considering all common sources of protein, the average phosphorus content per gram of protein is 17.8.

If all dairy products, nuts, beans, and seeds are eliminated, but meats and tofu are considered, the average phosphorus content per gram of protein is 10.3.

**Note:** A common way to determine a dietary phosphorus limit is to use an average of 10-12 mg/g of protein (multiply protein goal times 10-12 mg phosphorus). Thus, for a 70 kg-individual requiring 84 g of protein, the phosphorus range is 840-1,008 mg.

## GUIDELINE 5. USE OF PHOSPHATE BINDERS IN CKD

***In CKD Patients (Stages 3 and 4):***

**5.1 If phosphorus or intact PTH levels cannot be controlled within the target range (see Guidelines 1, 3), despite dietary phosphorus restriction (See Guideline 4), phosphate binders should be prescribed. (OPINION)**

**5.2 Calcium-based phosphate binders are**

**effective in lowering serum phosphorus levels (EVIDENCE) and may be used as the initial binder therapy. (OPINION)**

***In CKD Patients With Kidney Failure (Stage 5):***

**5.3 Both calcium-based phosphate binders and other noncalcium-, nonaluminum-, nonmagnesium-containing phosphate-binding agents (such as sevelamer HCl) are effective in lowering serum phosphorus levels (EVIDENCE) and either may be used as the primary therapy. (OPINION)**

**5.4 In dialysis patients who remain hyperphosphatemic (serum phosphorus >5.5 mg/dL [1.78 mmol/L]) despite the use of either of calcium-based phosphate binders or other noncalcium-, nonaluminum-, nonmagnesium-containing phosphate-binding agents, a combination of both should be used. (OPINION)**

**5.5 The total dose of elemental calcium provided by the calcium-based phosphate binders should not exceed 1,500 mg/day (OPINION), and the total intake of elemental calcium (including dietary calcium) should not exceed 2,000 mg/day. (OPINION)**

**5.6 Calcium-based phosphate binders should not be used in dialysis patients who are hypercalcemic (corrected serum calcium of >10.2 mg/dL [2.54 mmol/L]), or whose plasma PTH levels are <150 pg/mL (16.5 pmol/L) on 2 consecutive measurements. (EVIDENCE)**

**5.7 Noncalcium-containing phosphate binders are preferred in dialysis patients with severe vascular and/or other soft tissue calcifications. (OPINION)**

**5.8 In patients with serum phosphorus levels >7.0 mg/dL (2.26 mmol/L), aluminum-based phosphate binders may be used as a short-term therapy (4 weeks), and for one course only, to be replaced thereafter by other phosphate binders. (OPINION) In such patients, more frequent dialysis should also be considered. (EVIDENCE)**

#### Background

When dietary phosphate restriction is inadequate to control serum levels of phosphorus and/or PTH, the second line of therapy is the administration of phosphate binders. Different phosphate binder compounds have been utilized to control serum phosphorus levels, but the search still continues for the best possible binder. It is generally accepted that no one binder is effective and acceptable to every patient. Most commonly, a combination of binders may be used to control serum phosphorus levels to minimize the potentially serious side effects of any specific binder. The willingness of the patient to adhere to the binder prescription is paramount to control phosphorus absorption from the gastrointestinal tract and subsequently serum phosphorus level. Table 21 describes the steps to calculate the initial prescription of phosphate binders, and Table 22 provides the characteristics of various phosphate-binding agents.

#### Rationale

The goal of phosphate-binder therapy is to maintain serum phosphorus levels within the range as outlined in Guideline 3 without negatively impacting nutritional status or causing serious side-effects. Thus, it is logical to initiate phosphate binder therapy when:

(1) Serum phosphorus levels are elevated, even though the patient is compliant with a dietary phosphate restriction;

(2) The serum phosphorus levels can be controlled by a dietary phosphate restriction only, but such dietary intervention hinders the intake of other critical nutrients;

(3) Blood PTH levels remain elevated after dietary phosphate restriction, even if the serum phosphorus levels are not elevated.

During the use of aluminum-based phosphate binders, patients should be monitored to avoid additional morbidity described with *prolonged* use of aluminum-containing phosphate binders[146,147] to avoid aluminum toxicity (see Guidelines 11 and 12). The majority of research in the recent decade has focused on calcium-based binders, but other binder forms are now available. With recent concern about soft-tissue calcification which may be worsened by calcium-based phosphate binders, these noncalcium, nonaluminum binders are being used more frequently.

**Table 21. Steps To Calculate the Initial Binder Prescription**

| Step | Example | Example |
|---|---|---|
| **Phosphorus intake** | Total dietary P intake | 1,000 per day or 7,000/week |
| **Amount absorbed (50%-70% of mixed diet in nonrenal) (53% renal versus 77% in nonrenal)[139]** | Dietary P intake multiplied by average 50%-60% absorbed | 600 per day or 4,200/week |
| **Average HD/PD clearance** | Amount abs – dialysis clearance = | HD: 4,200 – 2,400 = 1,800 mg P/wk or 257 mg/d |
| **HD = 800 per treatment** | remaining P to be bound by phosphate binder | PD: 4,200 – 2,205 = 1,995 mg P/wk or 285 mg/d |
| **PD = 300-315 per day** | | |
| **Divided by the estimated binding power of the binder of choice:** | Remaining P/binding power | 257/39 (approx. P bound by 1 g $CaCO_3$) = 6.5 g $CaCO_3$)[140] |
| | | 257/45 (approx. P bound by 1 g calcium acetate) = 5.7 gm[141] |
| | | 257/15-30 (approx. P bound by one $Al(OH)_3$ tablet) = 12-17 tabs[142] |
| | | 257/64 (approx. binding power of 800 mg sevelamer HCl) = 4 caplets |
| | | 257/32 (approx. binding power per 400 mg sevelamer HCl) = 8 caplets |
| | | Note: Calculations for PD would use the 285 in place of 257. |

**Note:** Binder doses are usually established by trial and error. The above table estimates the initial binder prescription based on average phosphorus absorption, average dialysis clearance, and the approximate binding potential for the binder of choice. Binding potential can be altered by variations in pH. The dose should be monitored and adjusted based on the response of the individual patient.

Increasing frequency of dialysis can enhance phosphorus clearance in hemodialysis patients. Among patients treated with thrice-weekly nocturnal hemodialysis in Tassin, France, serum levels of phosphorus were reduced despite increased dietary intake and reduced use of binders.[148] Some patients treated with nocturnal dialysis six times per week have required phosphate supplements in the dialysate.[149] Where the escalation of phosphate-binder dose is incapable of controlling serum phosphorus levels or not tolerated, increasing dialysis time, and—if possible—frequency (4 or more times per week) should be strongly considered.

### *Strength of Evidence*

In order to determine what the best phosphate binder is, studies that evaluated the efficacy and adverse effects of phosphate binders were analyzed. There were no prospective, controlled studies that evaluated phosphate binders in CKD Stages 3 and 4. However, since serum PTH levels in these patients are elevated due to phosphate retention, it was the opinion of the Work Group that the use of phosphate binders may become necessary if the serum levels of intact PTH could not be lowered to the target levels (see Table 15, Guideline 1) by dietary phosphate restriction and/or vitamin D therapy.

In CKD Stage 5, there were 16 prospective, controlled studies that evaluated 552 patients for various outcomes to quantify the efficacy of serum phosphorus control by phosphate binders. In all these studies, the patients were treated with dialysis and the primary focus of the analysis was on the use of calcium carbonate and calcium acetate, although some data on aluminum hydroxide, calcium gluconate, calcium carbonate plus magnesium carbonate, and sevelamer HCl were also available. It was possible to use these studies to perform a meta-analysis to compare the efficacy of the phosphate binders on outcomes, including: serum levels of phosphorus, PTH and calcium; bone biochemical markers; and extraskeletal calcification.[143,150,151] No studies evaluated the effect of phosphate binders on patient quality of life, mortality rate, incidence of bone disease or fractures, or bone histomorphometry by bone biopsy measurements.

- Effect on Phosphorus. In all studies, serum phosphorus was lowered by the phosphate

## Table 22. Phosphorus-Binding Compounds

| Compound | Common Product Names | Estimate of % Calcium Absorbed | Phosphorus (mg) Bound per mg Ca++ Absorbed | Estimate of Potential Binding Power | Advantages | Potential Side Effects/ Disadvantages | Possible Indications for Use |
|---|---|---|---|---|---|---|---|
| **Calcium Carbonate** | TUMS, Oscal, Calcichew, Caltrate, Calci-Mix Titralac Chooz Gum | Approximately 20%-30% is absorbed[143] | Approximately 1 mg P bound per 8 mg Ca abs (Adapted from[143]) | Approximately 39 mg P bound per 1 g Calcium Carbonate[141] | Inexpensive, wide variety of products/ availability | Hypercalcemia, extraskeletal calcification, GI side effects, constipation | Serum parameters within target ranges to minimize risk for extraskeletal calcification |
| **Calcium Acetate** | PhosLo | With meals: 21±1% Between meals: 40±4%[140] | Approximately 1.04 mg P bound per mg Ca abs[144] 1 mg P bound per 2.9 mg Ca abs (Adapted from[143]) | Approximately 45 mg P bound per 1 g Calcium Acetate[140] | Less calcium absorption than $CaCO_3$; P binding similar to $Al(OH)_3$[144] | Hypercalcemia, extraskeletal calcification, GI side effects | Same as above |
| **Calcium Citrate** | Citracal | 22%[144] | NA | NA | NA | Increases aluminum absorption | Not recommended |
| **Magnesium Carbonate/ $CaCO_3$** | MagneBind 200/300 | Has 450/300 mg calcium acetate | Approximately 1 mg P bound per 2.3 mg Ca abs | NA | Potential to minimize calcium load | Hypermagnesemia, no long term studies of efficacy and safety | Need to monitor serum magnesium |
| **Aluminum Hydroxide** | AlternaGEL Alu-Cap Alu-Tab Amphojel Dialume | None | NA | Liquid: Mean binding 22.3 mg P per 5 mL; Tablet/capsule mean binding 15.3 mg P per pill[142] | Effective phosphate binding | Constipation/fecal impaction, bone mineral defects, aluminum toxicity chalky taste, GI distress, N/V | Time- and dose-limited use for hyperphosphatemia that is unresponsive to other binders |
| **Aluminum Carbonate** | Basaljel | None | NA | Same as above | Same as above | Same as above | Same as above |
| **Sevelamer HCl** | Renagel | None | NA | unknown[145] | Noncalcium, nonaluminum | GI side effects, cost | Eliminates binder-related calcium load; especially appropriate for patients with hypercalcemia or extraskeletal calcification |

$CaCO_3$ –43 mg P bound per 1 g elemental Ca[144]
Phoslo – 106 mg P bound per 1 g elemental Ca[144]
Sevelamer – 80 mg P bound per 1 g Sevelamer – animal data only[145]

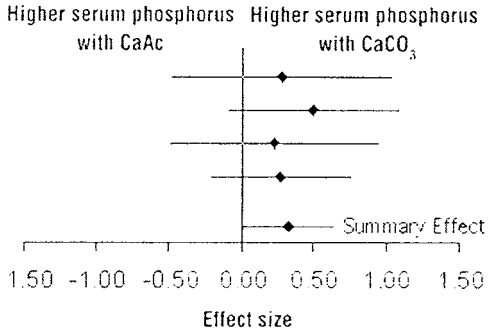



**Fig 10. Meta-analysis of size of effect on serum phosphorus levels of calcium acetate versus calcium carbonate.**

binder studied. In assessing the relative efficacy of the various phosphate binders in controlling serum phosphorus levels, 15 studies were evaluated: 9 studies examined calcium carbonate and 6 examined calcium acetate. Two sets of meta-analyses were performed. The first analysis compared the relative effectiveness of various phosphate binders to that of calcium carbonate and no significant difference was observed. The second meta-analysis compared calcium acetate to a variety of phosphate binders.[150,152-156] It showed that calcium acetate decreased serum phosphate levels to a greater degree than the other phosphate binders, although it should be emphasized that the "other" phosphate binders group was a mixture of different phosphate binders such that this comparison may not be completely valid. A subgroup analysis of 4 studies that directly compared calcium carbonate to calcium acetate[153-156] found that post-treatment serum phosphate levels were significantly higher following treatment with calcium carbonate compared to calcium acetate (Fig 10). One possible explanation for this difference is that calcium acetate leads to less hypercalcemia (see below), thereby allowing more binder to be administered to control phosphorus better.

Two studies included a placebo group for comparison against calcium acetate[143] and sevelamer,[157] and both showed a superior efficacy of these binders compared to placebo.

There was only a single study evaluating magnesium as a phosphate binder: it is a crossover study that evaluated patients on calcium carbonate compared to a combination of calcium carbonate and magnesium carbonate.[158] The magnesium arm had equivalent phosphorus control. However, the Work Group cautions that, in this study, the magnesium concentration in the dialysate was decreased. This is difficult to do in most units due to centralized dialysate delivery systems. Furthermore, there are no long-term studies on the safety and efficacy of magnesium as a phosphate binder, and thus the Work Group agreed that the use of magnesium-based phosphate binders may be justified only if all other compounds fail and the appropriate precautions are undertaken.

Effect on Calcium and Calcium-Phosphorus Product. Ten studies evaluated the effect of different phosphate binders on corrected serum calcium levels, ionized calcium, total calcium, or calcium-phosphorus product.[143,153-157,159-162] Five of these studies compared different binders to calcium carbonate,[143,154,155,158,161] but a meta-analysis failed to detect a difference in the corrected serum calcium levels. A placebo-controlled study found higher total calcium levels and lower calcium-phosphorus product in the calcium acetate-treated group compared to placebo.[143] Although the overall change in serum calcium levels in 10 studies was not affected, meta-analysis of the data showed that calcium carbonate led to more hypercalcemic events compared to other phosphate binders, or when directly compared to calcium acetate only (Fig 11).[151,153-156,158,160-163] Six studies assessed calcium-phosphorus product, 1 placebo-controlled and the others comparing different phosphate binders. Differences were observed in only 2 of

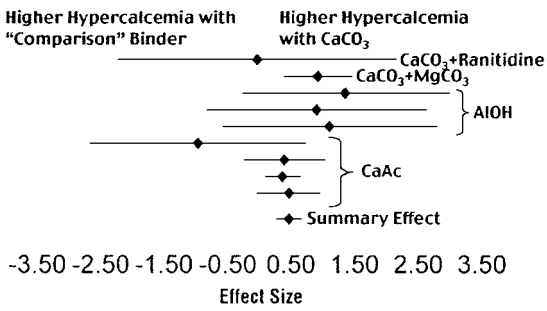



**Fig 11. Meta-analysis of size of hypercalcemic effect of calcium carbonate versus other phosphate binders.**

these studies: calcium acetate led to a lower calcium-phosphorus product than placebo,[143] and calcium carbonate led to a greater product than calcium ketoglutarate.[162] This latter study found that ionized calcium levels were higher in patients treated with calcium carbonate compared to calcium ketoglutarate.[162] Thus, the available data do not provide guidance regarding the choice of the appropriate calcium-based phosphate binder. The choice is a prerogative of the physician and depends on the binder's tolerance by the patient.

Other Outcomes. The major side-effects observed as a result of phosphate-binder therapy were hypercalcemia, as described above, or gastrointestinal side effects. A meta-analysis indicated that gastrointestinal side effects were lowest with patients treated with calcium carbonate compared to other binders, although the effect size was small and thus no firm conclusions could be reached.[154,156,158,160,162,163]

Six studies evaluated the effect of phosphate binders on nutritional outcomes,[150,152,157-159,162] but different outcome measures were utilized, precluding comparative analyses. Two studies found that sevelamer led to lower serum cholesterol levels compared to placebo or calcium acetate, primarily due to a decrease in LDL cholesterol levels.[152,158]

Patient compliance with prescribed binder therapy was not consistently reported, but ranged from 30% to 100%.[132,138,164-170] None of the available data dealt with the effect of noncompliance on clinical outcomes. One study suggested that noncompliance was related to gastrointestinal side effects. While maintenance of high serum phosphorus levels could be due to noncompliance with phosphate binders, other factors, such as dietary indiscretion and phosphate release from the bone must also be considered.

There are few studies that demonstrated optimal timing for ingestion of phosphate binders, but the general consensus among the Work Group is that binders should be taken 10 to 15 minutes before, or during, the meal.

In comparing calcium carbonate and aluminum hydroxide, 1 prospective study found lower bone mineral content in aluminum hydroxide-treated patients. Minor, and inconsistent, differences were found. Because of the potential for neurotoxicity and osteomalacia that are associated with aluminum-containing phosphate binders,[146,147,171] the use of these compounds should be reserved for patients with serum phosphorus greater than 7.0 mg/dL (2.26 mmol/L) and only for short-term therapy. However, the Work Group acknowledges that while there is morbidity associated with long-term aluminum intake, there is also increased mortality with phosphorus levels greater than 6.5 to 7.0 mg/dL (2.10 to 2.26 mmol/L). Thus, the 2 issues must be balanced. At the present time, there is no evidence that short-term use of aluminum-containing phosphate binders is associated with the development of aluminum bone disease or neurotoxicity. Therefore, the short-term (4 weeks) use of these compounds is not contraindicated. However, calcium citrate should be avoided while the patients receive aluminum-based compounds, since citrate increases the absorption of aluminum from the intestine[171] and may precipitate acute aluminum toxicity.

In summary, the available evidence supports the hypothesis that all of the current phosphate binders are efficacious in controlling serum phosphorus levels. The majority of studies evaluated calcium-containing phosphate binders. However, recent studies on the use of the new nonaluminum-, nonmagnesium-, noncalcium-containing phosphate binder sevelamer was effective,[83,152,157,172,173] and the Work Group felt that this agent has an important emerging role in the control of serum phosphorus in dialysis patients.

In CKD Stages 3 and 4 calcium levels are often low, contributing to secondary hyperparathyroidism. Furthermore, because these patients have some residual kidney function, phosphate and/or PTH control is usually achievable with lower doses of calcium-based phosphate binders. In CKD Stage 5, the current evidence and the opinion of the Work Group support the recommendation that the choice of phosphate binder should be determined by patient preference (number and size of binder, tablets or capsules), compliance, comorbid illnesses, side effects, cost, and the ability to control serum phosphorus levels while maintaining the desired calcium-phosphorus product ($<55$), and limiting the total calcium intake. However, the Work Group also recommends a noncalcium, nonmagnesium, nonaluminum phosphate binder as the therapy of

choice in dialysis patients with low parathyroid hormone. The rationale for this recommendation is that these patients will usually have low-turnover bone disease, and the bone will be unable to incorporate a calcium load,[174] predisposing to extraskeletal calcification. Also, calcium-based phosphate binders should not be used in patients with hypercalcemia or with severe vascular calcification (see below). In these situations, a noncalcium, nonmagnesium, nonaluminum phosphate binder should be used to control serum levels of phosphorus while avoiding excessive calcium intake.

#### Limitations

The available data do not quantify an exact amount of calcium that could be given safely as a calcium-based phosphate binder. This is an important issue as recent studies suggest excessive calcium intake may worsen vascular and other extraskeletal calcification.[87,91,175] Additional data, that either did not fully meet the inclusion criteria or became available after the evidence report was completed, support this consensus of the Work Group. These data were reviewed by the Work Group and are summarized as follows.

In a cross-sectional study evaluating the presence of vascular calcification as assessed by electron-beam computed tomography scan in children and adolescents, the calcium-phosphorus product and prescribed calcium intake from phosphate binders were much higher in the patient group with calcification. In the group with calcification, the mean dose of prescribed binder was 6.456 g/day (elemental calcium/day), compared to 3.325 g/day in the no calcification group.[87] Another cross-sectional study evaluating risks for significant vascular calcification assessed by ultrasound, found by multivariate analysis that the calcium load from phosphate binders was greater in those with calcification compared to those without calcification.[91] There was a progressive increase from $1.35 \pm 1.10$ g/day of elemental calcium in patients with no calcification by ultrasound, to $1.50 \pm 0.81$ g/day in those with a calcification score of 2, and $2.18 \pm 0.93$ in those patients with a calcification score of 4 ($P = 0.001$ by ANOVA).[91] Lastly, a prospective, randomized, controlled trial compared sevelamer HCl to calcium-based phosphate binders in 202 dialysis patients. The study compared the effect on serum phosphorus, calcium, calcium-phosphorus product, cholesterol and LDL levels, and aortic and coronary artery calcification evaluated by electron-beam tomography. Sevelamer and calcium-based phosphate binders achieved control of serum phosphorus levels similar to the recommended K/DOQI levels; calcium-phosphorus product was slightly higher in the calcium-treated group. There were more hypercalcemic episodes and more suppression of PTH in the calcium-treated group. Blood levels of cholesterol and LDL were significantly lower in the sevelamer-treated group. In the 80% of patients with calcification at baseline, there was significant progression in aortic and coronary artery calcification in the calcium-treated group, but no progression in the sevelamer-treated group. In the calcium arm, the average dose of calcium acetate was 4.6 g/day (1,183 mg elemental calcium per day). The average dose of calcium carbonate was 3.9 g (1,560 mg elemental calcium). It should be cautioned that the observed results could be due to calcium load or lowering LDL cholesterol. However, taken together, these studies support the conclusion that calcium intake from phosphate binders should be limited in CKD patients on dialysis (Stage 5) to under 1,500 mg/day, and possibly lower.

The total calcium intake from diet, calcium-containing phosphate binders, and dialysate ideally should be equal to the recommended daily adequate intake (AI) for adults (1,000 to 1,500 mg/day). Given that the daily dietary intake of calcium for most dialysis patients is only 500 mg due to the restricted phosphorus diet, this leaves only 500 to 1,000 mg elemental calcium from calcium-containing phosphate binders. However, the Work Group recognizes the overwhelming importance of controlling serum phosphorus levels, which can rarely be done with calcium-containing phosphate binders while adhering to this limited daily calcium intake. Based on this and the above data, the Work Group recommends that the amount of calcium provided by calcium-based phosphate binders and diet should not exceed 2 g/day. This recommendation is not evidence-based and thus the clinician must individualize therapy taking into account cost, other vascular risk factors, and the patient's tolerance of calcium-containing binders. For further discussion of the issue of daily calcium intake in CKD

patients, see the discussion in the section, "Strength of Evidence" in Guideline 6.

For those patients who are on calcium-containing phosphate binders in amounts exceeding 2,000 mg total elemental calcium content, the Work Group strongly recommends adding a noncalcium, nonmagnesium, nonaluminum phosphate binder to decrease the total calcium intake. Sevelamer is such an agent currently available. It has the additional advantage of decreasing the serum levels of LDL cholesterol.

#### Clinical Applications

Obviously, the best phosphate binders are those that the patient will take consistently and as prescribed while limiting total calcium intake. As stated earlier in this document, the ability to adequately control serum phosphorus rests on appropriate education, patient compliance, and the use of tolerable phosphate binders. The latter needs to be individualized for patients and thus will require continuous monitoring with renal dietitians.

#### Recommendations for Research

Longitudinal studies evaluating phosphate binders and their efficacy, side effects, and impact on morbidity and mortality are needed. Although the recently completed study demonstrated an advantage of sevelamer HCl compared to calcium-based phosphate binders in preventing progression of aortic and coronary arteries calcification, studies evaluating this positive effect on cardiovascular morbidity and mortality in dialysis patients are needed.

## GUIDELINE 6. SERUM CALCIUM AND CALCIUM-PHOSPHORUS PRODUCT

***In CKD Patients (Stages 3 and 4):***

**6.1 The serum levels of corrected total calcium should be maintained within the "normal" range for the laboratory used. (EVIDENCE)**

***In CKD Patients With Kidney Failure (Stage 5):***

**6.2 Serum levels of corrected total calcium should be maintained within the normal range for the laboratory used, preferably toward the lower end (8.4 to 9.5 mg/dL [2.10 to 2.37 mmol/L]). (OPINION)**

**6.3 In the event corrected total serum calcium level exceeds 10.2 mg/dL (2.54 mmol/L), therapies that cause serum calcium to rise should be adjusted as follows:**

**6.3a In patients taking calcium-based phosphate binders, the dose should be reduced or therapy switched to a noncalcium-, nonaluminum-, nonmagnesium-containing phosphate binder. (OPINION) See Guideline 5.**

**6.3b In patients taking active vitamin D sterols, the dose should be reduced or therapy discontinued until the serum levels of corrected total calcium return to the target range (8.4 to 9.5 mg/dL [2.10 to 2.37 mmol/L]). (OPINION) See Guideline 8B.**

**6.3c If hypercalcemia (serum levels of corrected total calcium >10.2 mg/dL [2.54 mmol/L]) persists despite modification of therapy with vitamin D and/or discontinuation of calcium-based phosphate binders, dialysis using low dialysate calcium (1.5 to 2.0 mEq/L) may be used for 3 to 4 weeks (OPINION) See Guideline 9.**

***In CKD Patients (Stages 3 to 5):***

**6.4 Total elemental calcium intake (including both dietary calcium intake and calcium-based phosphate binders) should not exceed 2,000 mg/day. (OPINION) See Guideline 5.**

**6.5 The serum calcium-phosphorus product should be maintained at $<55\ mg^2/dL^2$. (EVIDENCE) This is best achieved by controlling serum levels of phosphorus within the target range. (OPINION) See Guidelines 3, 4, and 5.**

**6.6 Patients whose serum levels of corrected total calcium are below the lower limit for the laboratory used (<8.4 mg/dL [2.10 mmol/L]) should receive therapy to increase serum calcium levels if:**

**6.6a There are clinical symptoms of**

**hypocalcemia such as paresthesia, Chvostek's and Trousseau's signs, bronchospasm, laryngospasm, tetany, and/or seizures (OPINION); or**

**6.6b The plasma intact PTH level is above the target range for the CKD Stage (See Table 15 in Guideline 1). (OPINION)**

**6.7 Therapy for hypocalcemia should include calcium salts such as calcium carbonate (EVIDENCE) and/or oral vitamin D sterols. (EVIDENCE) See Guideline 8B.**

### Background

Maintenance of normal calcium balance and serum calcium levels depend on integrated regulation of calcium absorption and secretion by the intestinal tract, the excretion of calcium by the kidney, and calcium release from and calcium deposition into bone. Parathyroid hormone, by stimulating bone resorption and kidney distal tubular calcium reabsorption in the kidney, and activating renal hydroxylation of $25(OH)D_3$ to $1,25(OH)_2D_3$ increases serum calcium levels. Depression in serum levels of calcium by itself stimulates, through the calcium-sensing receptor (CaR) in the parathyroid gland, the secretion of preformed PTH from parathyroid gland within seconds. Subsequently, PTH biosynthesis by parathyroid gland increases over 24 to 48 hours and, if persistent, is followed by parathyroid gland hypertrophy and hyperplasia. Vitamin D metabolites and serum phosphorus levels also regulate PTH levels in blood. These homeostatic mechanisms are distorted in early stages of CKD and continue to deteriorate as loss of kidney function progresses.

The adult human body contains approximately 1,300 g of calcium with 99% in skeleton, 0.6% in soft tissues, and 0.1% in extracellular fluid.[176] Normal values for serum total calcium concentration vary among clinical laboratories, depending on the methods of measurement, with a normal range being 8.6 to 10.3 mg/dL (2.15 to 2.57 mmol/L) for adults.[177,178] Variations in serum levels of calcium depending on age and gender have been observed.[179] Calcium in blood exists in three distinct fractions: protein-bound calcium (40%), free (formerly called ionized) calcium (48%), and calcium complexed with various anions such as phosphate, lactate, citrate, and bicarbonate (12%). Free calcium can be measured using ion-selective electrodes in most hospitals and values in adults range between 4.65 and 5.28 mg/dL (1.16 and 1.32 mmol/L).[177,178] Free calcium should be assessed if subtle changes are expected or total calcium measurements are not adequate. Generally, reproducibility of free calcium measurement is worse than those of total calcium; the technique is time-consuming and more expensive than total calcium measurements. For these reasons, and because free calcium is not routinely measured, this Guideline will be based on the levels of total calcium in the blood. The latter does reflect the measured levels of free calcium if plasma levels of protein are normal. If plasma levels of albumin are low, a correction of the measured serum levels of calcium should be made. Several formulas have been developed to correct total calcium for abnormal albumin or to calculate free calcium both in healthy subjects and patients with CKD, but all of them are encumbered with limitations (see Guideline 6, Rationale). Also, a fall in pH of 0.1 unit will cause approximately a 0.1 mEq/L rise in the concentration of ionized calcium since hydrogen ion displaces calcium from albumin, whereas alkalosis decreases free calcium by enhancing binding of calcium to albumin.[179]

There are no biochemical measurements that reflects calcium nutritional status in normal subjects and in patients with kidney disease. The major indirect measures of calcium adequacy are skeletal health assessed by risk of fractures, bone mass measurements, and desirable rates of calcium retention in bone. Based on these surrogate markers, the Dietary Reference Intake (DRI) Committee[180] recommended the term "adequate intakes" (AIs) of calcium. This represents an approximation of the calcium intake that, in the judgment of the DRI Committee, is sufficient to maintain calcium nutriture based on observed or experimentally determined estimates of average calcium intake by groups of healthy people. The recommended dietary allowance (RDA), the term used for average daily dietary intake level that is sufficient to meet the nutritional requirements of 97% to 98% of all healthy individuals in a life stage and gender group, could not be established. At the same time, the tolerable upper level for

**Table 23. Adequate and Upper Intake Levels of Calcium for Healthy People by Age**

| Group | Age (years) | Adequate Intake (mg/day) | Upper Intake Level (mg/day) |
|---|---|---|---|
| Children | 4 through 8 | 800 | 2500 |
| Boys and girls | 9 through 18 | 1,300 | 2500 |
| Men and women | 19 through 50 | 1,000 | 2500 |
| Men and women | 50 through >70 | 1,200 | 2500 |

*Data obtained from Institute of Medicine.[180]

calcium intake was established; this represents the maximal intake of calcium that is likely to pose no risks of adverse effects in healthy individuals. The examples of adequate intake and upper intake levels of calcium in various age groups of healthy subjects are presented in Table 23.

The total daily intake of elemental calcium in CKD patients should not exceed 2,000 mg per day. Table 24 provides the calcium content of various commercially available calcium-based binders.

Adequate dietary intake of calcium in patients with different stages of CKD is more difficult to estimate than in healthy subjects when one takes into consideration the changes in calcium, phosphorus, vitamin D, PTH, and bone metabolism that occur in CKD. Ideal dietary calcium intake should provide enough calcium to maintain calcium balance as close as possible to that of the age- and gender-matched healthy population. Calcium balance (intake minus the sum of all losses) in the healthy population is generally positive (+200 mg to +300 mg/day) during adolescence, slightly positive (10 to 50 mg/day) at age 19 through 30, neutral in mature adults, and becomes negative at advanced age.[180] Whether negative calcium balance in the healthy aged population is the optimal status is a question for debate.

Additionally, in CKD patients, the fraction of intestinal calcium absorption in the duodenum and jejunum is reduced[103] because this process is vitamin D-dependent,[181] and CKD patients have reduced blood levels of $1,25(OH)_2D$.[182] However, passive intestinal calcium absorption which

**Table 24. Calcium Content of Common Calcium-Based Binders**

| Compound | Brand Name | Compound Content | % Ca | Elemental Ca | Number of Pills To Equal Approximately 1,500 mg Elemental Calcium |
|---|---|---|---|---|---|
| Calcium Acetate | Phoslo™ | 667 mg | 25% | 167 mg | 9 |
| Calcium Carbonate | Chooz™ (Gum) | 500 mg | 40% | 200 mg | 7.5 |
| | TUMS™ | | | | |
| | TUMS EX™ | 750 mg | 40% | 300 mg | 5 |
| | TUMS Ultra™ | 1,000 mg | 40% | 400 mg | 3.75 |
| | LiquiCal | 1,200 mg | 40% | 480 mg | 3 |
| | CalciChew™ | 1,250 mg | 40% | 500 mg | 3 |
| | CalciMix™ | | | | |
| | Oscal 500™ | | | | |
| | TUMS 500™ | | | | |
| | Caltrate 600™ | 1,500 mg | 40% | 600 mg | 2.5 |
| | NephroCalci™ | | | | |
| Calcium Citrate | CitraCal™ | | | | Not Recommended |
| Calcium Acetate/ Magnesium Carbonate | MagneBind™ 200 | 200 Mg carb 450 Ca acetate | | (Mg = 57 mg) 113 mg | 13 |
| | MagneBind™ | 300 Mg carb 300 Ca acetate | | (Mg = 85 mg) 76 mg | 20 |

**Reference:** Manufacturers' Information, Internet.

is gradient-dependent can be augmented by increasing calcium intake.[181]

Patients with CKD who are treated with metabolites of vitamin D or calcium supplementation are particularly prone to develop hypercalcemia. This complication occurs especially in those with low-turnover bone disease. The clinical presentation of hypercalcemia varies from a mild, asymptomatic, biochemical abnormality detected during routine screening to a life-threatening emergency.[183,184]

Hypercalcemia, together with hyperphosphatemia, or each individually can be responsible for increased blood Ca-P product. Since serum phosphorus levels in patients with CKD are usually increased by a higher factor (from 3.5 mg/dL [1.13 mmol/L] to 7 mg/dL [2.26 mmol/L], giving a factor of 2), compared to calcium (from 9.5 mg/dL [2.37 mmol/L] to 11 mg/dL [2.74 mmol/L], giving a factor of 1.2), the relative importance of serum phosphorus levels in generating higher Ca-P product, expressed as $mg^2/dL^2$, is greater than the serum calcium levels. Still, the serum calcium levels could be critical[185] if the serum phosphorus levels are very high, which is indeed the case in patients with Stage 5 CKD.

In the presence of high Ca-P product in blood, soft-tissue calcification is likely but not always associated with high Ca-P product, since many factors are involved in the genesis of soft-tissue calcification (Table 6).

#### Rationale

It is important that patients with CKD have normal serum levels of corrected total calcium, since chronic lower levels of calcium cause secondary hyperparathyroidism, have adverse effects on bone mineralization, and may be associated with increased mortality. Therefore, hypocalcemia should be treated. Also, adequate calcium intake in CKD patients is needed to prevent negative calcium balance and since dietary intake of calcium in CKD patients is restricted, calcium supplementation may be required. *At the same time, high calcium intake should be avoided since patients with CKD may encounter difficulties in buffering increased calcium loads, and such difficulty may result in hypercalcemia and/or soft-tissue calcification.* Indeed, hypercalcemia is a frequent occurrence during therapy with calcium-based phosphate binders and/or active vitamin D sterols. Spontaneous hypercalcemia also occurs in CKD patients.

#### *Strength of Evidence*

It is accepted that total calcium levels need to be adjusted for the level of albumin to better reflect the free calcium.[179] The Evidence Report of these Guidelines cites 2 major studies that evaluated various formulas for correction of total calcium for albumin in 82 hemodialysis and 34 continuous ambulatory peritoneal dialysis (CAPD) patients.[186,187] One of these studies[186] used preferable statistical methods and also employed strict control of blood drawing and handling. Albumin was assayed by an automated bromocresol green method (BCG), total calcium by arenazo III binding, and ionized calcium by ion-selective electrode. Therefore, the equation derived from this study most closely approximates corrected total calcium in patients with CKD with an interclass correlation value of 0.84:

$$\text{Corrected calcium (mg/dL)} = \text{Total calcium (mg/dL)} + 0.0704 \times [34 - \text{Serum albumin (g/L)}]$$

The use of different methods for measuring either albumin or calcium may yield different correlations from the one derived from this study. For the routine clinical interpretation of serum calcium needed for appropriate care of patients with kidney diseases, a simple formula, which yields similar results, for adjusting total serum calcium concentration for changes in plasma albumin concentration, can be used by clinicians[179]:

$$\text{Corrected total calcium (mg/dL)} = \text{Total calcium (mg/dL)} + 0.8 \times [4 - \text{Serum albumin (g/dL)}]$$

Patients with GFR below 60 mL/min/1.73 $m^2$ (Stage 3 CKD) usually, but not invariably, show a detectable decrease in the blood levels of total and free calcium.[31,188] The serum calcium levels decrease further as kidney function deteriorates. In advanced stages of CKD, the fraction of total calcium bound to complexes is increased[189]; thus,

free (ionized) calcium levels are decreased despite normal total serum calcium levels. Acidosis, on the other hand, may increase the serum levels of free calcium. With initiation of regular hemodialysis, the levels of serum total calcium usually normalize.

Hypocalcemia as a risk factor for negative outcomes such as increased mortality, incidence of fractures and bone disease, and quality of life was not adequately addressed in reported clinical studies. A few studies published in the early 1970s suggest that hypocalcemia may have detrimental consequences for patients with CKD.[104,105,108,190-192] In 1 cohort study, 433 patients beginning dialysis therapy were followed prospectively for an average of 41 months.[193] In 281 of the patients, the level of total calcium was $<$8.8 mg/dL. After adjusting for comorbid conditions, plasma albumin and blood hemoglobin, chronic hypocalcemia was associated with increased mortality ($P < 0.006$). This association was similar among patients treated with hemodialysis or peritoneal dialysis. Covariant analysis showed that hypocalcemia in these patients was associated with de novo and recurrent cardiac ischemic heart disease and congestive heart failure.

A positive relationship has been found between serum calcium level and mineralization surface and osteoid surface,[105] and a statistically significant relationship between the serum calcium level and the percentage of metacarpal cortical/total bone area assessed by X-ray.[108] However, this was not the case when the cortical area of bone in the patients was calculated as a percentage of cortical area of bone in normal subjects.[104] Serum levels of total alkaline phosphatase activity, used as a marker of the severity of secondary hyperparathyroidism in patients with CKD, did not correlate with the serum levels of calcium.[104,105,108,190-192] Despite moderate significant inverse correlation between serum calcium levels and serum PTH levels,[190,191] it was not possible to calculate the relative risk for development of secondary hyperparathyroidism for particular levels of serum calcium. Some of the newer studies[45] did not find a relationship between elevated serum levels of PTH observed in CKD patients with different levels of GFR and the levels of serum calcium, which were within the normal range independent of the stage of kidney disease.

Taken together, the results of the Evidence Report with regard to this Guideline indicate that hypocalcemia is a risk for bone disease and for development of secondary hyperparathyroidism and/or increased risk of mortality. Thus, the detection of true hypocalcemia and its appropriate treatment is important for management of patients with CKD.

There are no data suggesting that transient mild hypercalcemia has detrimental effects on morbidity in patients with CKD. In 1 study, there was no evidence that isolated hypercalcemia is associated with increased morbidity in the hemodialysis population.[92] Hypercalcemia poses a risk for CKD patients as it would increase the Ca-P product index in blood. Severe hypercalcemia with clinical symptoms must be treated appropriately.

Net calcium absorption is reduced in chronic renal failure as a consequence of both decreased calcium intake and decreased fraction of calcium absorbed by the intestine. The fraction of intestinal absorption of calcium is decreased early in the course of kidney disease. This is observed in Stage 3 CKD and worsens as CKD progresses.[103,194-197] Initiation of dialysis does not improve calcium absorption.[195-197] It is common to observe significant variability in intestinal calcium absorption within a group of patients with the same degree of kidney dysfunction,[103,194-197] and, therefore, population studies may not be adequate to address the status of intestinal calcium absorption in individual patients.

Dietary calcium intake is low in patients with CKD. Intake of calcium in adults with advanced CKD ranged between 300 and 700 mg/day[195,198]; in those treated with hemodialysis, calcium intake averaged 549 mg/day[199]; and it was 80% of the recommended daily allowance in children with GFR between 20 and 75 mL/min/1.73 $m^2$.[200] When dietary calcium intake was less than 20 mg/kg /day, patients with CKD had negative net intestinal calcium balance, but neutral calcium balance was achievable with calcium intake around 30 mg/kg/day.[201]

There are no data on calcium retention as a function of increased long-term calcium intake in patients with CKD that are similar to data calculated for healthy adolescents, young adults,

**Table 25. Factorial Analysis for Determining Calcium Requirements in Adults Aged 19-30 Years**

| | Creatinine Clearance 20-40mL/min/1.73 m² (0.33-0.67 mL/s/1.73 m²] | | Creatinine Clearance <20 mL/min/1.73 m² (0.33 mL/s/1.73 m²) | |
|---|---|---|---|---|
| Factor | Female (mg/day) | Male (mg/day) | Female (mg/day) | Male (mg/day) |
| Peak calcium accretion | 10[a] | 50[a] | 10[a] | 50[a] |
| Urinary losses | 89[b] | 89[b] | 59[b] | 59[b] |
| Endogenous fecal calcium | 132[a] | 156[a] | 132[a] | 156[a] |
| Sweat losses | 63[a] | 63[a] | 63[a] | 63[a] |
| Total calcium | 294 | 358 | 264 | 328 |
| Absorption, percent | 18[c] | 18[c] | 18[c] | 18[c] |
| As adjusted for absorption | 1,633 | 1,988 | 1,466 | 1,822 |

[a] Data from Reference [180]
[b] Data from Reference [202]
[c] Data from Reference [195]

and adult men, which shows that calcium retention reaches a plateau despite an increase in calcium intake from 1,000 to 2,500 mg/day.[181] Thus, we are poorly equipped to establish values for adequate intake of calcium in patients with kidney disease. The opinion of the Work Group is that an intake of 2.0 g/day of calcium (dietary and supplements) is appropriate for CKD patients.

While this recommendation of the Work Group is not based on evidence provided in the Evidence Report, there are data from different studies identifying the requirement of calcium for various components of calcium balance (intestinal calcium absorption and calcium secretion) and calcium losses (urinary, fecal, and sweat) in CKD patients (Table 25). These data show that the requirement of daily calcium intake in Stage 3 CKD is 1.5 to 2.0 g/day and in Stages 4 and 5 CKD (patients not on dialysis), it is 1.5 to 1.8 g/day. The Work Group's recommendation of total daily calcium intake of 2.0 g/day is in agreement with these data.

Furthermore, in dialysis patients, calcium supplementation of 3.0 g/day in addition to the 400 to 500 mg in dietary calcium resulted in hypercalcemia in up to 36% of patients.[203] Other studies show lower, but still significant, incidences of hypercalcemia during high calcium intake.[141,204] This clearly suggests that there is a tolerable upper intake level for patients with CKD and, therefore, higher daily calcium intake (>2.0 g/day) should be avoided.

The effectiveness of different calcium salts used for calcium supplementation was partially addressed by 4 studies.[41,173,205,206] Only 1 of these studies[206] directly compared the efficacy of 2 different calcium salts (calcium carbonate versus calcium citrate). However, this study followed the patients for only 3 hours after administration of the calcium supplements, and therefore the results represent only short-term effects. The other 3 studies compared the use of calcium carbonate to placebo or no calcium supplement. Because of the different study conditions and patient populations, and because these studies did not directly address the question being asked, it was not useful to conduct a meta-analysis. Therefore, the recommendation for the use of calcium carbonate for calcium supplementation in this Guideline is opinion-based and endorsed by the Work Group.

Similarly, the 4 studies cited above did not provide information that could be utilized to ascertain whether giving the calcium salts before, during, or after meals is more effective. Further, the data are not helpful in deciding whether it is better to give the calcium salts in 1 dose per day or divided into multiple doses.

The question as to when to initiate calcium supplementation during the course of CKD is not answered by the available data in the literature. Certainly, in the presence of overt hypocalcemia, calcium supplementation is indicated. However, determining when to initiate calcium therapy in patients with CKD involves a consideration of

multi-dimensional biological parameters on the part of the clinician. It seems, however, that calcium supplementation should be considered in CKD patients when serum levels of PTH begin to rise, ie, GFR <60 mL/min/1.73 $m^2$ (Stage 2 CKD).

An association was observed between Ca-P product and the risk of death in a random sample of the US population of 2,669 patients treated for at least 1 year with hemodialysis between 1990 and 1993.[92] Patients with Ca-P product above 72 (20% of all patients) had a 34% higher relative risk of death compared to patients with Ca-P product in the range of 42 to 52.[92] The increased risk was observed in proportion to the elevation of Ca-P product; indeed, for every increase of 10 in Ca-P product, there was an 11% increase in relative risk of death.

The Evidence Report cites 4 studies that address the issue of Ca-P product as a risk for soft-tissue calcification. One prospective, uncontrolled study of 137 patients showed that 35 patients ages 55 to 64, with poorly controlled Ca-P product levels (above 60) had increased aortic calcification index (ACI = 26.1) as compared to 20 patients of the same age with well-controlled Ca-P product <60 (ACI = 17.7).[86] Another prospective, controlled study using stepwise discrimination analysis showed significantly higher risk for mitral annular calcification in hemodialysis patients with Ca-P product of 63 ± 13 compared to those with Ca-P product of 56 ± 13.[207] An additional study showed that, in young adults on hemodialysis who had Ca-P product of 65 ± 10.6, coronary artery calcification was significantly higher than in those with Ca-P product of 56 ± 12.7.[87] One retrospective, controlled study in CAPD patients showed no significant differences in Ca-P product levels in 17 patients with mitral annular calcification as compared to 118 patients without this abnormality.[208] *Despite the fact that these studies were not controlled for potential confounding variables and are encumbered with selection bias, it seems reasonable to conclude that high levels of Ca-P product can pose a risk of vascular calcification.*

The level of Ca-P product in CKD patients at which risk for calcification is very low or unlikely to occur, has been debated over the last 40 years, but no strong evidence is available to answer this question. As discussed above, Ca-P products are most likely a risk for calcification, but assessing calcification risk does not involve arriving at "yes" or "no" answers. The theory is that calcification risk increases as Ca-P product increases; however, evidence on this relationship is scant and will be presented below.

Five studies[207-211] examined some measure that evaluate Ca-P product as a risk for extraskeletal calcification. None examined risk for future calcification. All were cross-sectional studies. Three were retrospective[208,210,211] and 2 prospective.[207,209] They used different methods (radiography, scintigraphy, CT, echocardiography) for detection of calcification and examined different organs for calcification (eg, soft tissue, mitral and aortic valve, aorta, lung). Only 2 studies[208,211] provided enough information to calculate risk ratios for Ca-P product for inducing soft-tissue calcification. One study[208] included 135 Stage 5 CKD predialysis patients and 76 patients on CAPD, and the other[211] reported on 47 patients for more than 2 years on CAPD. This limited information suggests that Ca-P product may not be a useful indicator of calcification in patients with Stage 5 CKD, as no trend for risk was seen.[208] Data on patients treated with CAPD for 2 years showed that the risk for mitral calcification increased as Ca-P increased.[211] In contrast, in patients treated with CAPD for 1 year, there was no relationship between the risk for calcification and the levels of Ca-P product.[208] The confidence intervals in this small study are very wide, and thus firm conclusions cannot be reached. Neither of these studies examined whether Ca-P product can be used as a predictor of future calcification.

Two case-controlled studies indicated that there were significant differences in Ca-P product between patients with and without aortic valve calcification and mitral annular calcification[207,210] and normal and abnormal visceral uptake of $^{99}$Tc-PP or $^{99}$Tc-MDP.[209]

The incidence of visceral calcification in a selected dialysis population was high when mean Ca-P product exceeded 68 and low when mean Ca-P product was 51.[209] Frequent incidence of visceral calcification[207] and mitral valve calcification[210] was reported when Ca-P product exceeded 60 and calcification was unlikely when mean Ca-P product was around 50.[209,210] It must be noted that a significant number of patients did

not develop extraskeletal calcification despite a high Ca-P product.[87,209,210]

Thus, the available evidence is limited but convincing that primary outcome (increased death rate) and secondary outcome (extraskeletal calcification) are related to Ca-P product. If this product exceeds 55, there is increased risk for development of calcification and possibly increased risk for lower patient survival. Thus, the goal level of Ca-P product should be below 55.

#### Limitations

There are no long-term epidemiological studies in patients with CKD to support the current recommendation on the "normal" blood calcium range for the CKD population, the amount of calcium supplementation, the time at which calcium supplementation should be initiated, or the type of calcium salts to be used.

The evidence that hypocalcemia is a risk factor for negative outcomes such as increased mortality, incidence of fracture and bone disease, and quality of life was not addressed in long-term studies of CKD patients, except for 1 study that followed mortality associated with chronic hypocalcemia (serum total calcium of 8.8 mg/dL [2.20 mmol/L]) for 4 years. There is no randomized, controlled trial suggesting that adequate calcium intake or calcium supplementation will improve bone mineralization, quality of life, and mortality.

Although an increased risk of mortality is associated with elevated Ca-P product, there are no data on the cause of death associated with the high Ca-P product.

#### Clinical Application

This Guideline supports the use of corrected total serum calcium in the evaluation of the derangements of calcium, phosphorus, PTH, and bone in CKD patients. It must be recognized that limited data are available with regard to adequate calcium intake in Stages 3 and 4 CKD patients, and particularly in Stage 5 CKD patients. The avoidance of excessive exposure of CKD patients to calcium while maintaining adequate intake of calcium has significant clinical implications, and effort is needed to achieve this goal. Successful implementation will require increased time of the dietitian for the guidance and support of patients in this regard.

#### Recommendation for Research

Further studies are required to find the appropriate reference range of serum calcium for different age, gender, and race in CKD patients and those treated with dialysis. Studies are needed to determine the appropriate calcium intake, the time in the course of CKD when calcium supplementation should be initiated, and the type of calcium salts to be used. Also, studies are needed to further understand the relationship between Ca-P product and morbidity and mortality.

## GUIDELINE 7. PREVENTION AND TREATMENT OF VITAMIN D INSUFFICIENCY AND VITAMIN D DEFICIENCY IN CKD PATIENTS (ALGORITHM 1)

***In CKD Patients (Stages 3 and 4):***

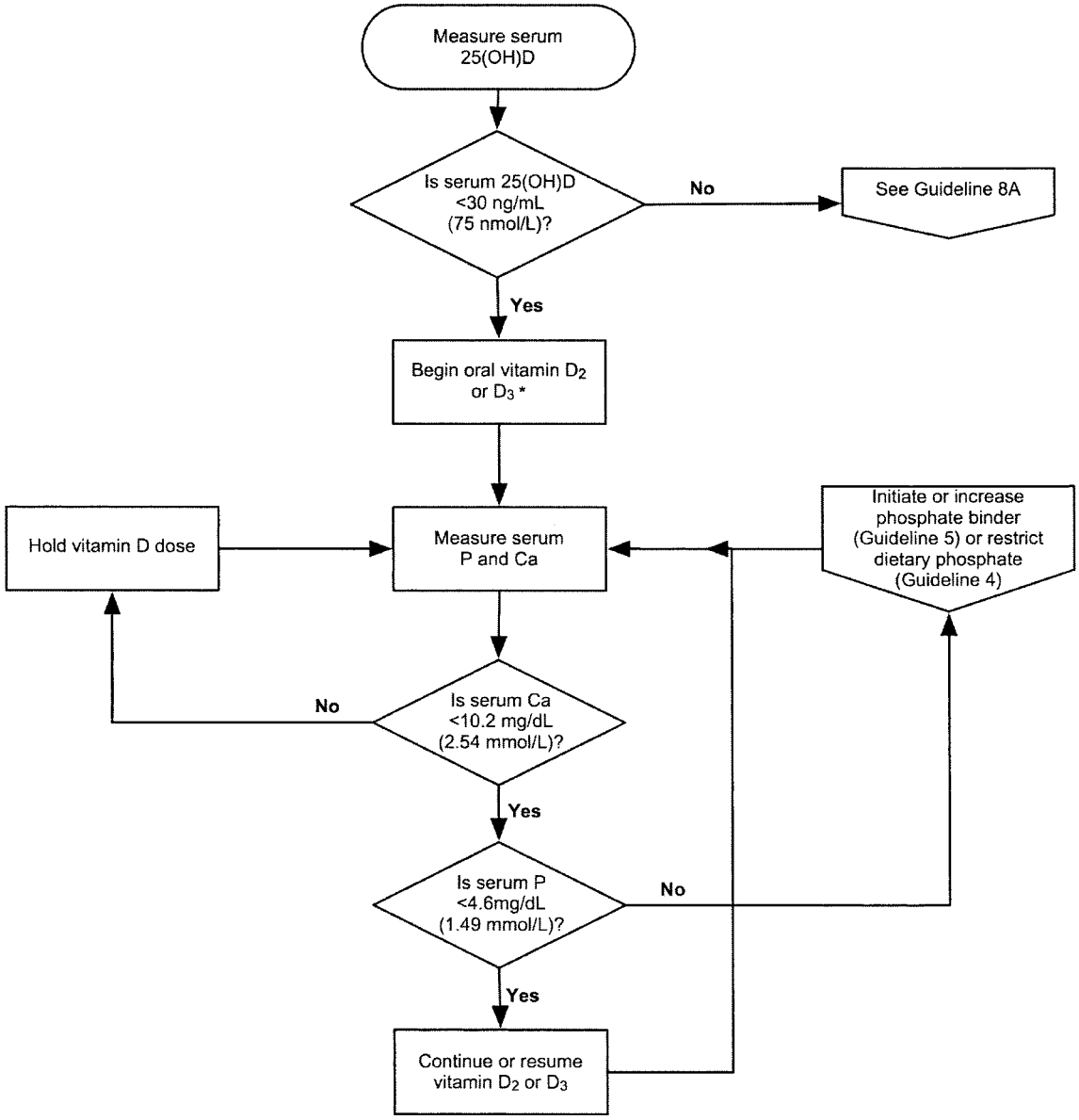
**7.1 If plasma intact PTH is above the target range for the stage of CKD (Table 15, Guideline 1) serum 25-hydroxyvitamin D should be measured at first encounter. If it is normal, repeat annually. (EVIDENCE)**

**7.2 If the serum level of 25-hydroxyvitamin D is <30 ng/mL, supplementation with vitamin $D_2$, (ergocalciferol) should be initiated (Table 26). (OPINION)**

**7.3 Following initiation of vitamin D therapy:**

- **7.3a The use of ergocalciferol therapy should be integrated with the serum calcium and phosphorus (Algorithm 1).**
- **7.3b The serum levels of corrected total calcium and phosphorus should be measured at least every 3 months. (OPINION)**
- **7.3c If the serum levels of corrected total calcium exceeds 10.2 mg/dL (2.54 mmol/L), discontinue ergocalciferol therapy and all forms of vitamin D therapy. (OPINION)**
- **7.3d If the serum phosphorus exceeds 4.6 mg/dL (1.49 mmol/L), add or increase the dose of phosphate binder. (See Guidelines 4 and 5) If hyperphosphatemia persists, discontinue vitamin D therapy. (OPINION)**

In CKD patients with serum P <4.6 mg/dL (1.99 mmol/L), serum Ca <9.5 mg/dL (2.37 mmol/L), and serum PTH in the higher level of the target range for CKD stage (Stage 3: 35-70 pg/mL [3.85-7.7 pmol/L]; Stage 4: 70-110 pg/mL [7.7-12.1 pmol/L])




* Vitamin $D_2$ (ergocalciferol) may be safer than $D_3$ (cholecalciferol). When the 25(OH)D level is <15 ng/ml (37 nmol/L), 50,000 IU weekly for 4 doses followed by monthly for 4 doses is effective. With 25(OH)D levels of 20-30 ng/mL (50-75 nmol/L), 50,000 IU monthly for 6 months is recommended

**Algorithm 1. Vitamin D supplementation in CKD (Stages 3 and 4).**

**Table 26. Recommended Supplementation for Vitamin D Deficiency/Insufficiency in Patients with CKD Stages 3 and 4**

| Serum 25(OH)D (ng/mL) [nmol/L] | Definition | Ergocalciferol Dose (Vitamin $D_2$) | Duration (months) | Comment |
|---|---|---|---|---|
| <5 [12] | Severe vitamin D deficiency | 50,000 IU/wk orally x 12 wks; then monthly | 6 months | Measure 25(OH)D levels after 6 months |
| | | 500,000 IU as single I.M. dose | | Assure patient adherence; measure 25(OH)D at 6 months |
| 5-15 [12-37] | Mild vitamin D deficiency | 50,000 IU/wk x 4 weeks, then 50,000 IU/month orally | 6 months | Measure 25(OH)D levels after 6 months |
| 16-30 [40-75] | Vitamin D insufficiency | 50,000 IU/month orally | 6 months | |

**7.3e Once patients are replete with vitamin D, continued supplementation with a vitamin-D-containing multivitamin preparation should be used with annual reassessment of serum levels of 25-hydroxyvitamin D, and the continued assessment of corrected total calcium and phosphorus every 3 months. (OPINION)**

***In CKD Patients With Kidney Failure (Stage 5):***

**7.4 Therapy with an active vitamin D sterol (calcitriol, alfacalcidol, paricalcitol, or doxercalciferol) should be provided if the plasma levels of intact PTH is >300 pg/mL (300 ng/L). (OPINION) See Guideline 8B.**

### Background

Serum levels of 25-hydroxyvitamin D (*not* the levels of 1,25-dihydroxyvitamin D) are the measure of body stores of vitamin D. In *normal* individuals over age 60, levels of 25-hydroxyvitamin D below the "normal" limit of 15 ng/mL and also low to normal levels of 16 to 32 ng/mL are *both* associated with increased PTH levels, reduced bone mineral density (BMD), and increased rates of hip fracture. Such levels of 25(OH)D are common in patients with CKD and GFR of 20 to 60 mL/min/1.73 $m^2$, and in CKD patients undergoing dialysis. The prevention and treatment of vitamin D insufficiency in patients with CKD Stages 3 and 4 most certainly reduce the frequency and severity of secondary hyperparathyroidism. In patients with more advanced CKD (Stage 5) and in dialysis patients, it is not established that nutritional "replacement" with vitamin D (ergocalciferol or cholecalciferol) will be effective since the ability to generate adequate levels of $1,25(OH)_2D_3$ is markedly reduced or is unlikely.

### Rationale

A reduction of serum 25-hydroxyvitamin D, the substrate for the kidney's generation of calcitriol [$1,25(OH)_2D_3$], produces secondary hyperparathyroidism (2°HPT) in individuals with normal kidney function,[212-214] and may aggravate 2°HPT in those with CKD and decreased kidney function.[215,216] Severe vitamin D deficiency, with osteomalacia and hypocalcemia, is rare unless 25-hydroxyvitamin D levels are <5 ng/mL (12 nmol/L); however, levels below 30 ng/mL are indications of vitamin D "insufficiency,"[217] as manifested by significant elevations of serum levels of intact PTH.[217,218] "Normal" individuals with low "normal" 25-hydroxyvitamin D levels of 16 to 32 ng/mL (40 to 80 nmol/L) have lower bone mineral density[214]; also, patients with hip fractures have lower 25(OH)D levels than age-matched patients without hip fracture.[219] The only real disagreement is the upper range of 25(OH)D levels at which one does not encounter significant numbers of patients with secondary hyperparathyroidism,[217] indicating that 25(OH)D should be maintained at higher levels.

Studies of 25-hydroxyvitamin D levels in patients with CKD and varying degrees of decreased kidney function from 4 reports were reviewed.[45,63,65,220] Among 63 non-nephrotic CKD patients, the median values of 25(OH)D levels in those with GFR of 60 to 90, 40 to 60, and 20 to

40 mL/min/1.73 $m^2$ were 12, 19, and 18 ng/mL (30, 47, and 45 nmol/L), respectively.[45] Obviously, a high fraction of these patients had levels below 30 ng/mL (75 nmol/L) and many were below 16 ng/mL (40 nmol/L). In a report of 76 CKD patients, 37 had CKD due to diabetes and 39 from other causes.[63] The 25(OH)D level averaged 22.3 ± 9.4 ng/mL (56 ± 23 nmol/L) in nondiabetics and 11.4 ± 5.6 ng/mL (28 ± 14 nmol/L) in the diabetic patients; in the diabetics, serum albumin levels were lower and 76% had urinary protein concentrations above 300 mg/dL compared to 23% of nondiabetics.[63] For the total group with GFR of 20 to 50 mL/min/1.73 $m^2$, 47% had 25(OH)D levels below 16 ng/mL (40 nmol/L) and 76% had 25(OH)D levels below 26 ng/mL (65 nmol/L). In these 2 studies,[45,63] serum $1,25(OH)_2D$ levels correlated with 25(OH)D levels [$r = 0.51$[45] and $r = 0.47$[63]], and $P < 0.001$. In the third study of the 19 CKD patients with GFR of 20 to 90 mL/min/1.73 $m^2$, 79% had 25(OH)D levels below 26 ng/mL (65 nmol/L) and 18% had 25(OH)D levels below 16 pg/mL (0.4 nmol/L). In a US study that included 9 CKD patients with GFR of 12 to 60 mL/min/1.73 $m^2$, 25(OH)D levels averaged 20 ± 6 ng/mL (50 ± 15 nmol/L) indicating that values were below 30 ng/mL (75 nmol/L) in the majority of patients. The findings that $1,25(OH)_2D$ levels correlated with 25(OH)D levels in the 2 largest series[45,63] differ from observations in the normal population, where $1,25(OH)_2D$ levels are not dependent on the 25(OH)D levels, even in patients with vitamin D deficiency.[221] The normal, highly efficient production of $1,25(OH)_2D$ by the kidneys when the supply of 25(OH)D is markedly reduced is altered in CKD, and the data indicate that $1,25(OH)_2D$ levels may be more dependent on the availability of 25(OH)D in CKD patients with impaired kidney function.

Patients with CKD or those who are dialysis-dependent are much more likely to have low levels of 25(OH)D in comparison to those with no kidney disease for several reasons:

(1) Many are inactive with reduced exposure to sunlight.

(2) The ingestion of foods that are natural sources of vitamin D (fish, cream, milk, and butter) is likely to be lower than in the normal population;

(3) Serum 25-hydroxyvitamin D levels may be subnormal in CKD patients because the endogenous synthesis of vitamin $D_3$ in the skin following identical exposure to sunlight is reduced in those with reduced GFR,[222] in individuals over age 60,[223] and in individuals with increased melanin content of the skin.[224]

The ingestion of a diet low in calcium content leads to greater conversion of 25-hydroxyvitamin D to calcitriol and the need for more vitamin D intake and/or production,[225] and dietary calcium intake is frequently low in CKD patients.[195] Furthermore, there is increased need for vitamin D in CKD patients with nephrotic-range proteinuria, because urinary losses of 25-hydroxyvitamin D and vitamin D-binding protein (DBP) are high.[220,226] Kidney disease was found to be a major risk factor for low plasma 25-hydroxyvitamin D levels in a population study of patients hospitalized in New England (with patients on dialysis excluded from the analysis).[218]

In countries such as the United States where many foods are supplemented with vitamin D, and others such as Japan and the Scandinavian countries, where fish intake is high, the incidence of vitamin D insufficiency is lower than in European countries of similar latitudes but where fish intake is low and vitamin-D-supplemented foods are unavailable.[217] Nonetheless, 14% to 42% of apparently healthy individuals, over age 60, in the United States had plasma levels of 25(OH)D below 24 or 25 ng/mL (60 or 62 nmol/L).[227,228]

In patients with kidney failure (Stage 5) and in those on dialysis, there may be less need for vitamin D as there is little or no generation of calcitriol by the kidneys. However, the data show that 25(OH)D levels below 15 ng/mL (37 nmol/L) are associated with a greater severity of secondary hyperparathyroidism even in CKD patients on dialysis.[229] Nonetheless, the value of supplementation with ergocalciferol with these patients is less certain; although in dialysis-dependent patients, including anephric individuals, high doses of ergocalciferol or 25-hydroxyvitamin D can raise the serum levels of calcitriol.[230-232]

In patients with CKD and GFR of 20 to 60 mL/min/1.73 $m^2$, nutritional vitamin D deficiency and insufficiency can both be prevented by supplementation with vitamin $D_2$ (ergocalciferol) or vitamin $D_3$ (cholecalciferol). If there is evidence of *true* vitamin D deficiency, this should be treated, and the best available treatment is vitamin $D_2$, although the doses needed are larger

than those needed for vitamin D insufficiency. For the prevention of vitamin D deficiency, the recommended daily allowance for vitamin D in individuals over 60 years is 800 IU, and for younger adults 400 IU.

There are problems with the dosage forms available. In the United States, the only forms available are 400 IU (over the counter) and capsules containing 50,000 IU, requiring a prescription. In normal individuals, the recommended upper limit of vitamin D is 2,000 IU/day according to the Food and Nutrition Board, National Research Council, National Academy of Sciences.[233,234] This dose can be achieved by giving 1 capsule (50,000 IU) once a month.[235,236] Dosage preparations of 10,000 IU of ergocalciferol have been given daily to French patients with advanced CKD for periods longer than 1 year, with no evidence of vitamin D overload or renal toxicity.[237,238] The safer vitamin D sterol may be ergocalciferol rather than cholecalciferol,[239,240] although there are no controlled comparisons of cholecalciferol and ergocalciferol in humans, and the available commercial preparations employ ergocalciferol (as Calciferol™ or Drisdol™). Calcitriol or another 1$\alpha$-hydroxylated vitamin D sterol *should not* be used to treat vitamin D deficiency. When evidence of *severe vitamin D deficiency* is found, with 25(OH)D levels $<$5 ng/mL (12 nmol/L), rickets or osteomalacia may be present; treatment can be given using ergocalciferol, 50,000 IU given weekly for 12 weeks and monthly thereafter (see Table 26).[236]

### *Strength of Evidence*

There is strong evidence that vitamin D insufficiency, defined as 25-hydroxyvitamin D levels below 27 to 32 ng/mL (67 to 80 nmol/L), is common in individuals over 60 years in the United States,[227,228] and many locations in Europe.[241] Such low levels have clinical significance based on the finding of (1) the elevated serum levels of intact PTH as evidence of secondary hyperparathyroidism; and (2) reduced BMD[214] and higher rates of hip fracture compared to age-matched controls.[242] The clinical significance of this is further demonstrated by data showing that supplementation with vitamin D, 800 IU/day, along with a modest dietary calcium supplement reduced hip fracture rate by 43% in a double-blinded, placebo-controlled trial.[241,243] There have been reports in patients with CKD that suggest there may be adverse clinical consequences of suboptimal serum levels of 25(OH)D, including the finding that 25-hydroxyvitamin D levels below 15 ng/mL pose a major risk factor for the presence of severe secondary hyperparathyroidism (with radiographic abnormalities) in CKD patients on dialysis,[229] although the dialysis dose provided to the patients in this study was suboptimal. A substantial prevalence of suboptimal levels of 25(OH)D in CKD patients with GFR of 20 to 60 mL/min/1.73 $m^2$ has been identified in every study of such patients, but the number of individuals studied has been small. Regarding safety, the experience with ergocalciferol doses of 10,000 IU/day[237,238] indicates a recommended dose of 1,000 to 2,000 IU/day would be safe.

#### Limitations

In patients with GFR $<$20 mL/min/1.73 $m^2$ and those requiring dialysis, there is no evidence that modest supplementation with ergocalciferol to raise serum 25-hydroxyvitamin D levels to 30 to 60 pg/mL (8.25 to 16.5 pmol/L) will increase the plasma levels of 1,25-dihydroxyvitamin D (calcitriol) or lower the elevated serum levels of intact PTH. In CKD patients with higher GFRs, there is a strong probability that such treatment would have benefit, although there are no data to support this view. One study demonstrated that serum $1,25(OH)_2D$ levels were increased in patients with CKD and moderate kidney failure following the administration of a low-calcium diet, indicating that there is some "reserve" for the generation of $1,25(OH)_2D$ in such patients.[244]

#### Clinical Applications

The treatment of vitamin D insufficiency or deficiency when present in CKD patients is warranted since such therapy may reduce or prevent secondary hyperparathyroidism in the early stages of CKD, and decrease the incidence of hip fractures in patients with advanced CKD and in those treated with dialysis.

#### Recommendations for Research

Prospective, controlled clinical trials with the daily administration of ergocalciferol in a monthly amount equivalent to 1,000 to 2,000 IU/day, are clearly warranted in patients with CKD and those

undergoing dialysis, to assess the effects on serum levels of intact PTH, serum $1,25(OH)_2D$ levels, and even BMD. With the higher fracture rates known to occur in patients with Stage 5 CKD,[76] studies to evaluate measures to minimize early secondary hyperparathyroidism would be warranted.

## GUIDELINE 8. VITAMIN D THERAPY IN CKD PATIENTS

**This Guideline encompasses 2 parts: Guideline 8A, which deals with active vitamin D sterol therapy in CKD Stages 3 and 4, and Guideline 8B, which deals with CKD Stage 5.**

## GUIDELINE 8A. ACTIVE VITAMIN D THERAPY IN PATIENTS WITH STAGES 3 AND 4 CKD (ALGORITHM 2)

**8A.1 In patients with CKD Stages 3 and 4, therapy with an active oral vitamin D sterol (calcitriol, alfacalcidol, or doxercalciferol) is indicated when serum levels of 25(OH)-vitamin D are >30 ng/mL, and plasma levels of intact PTH are above the target range for the CKD stage (see Table 15, Guideline 1). (EVIDENCE) Initial doses are provided in Table 27.**

**8A.1a Treatment with an active vitamin D sterol should be undertaken only in patients with serum levels of corrected total calcium <9.5 mg/dL and serum phosphorus <4.6 mg/dL. (OPINION)**

**8A.1b Vitamin D sterols should not be prescribed for patients with rapidly worsening kidney function or those who are noncompliant with medications or follow-up. (OPINION)**

**8A.2 During therapy with vitamin D sterols, serum levels of calcium and phosphorus should be monitored at least every month after initiation of therapy for the first 3 months, then every 3 months thereafter. Plasma PTH levels should be measured at least every 3 months for 6 months, and every 3 months thereafter. (OPINION)**

**8A.3 Dosage adjustments for patients receiving active vitamin D sterol therapy should be made as follows:**

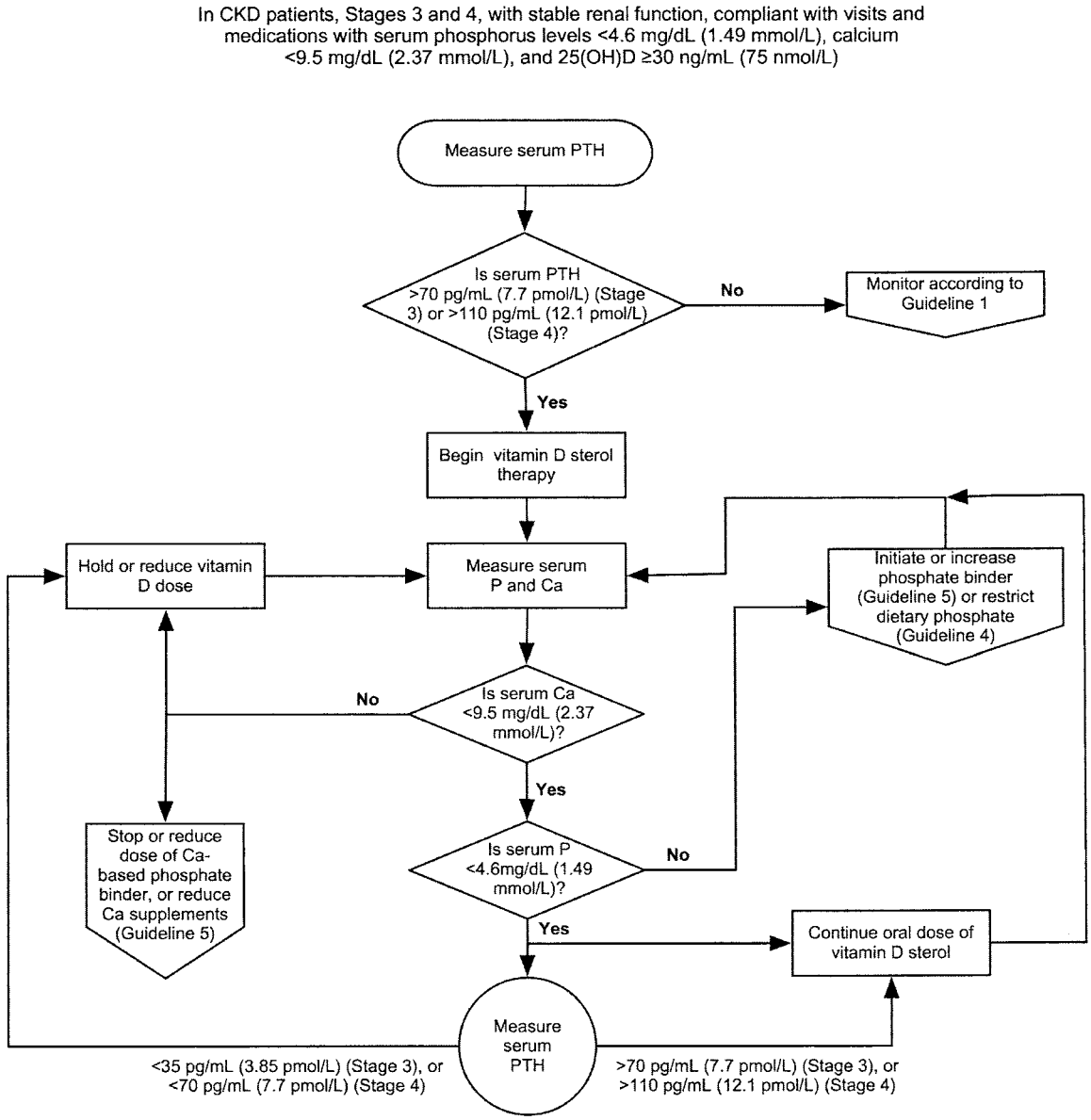
**8A.3a If plasma levels of intact PTH fall below the target range for the CKD stage (Table 15, Guideline 1), hold active vitamin D sterol therapy until plasma levels of intact PTH rise to above the target range, then resume treatment with the dose of active vitamin D sterol reduced by half. If the lowest daily dose of the active vitamin D sterol is being used, reduce to alternate-day dosing. (OPINION)**

**8A.3b If serum levels of corrected total calcium exceed 9.5 mg/dL (2.37 mmol/L), hold active vitamin D sterol therapy until serum calcium returns to <9.5 mg/dL (2.37 mmol/L), then resume treatment at half the previous dose. If the lowest daily dose of the active vitamin D sterol is being used, reduce to alternate-day dosing. (OPINION)**

**8A.3c If serum levels of phosphorus rise to >4.6 mg/dL (1.49 mmol/L), hold active vitamin D therapy, initiate or increase dose of phosphate binder until the levels of serum phosphorus fall to ≤4.6 mg/dL (1.49 mmol/L); then resume the prior dose of active vitamin D sterol. (OPINION)**

### Background

In CKD patients with GFR below 60 mL/min/1.73 $m^2$ (Stage 3), secondary hyperparathyroidism with elevated PTH levels is common and bone biopsies disclose hyperparathyroid bone disease in a large fraction of patients. The administration of small doses of the active vitamin D sterols, calcitriol and alfacalcidol, reduce the serum levels of intact PTH, improve bone histology, and lead to increased bone mineral density (BMD). With the use of low dosages, these effects occur with no evidence of worsening of kidney function; however, *careful monitoring of serum levels of calcium, phosphorus and intact PTH is essential.*




Oral active vitamin D sterols available include calcitriol, alfacalcidol, and doxercalciferol; calcitriol (USA, Canada) and alfacalcidol (Canada and Europe) are approved for use in CKD, Stages 3 and 4. Initial doses should be low (calcitriol 0.25 µg/day or alfacalcidol, 0.25 µg/day). The dose of calcitriol should rarely exceed 0.5 µg/day and then only if the corrected levels of calcium increase by less than 0.2-0.3 mg/dL.

**Algorithm 2. Management of CKD patients (Stages 3 and 4) with active Vitamin D sterols.**

### Rationale

In CKD patients with GFR <60 mL/min/1.73 $m^2$ (Stage 3), there is the appearance of secondary hyperparathyroidism with elevated serum levels of intact PTH.[46,64,244,245] In such patients, bone biopsies show histomorphometric features of hyperparathyroid bone disease despite only modest elevations of intact PTH.[19,246-248] Plasma levels of $1,25(OH)_2D_3$ are either normal or in the lower range of normal,[46,64,244,245] despite the elevated intact PTH levels and serum levels of phosphorus that are often in the low range of

**Table 27. Serum Levels of PTH, Calcium and Phosphate Required for Initiation of Oral Vitamin D Sterol Therapy, and Recommended Initial Doses in Patients with Stages 3 and 4 CKD**

| Plasma PTH pg/mL or [pmol/L] | Serum Ca mg/dL [mmol/L] | Serum P mg/dL [mmol/L] | Dose Oral Calcitriol | Dose Oral Alfacalcidol | Dose Oral Doxercalciferol |
|---|---|---|---|---|---|
| >70 [7.7] (CKD Stage 3) Or >110 [ 12.1] (CKD Stage 4) | <9.5 [2.37] | <4.6 [1.49] | 0.25 μg/day | 0.25 μg/day | 2.5 μg 3x/week |

normal.[10,188,249] Normal $1,25(OH)_2D_3$ levels in the face of high levels of PTH are inappropriate and thus contribute to defective feedback suppression by $1,25(OH)_2D_3$ of pre-PTH synthesis in the parathyroid glands with a resultant increased secretion of PTH.[250]

In controlled trials in patients with Stage 3 CKD, the administration of oral calcitriol, 0.25 μg/day and occasionally up to 0.5 μg/daily,[246,251] or of alfacalcidol, 0.25 to 0.5 μg daily[19] were associated with lowering of intact PTH levels,[248,251] improvement of histological features of hyperparathyroid bone disease,[246-248,252] or an increase of bone mineral density.[251] Preliminary evidence also suggests that patients who had calcitriol therapy initiated when the creatinine clearance exceeded 30 mL/min/1.73 $m^2$ (0.50 nmol/L/min/1.73 $m^2$) had normal bone histology when they finally reached Stage 5 CKD and received a kidney transplant, while those whose treatment was started when kidney failure was more advanced were less likely to have normal bone histology when they reached end-stage kidney disease.[253]

There has been concern about the safety of the use of these vitamin D metabolites with regard to a possible adverse effect on kidney function. With the use of calcitriol in doses of 0.25 μg/day or less and doses of alfacalcidol that were generally below 0.5 μg/day, the progressive loss of kidney function did not differ from observations in placebo-treated or control patients.[19,246,248,252,254] In all CKD patients receiving vitamin D therapy, continued surveillance is needed, and hypercalcemia must be avoided. When calcitriol was given in doses of 0.5 μg/day or higher, reductions of creatinine clearance have been observed,[255,256] although it is not certain that true GFR (inulin clearance) was affected.[256,257] In CKD patients with serum levels of phosphorus >4.6 mg/dL (1.49 mmol/L), dietary phosphorus restriction and/or phosphate binders should be employed and the serum phosphorus normalized before initiation of treatment with an active vitamin D sterol.

***Strength of Evidence***

Each of the placebo-controlled trials of CKD patients with GFR of 20 to 60 mL/min/1.73 $m^2$[19,246,252] and 2 studies without a placebo-control group[247,248] have shown evidence of hyperparathyroid bone disease in a high fraction of baseline "control" bone biopsies. Also, these abnormalities were common in the CKD patients recruited *only* on the basis of their impaired kidney function (reduced GFR or elevated serum creatinine levels) with the degree of elevation of pretreatment levels of intact PTH totally unknown.[19,246,251,252] In each of the placebo-controlled trials, there was either no improvement or worsening[19,246,252] of the features of hyperparathyroid bone disease in patients assigned to placebo therapy. Following treatment for 8, 12, or 24 months, an improvement of bone biopsy features was noted in the vitamin D-treated patients.[19,246,247,252] Meta-analysis could not be done for these studies because 1 reported their data as mean ± SD,[247] 1 reported medians and ranges,[246] and another reported the fractions of patients who showed improvement or worsening of various histological features on bone biopsy.[19] Another study was excluded because the number of subjects was too small ($n < 10$).[252]

The safety of calcitriol or alfacalcidol in CKD with moderately reduced kidney function is a matter of concern; however, the data from the placebo-controlled studies show no reduction of kidney function compared to placebo in patients

**Table 28. Recommended Initial Dosing for Vitamin D Sterols by Serum Levels of Intact PTH, Calcium, Phosphorus, and Ca-P Product**

| Plasma PTH pg/mL or [pmol/L] | Serum Ca mg/dL [mmol/L] | Serum P mg/dL [mmol/L] | Ca-P Product | Dose per HD Calcitriol†* | Dose per HD Paricalcitol* | Dose per HD Doxercalciferol†* |
|---|---|---|---|---|---|---|
| 300-600 [33-66] | <9.5 [2.37] | <5.5 [1.78] | <55 | IV: 0.5-1.5 μg Oral: 0.5-1.5 μg | 2.5-5.0 μg | Oral: 5 μg IV: 2 μg |
| 600-1000 [66-110] | <9.5 [2.37] | <5.5 [1.78] | <55 | IV: 1.0-3.0 μg Oral: 1-4 μg | 6.0-10 μg | Oral: 5-10 μg IV: 2-4 μg |
| >1000 [110] | <10.0 [2.50] | <5.5 [1.78] | <55 | IV: 3.0-5.0 μg Oral: 3-7 μg | 10-15 μg | Oral: 10-20 μg IV: 4-8 μg |

*Intravenous; † Oral

entered into these trials and using relatively low doses.[19,246,247,251,252] Should hypercalcemia develop during vitamin D treatment, particularly with higher doses, transient or even long-lasting deterioration of kidney function has been observed.[258-260] With regard to the risk of producing "adynamic bone," the placebo-controlled trial that included the largest number of bone biopsies failed to show any increase in the appearance of adynamic bone disease following treatment with alfacalcidol.[19]

#### Limitations

The available evidence is obtained from short-term studies and on a relatively small number of patients. Also, no data are available on the effect of the new vitamin D analogs, which are less hypercalcemic.

#### Clinical Application

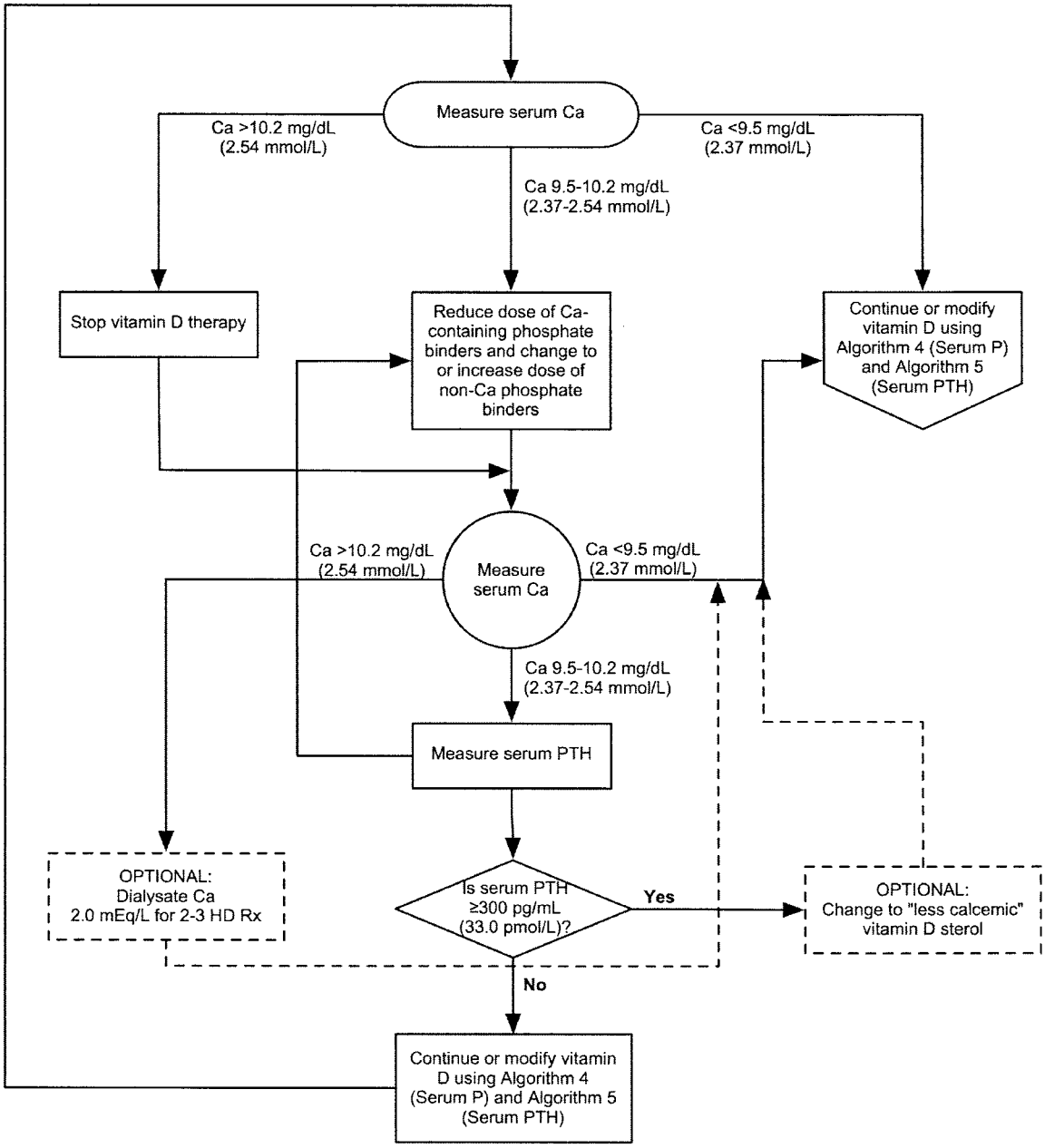
It appears that the active vitamin D sterols are useful in the treatment of secondary hyperparathyroidism and high-turnover bone disease in early stages of CKD. This provides a good therapeutic tool for the prevention and management of these 2 abnormalities in CKD patients, before these derangements advance and their treatment becomes more difficult.

#### Recommendations for Research

Further trials with longer-term treatment (24 months or longer) in larger numbers of patients are needed to satisfy the concern about the safety of the therapy with vitamin D sterols. *Trials with the newer vitamin D sterols which may be less calcemic will be of great interest.* An ideal goal of such treatment would be to reduce serum levels of intact PTH with little or no change in serum levels of calcium. Studies should evaluate the effect on bone, in particular to ascertain whether improvement in bone mineral content or in histological features of hyperparathyroid bone disease could be achieved. Investigational Review Boards may feel that it is inappropriate to withhold vitamin D therapy in placebo-controlled studies. However, comparisons of newer vitamin D sterols with calcitriol, alfacalcidol, or even ergocalciferol, at 50,000 IU monthly, would be ideal. It is apparent that the ideal target for serum levels of intact PTH that should be sought are not established, and biopsy evaluations in such trials with correlations between intact PTH or whole PTH levels with new assays of PTH (see discussion in Guidelines 1 and 2) and skeletal findings would be ideal. Also, in the trials that have been published,[19,248] it would be useful if the data were reanalyzed to evaluate the relationship between serum levels of intact PTH and the degree of parathyroid bone disease found on biopsy in relation to the degree of impairment of kidney function.

## GUIDELINE 8B. VITAMIN D THERAPY IN PATIENTS ON DIALYSIS (CKD STAGE 5)

**8B.1 Patients treated with hemodialysis or peritoneal dialysis with serum levels of intact PTH levels >300 pg/mL (33.0 pmol/L) should receive an active vitamin D sterol (such as calcitriol, alfacalcidol, paricalcitol, or doxercalciferol; see Table 28) to reduce the serum levels of PTH to a target range of 150 to 300 pg/mL (16.5 to 33.0 pmol/L).**



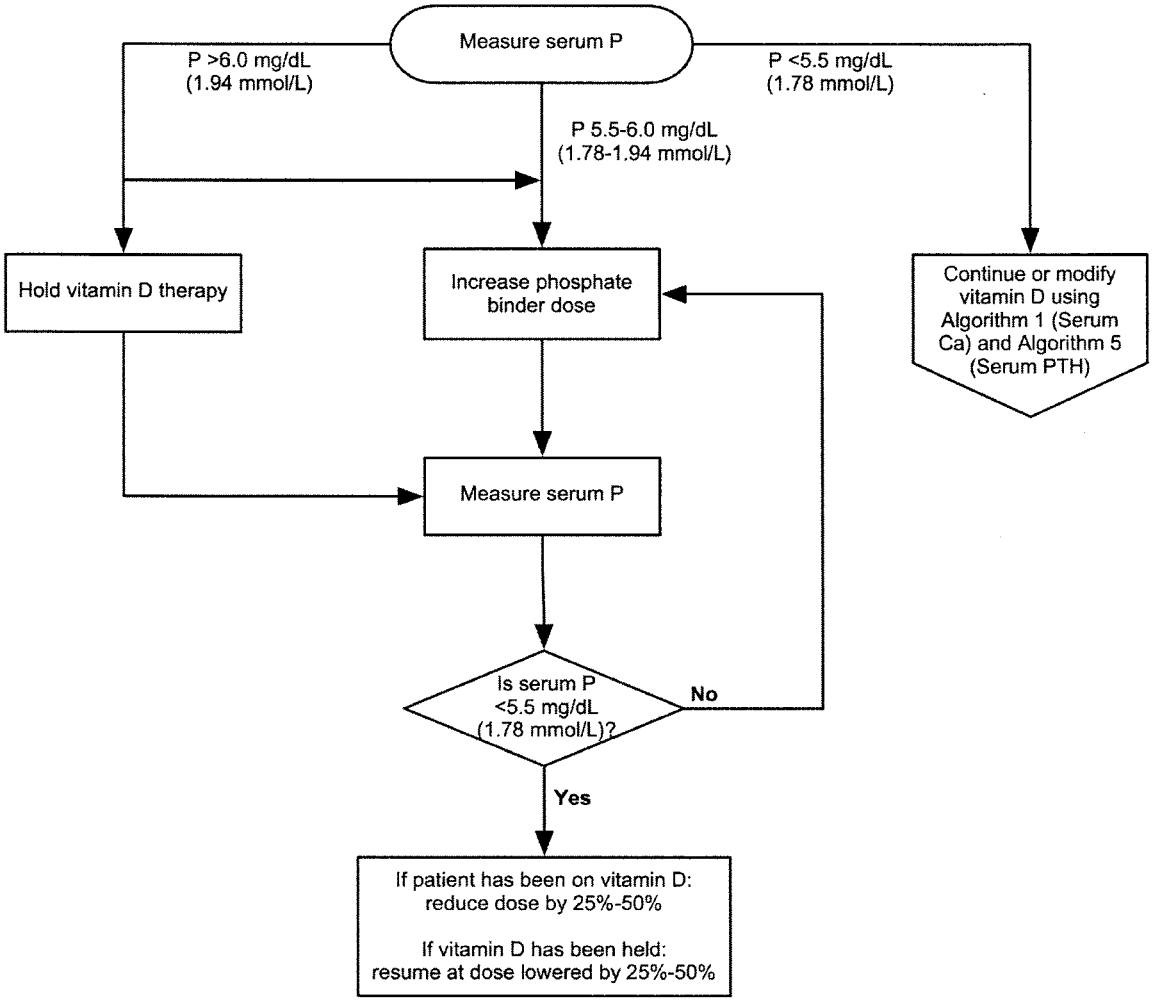

**Algorithm 3. Managing Vitamin D sterols based on serum calcium levels.**

**(EVIDENCE)**

**8B.1a The intermittent, intravenous administration of calcitriol is more effective than daily oral calcitriol in lowering serum PTH levels. (EVIDENCE)**

**8B.1b In patients with corrected serum calcium and/or phosphorus levels above the target range (see Guidelines 3 and 6, respectively), a trial of alternative vitamin D analogs, such as paricalcitol or doxercalciferol may be warranted. (OPINION)**

**8B.2 When therapy with vitamin D sterols**




**Algorithm 4. Managing Vitamin D sterols based on serum phosphorus levels.**

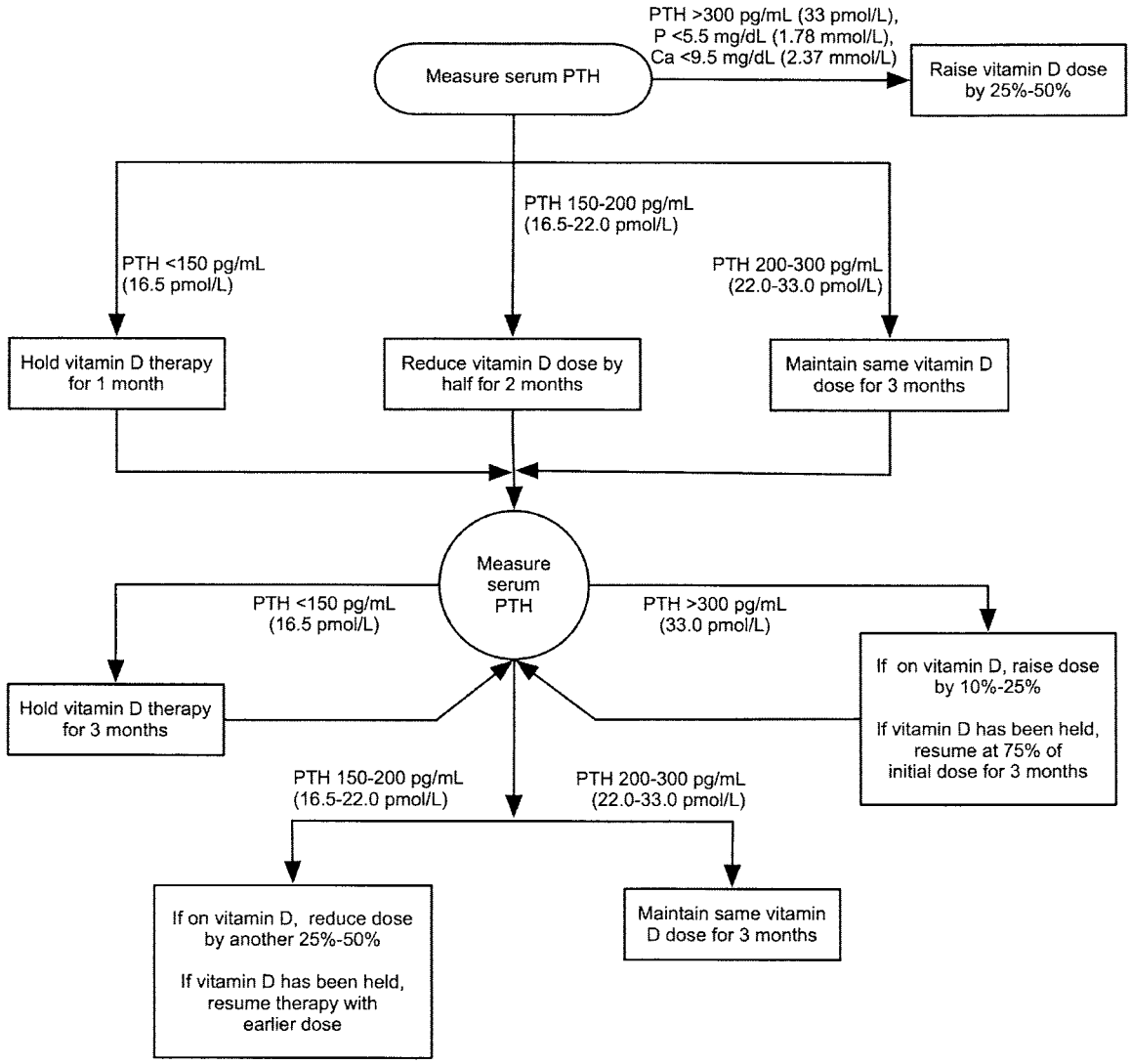
**is initiated or the dose is increased, serum levels of calcium and phosphorus should be monitored at least every 2 weeks for 1 month and then monthly thereafter. The plasma PTH should be measured monthly for at least 3 months and then every 3 months once target levels of PTH are achieved. (OPINION)**

**8B.3 For patients treated with peritoneal dialysis, oral doses of calcitriol (0.5 to 1.0 μg) or doxercalciferol (2.5 to 5.0 μg) can be given 2 or 3 times weekly. Alternatively, a lower dose of calcitriol (0.25 μg) can be administered daily. (OPINION)**

**8B.4 When either hemodialysis or peritoneal dialysis patients are treated with active vitamin D sterols, management should integrate the changes in serum calcium, serum phosphorus, and plasma PTH. Each of these three variables is considered separately with suggested interventions based on the various values obtained in Algorithm 3, Algorithm 4, and Algorithm 5. (OPINION)**

### Background

Patients with CKD who undergo dialysis have reduced plasma levels of $1,25(OH)_2D_3$. This leads to reduced intestinal absorption of calcium (thereby contributing to hypocalcemia) and impaired suppression of the parathyroid gene that




When intact serum PTH is between 300-500 pg/mL (33.0-55.0 pmol/L) and changes on two successive determinations are small (<25%), there is no need to modify vitamin D dose as long as P and Ca are within the desired limits (see Algorithms 3 and 4).

When intact PTH is persistently >500-800 pg/mL (55.0-88.0 pmol ng/L) and P is 5.5-6.5 mg/dL (1.78-1.94 mmol/L) and/or Ca is 10.2-10.5 mg/dL (2.54-2.62 mmol/L), a trial with a "less calcemic" analog may be warranted for 3-5 months; if such a patient fails to respond, parathyroidectomy may be required.

**Algorithm 5. Managing Vitamin D sterols based on intact PTH levels.**

initiates the synthesis of PTH. The result is secondary hyperparathyroidism that often progresses. Treatment with calcitriol or another active vitamin D sterol both reduces PTH secretion with resultant improvement of hyperparathyroid bone disease, and improves musculoskeletal symptoms, when these are present.

A major side-effect of vitamin D treatment is increased intestinal absorption of calcium and phosphorus; this can produce hypercalcemia and

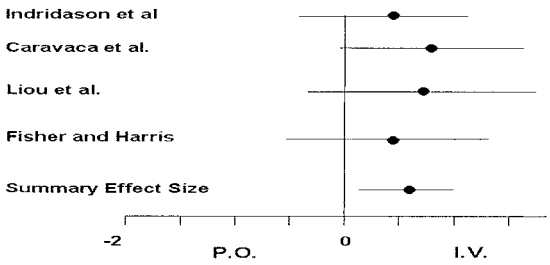



**Fig 12. Meta-analysis of oral versus intravenous calcitriol on PTH suppression.**

aggravate hyperphosphatemia. Treatment with active vitamin D sterols can also markedly lower serum levels of intact PTH and reduce bone formation strikingly; this can produce a condition with low bone turnover, termed *adynamic bone disease*. For these reasons, serum levels of calcium and phosphorus, and those of intact PTH, *must be monitored* during vitamin D therapy, and vitamin D therapy adjusted accordingly (Algorithm 3, Algorithm 4, and Algorithm 5).

### Rationale

Treatment of secondary hyperparathyroidism in end-stage kidney disease patients with oral or intravenous calcitriol, intravenous paricalcitol, oral or intravenous doxercalciferol, or oral or intravenous alfacalcidol can reduce the elevated levels of intact PTH,[11,261-270] and may be useful to treat various clinical features of symptomatic secondary hyperparathyroidism.[261,263,266] With such treatment, improved features of hyperparathyroid bone disease have been reported.[262,263,271,272] Reductions of both plasma total alkaline phosphatase and/or bone-specific alkaline phosphatase, consistent with a reduction of the elevated bone turnover state, have been shown during treatment with several of these vitamin D preparations.[11,262-264,266,271,273]

### *Strength of Evidence*

In dialysis patients who have not received vitamin D, or those who have received daily oral calcitriol in doses lower than 0.5 $\mu$g/day, serum levels of intact PTH correlate with the degree of secondary hyperparathyroidism[33,34,274]; moreover, patients with intact PTH levels $<$400 pg/mL (44.0 pmol/L) and normal (or low) serum levels of calcium, usually have only mild hyperparathyroidism.[33,274] In these patients, the optimal control of serum phosphorus levels, combined with the use of calcium-based phosphate binders, may result in no further rise of serum PTH levels. When serum levels of intact PTH exceed 500 to 600 pg/mL (55.0 to 66.0 pmol/L), moderate or even severe hyperparathyroid bone disease is usual. When intact PTH levels exceed 1,000 pg/mL (110.0 pmol/L), larger doses of the vitamin D sterols are generally required.[269,275-278] During treatment with intravenous calcitriol[275] or oral doxercalciferol[269] in prospective trials, there is evidence that larger doses are required for the treatment of patients with severe secondary hyperparathyroidism compared to patients with less severe hyperparathyroidism. Moreover, the suppression of serum levels of intact PTH in patients with severe hyperparathyroidism may require treatment for longer periods of time, eg, more than 12 to 24 weeks.[269,275-277] The reason for the delayed response of some patients is unclear; it might be related to upregulation of vitamin D receptors that are often reduced in the large nodular parathyroid glands in end-stage kidney disease patients with more severe secondary hyperparathyroidism.[279]

It is recommended that the dosage of a vitamin D sterol be adjusted in accordance with the severity of secondary hyperparathyroidism. The evidence that intact PTH levels correlate with the severity of bone disease in patients who have not received pulse-dose intravenous or oral calcitriol is quite good.[33,34] However, the optimal doses of vitamin D sterols and the optimal serum levels of intact PTH that should be the target in patients who have received such therapy for longer than 6 to 12 months is less certain.

Several trials that were not placebo-controlled have shown the effectiveness of intermittent intravenous and intermittent oral calcitriol to suppress serum levels of intact PTH in patients undergoing hemodialysis,[15,280] including some patients with severe hyperparathyroidism[280-283]; moreover, these results appeared more favorable than earlier experiences with daily oral dosing when reductions of dosage were commonly needed.[284,285] However, the meta-analysis of four trials that compared intermittent intravenous calcitriol with oral calcitriol in randomized, controlled studies[286,287] or cross-over trials[288,289] indicated that intravenous therapy was more effective

than oral treatment (either daily or "pulse" treatment) for the suppression of intact PTH levels (Fig 12). However, there are certain qualifications about the trials combined for this meta-analysis: Two trials compared daily oral treatment with thrice weekly intravenous treatment[287,289]; in the trial that studied patients with the highest pretreatment intact PTH levels, the oral "group" was a combination of one group randomly assigned to intermittent treatment and a second group assigned to daily therapy.[290] The degree of hyperparathyroidism was very mild in 2 trials, as the entry intact PTH levels averaged less than 400 pg/mL (44.0 pmol/L).[287,288] In 2 trials that prospectively compared intermittent oral and intravenous calcitriol in patients with more severe hyperparathyroidism,[291,292] the numbers of patients completing the study was too small ($n < 10$) to meet the criteria for the meta-analysis. In patients with more severe hyperparathyroidism (trials with intravenous calcitriol that adjusted the dosage upward if PTH levels were not suppressed), the use of calcitriol doses below 0.75 to 1.0 $\mu$g per treatment were often less effective in lowering intact PTH levels.[275,293] Moreover, the earlier placebo-controlled trials with daily oral calcitriol found that patients could rarely tolerate daily doses of 0.5 $\mu$g per day without developing hypercalcemia.[284,285]

The results of oral trials with calcitriol that were not placebo-controlled lead to the conclusion that pulse or intermittent therapy yielded better results than were reported with daily therapy; meta-analysis of the results of 3 randomized, controlled trials that compared daily oral with intermittent oral calcitriol failed to show any superiority of intermittent therapy over daily therapy.[265,290,294] Two of these studies[265,294] had patients with only mild hyperparathyroidism, and few patients entered into treatment with intact PTH levels above 600 pg/mL (66.0 pmol/L). Despite randomization of treatment in one study,[294] each of the 5 patients having pretreatment intact PTH levels above 600 pg/mL (66.0 pmol/L) were assigned to intermittent therapy. In another study,[290] the trial with the highest pretreatment intact PTH levels, the serum calcium levels were higher with daily than with intermittent therapy. Thus, conclusions about there being no difference depending on the frequency of dosing must be viewed with caution.

The major side effects of active vitamin D sterols, including calcitriol and alfacalcidol, are increases in the serum levels of calcium and phosphorus leading to hypercalcemia and worsening of hyperphosphatemia. These concerns have led to efforts to develop analogs of vitamin D which might have less calcemic and/or phosphatemic effects, while retaining efficacy for the suppression of high levels of PTH.[295,296] Several such analogs are now in clinical use. Paricalcitol and doxercalciferol are available in the United States, and maxicalcitol and falecalcitol are available in Asia.[11,270,297,298] Extensive data in normal animals and in experimental animals with uremia have demonstrated that maxicalcitol and paricalcitol are less calcemic and phosphatemic than calcitriol and yet retain effectiveness in suppressing PTH.[299-301] Studies in vitamin D-deficient animals with doxercalciferol have demonstrated no difference in calcium or phosphorus absorption from the intestine and in changes in serum calcium compared to alfacalcidol, but doxercalciferol was associated with a decreased mortality in toxicology studies.[302,303] Additional studies have shown that doxercalciferol is associated with less calciuria than alfacalcidol.[304,305] Definitive quantitative data comparing these vitamin D sterols to calcitriol or to each other in controlled clinical trials are not available at the present time.

In placebo-controlled trials with calcitriol, alfacalcidol, paricalcitol, and doxercalciferol, there were increments of serum phosphorus during treatment,[11,269,306-309] and analysis indicated no difference between the sterols regarding their effects on raising serum levels of phosphorus. Treatment with vitamin D should not be undertaken or continued if serum phosphorus levels exceed 6.5 mg/dL, because of this risk of further elevating serum phosphorus levels.

Another side-effect of intermittent treatment with an active vitamin D sterol is the appearance of subnormal bone formation, with "adynamic" or "aplastic" bone.[62,310] In end-stage kidney disease patients who had not received pulse doses of calcitriol and had intact PTH levels below 150 pg/mL (16.5 pmol/L), there was a high incidence of subnormal bone formation on bone biopsy, with "adynamic" or "aplastic" bone.[33] When

intact PTH levels are below 65 pg/mL (7.15 pmol/L), the occurrence of adynamic bone is nearly universal.[26,33] Mild hyperparathyroid bone disease may be preferable to adynamic bone because of the loss of the capacity of bone buffering for the added extracellular calcium;[174] this likely accounts for the increased risk of hypercalcemia in patients with adynamic bone.[14,62] Also, there may be increased risk of vascular calcification in patients with biochemical features that are consistent with adynamic bone.[91] In adolescents and young adults with end-stage kidney disease, adynamic bone[310] and even reduced linear growth occurred in association with intermittent calcitriol therapy when the intact PTH levels were reduced below 400 to 450 pg/mL (44.0 to 49.5 pmol/L).[311] Reported observations of the development of adynamic bone in adult end-stage kidney disease patients in association with pulse therapy with calcitriol are limited to a small number[312]; however, there is little reason to believe that the bone of adults would not show the effects observed in pediatric-age patients.

When one elects to observe dialysis patients with intact PTH levels $<$600 pg/mL (66.0 pmol/L) without initiating vitamin D therapy, serial intact PTH levels should be monitored. If the levels show a progressive rise, treatment should be initiated.

### Limitations

Many of the studies cited above with calcitriol and alfacalcidol that originated before 1980 lacked parallel control groups,[261-264,266,271,272,313-315] and the assays for PTH were variable and some involved PTH fragments[261-264,266] that are cleared by the kidney; thus, comparison with the current trials that utilize so-called "intact PTH" is not possible. Also, many patients in the early trials had "severe" and symptomatic bone disease, findings that have become more rare with better control of secondary hyperparathyroidism. With studies of the "newer" vitamin D sterols, such as falecalcitriol, paricalcitol, and doxercalciferol, there were often parallel controls.[11,268,269,298] However, the severity of secondary hyperparathyroidism was mild to moderate, based on pretreatment serum levels of intact PTH, in most patients entered into trials with falecalcitriol[268,298] or paricalcitol.[11] For these reasons, comparison of data with the different vitamin D sterols must be regarded as tentative, particularly for patients with severe secondary hyperparathyroidism, defined as serum levels of intact PTH $>$1,200 pg/mL (132.0 pmol/L). Also, it is almost certain that such patients would be considered inappropriate for a long-term, placebo-controlled trial.

The conclusions that pulse intravenous therapy is better then pulse oral treatment must also be regarded as tentative; similarly, the conclusions that daily oral therapy is as effective as pulse oral therapy given 2 or 3 times a week may only apply to patients with mild secondary hyperparathyroidism for the reasons noted above.

### Clinical Applications

Secondary hyperparathyroidism and hyperparathyroid high-turnover bone disease in CKD are treatable abnormalities with active vitamin D sterols. There are many of these sterols available and others are being developed. Since one of the side-effects of the therapy with these sterols is hypercalcemia, one would want to use a sterol effective in treatment of the bone disorder with less or no hypercalcemia.

### Recommendations for Research

Trials that compare different vitamin D sterols in patients with end-stage kidney disease are needed. Also, prospective trials are needed to evaluate the effect of pulse-dose calcitriol or other vitamin D sterol on bone, with study of the relationship between serum levels of intact PTH and bone turnover using double tetracycline, to assess a possibly important side-effect of vitamin D treatment. Moreover, little is known about the ideal target for serum levels of intact PTH during treatment with vitamin D. It is possible that the incidence of adynamic bone will increase substantially if vitamin D sterols are employed in patients who have only modest elevations of intact PTH levels. Studies are needed to examine the value of bone markers and to assess the relationship between the so-called "whole PTH molecule," "intact PTH," and bone histomorphometry during vitamin D treatment. Large studies that evaluate fracture rates should include data on previous vitamin D therapy in an effort to identify whether vitamin D treatment can modify the high incidence of fractures noted in end-stage kidney disease patients.

## GUIDELINE 9. DIALYSATE CALCIUM CONCENTRATIONS

**9.1 The dialysate calcium concentration in hemodialysis or peritoneal dialysis should be 2.5 meq/L (1.25 mmol/L). (OPINION)**

**9.2 Higher or lower dialysate calcium levels are indicated in selected patients. (See Clinical Applications.) (OPINION)**

### Background

The proposed dialysate calcium concentration appears most compatible with current clinical knowledge, the clinical necessity of vitamin D use, and the use of calcium-based phosphate binders. Such a dialysate calcium concentration will permit use of these agents with much less risk of calcium loading and hypercalcemia. With this level of calcium in dialysate, little or no calcium transfer occurs into the patient. When there is a need to remove calcium from the patient, a lower dialysate level will be appropriate. In patients in whom calcium supply is needed, calcium transfer into the patient may be achieved safely with dialysate levels up to 3.5 mEq/L.

### Rationale

The constituents of the dialysate have evolved over time in a generally logical fashion. Concentrations of the major electrolytes and acid/base components have been determined by studies directed at specific outcome measures. The reasons for the values selected have been defined and understood. The dialysate calcium concentration, on the other hand, has not been amenable to delineation or study. The problem has been to balance the dialysate calcium with the needs for control of other aspects of calcium pathophysiology in dialysis patients. It has not been possible to designate an optimal dialysate calcium concentration and it will not be possible until other aspects of the abnormal calcium metabolism in these patients are defined and stabilized. When these other aspects are clarified, studies can then be conducted to define and recommend the optimal dialysate calcium concentration.

The current dialysate calcium level has been arrived at over time, in conjunction with the evolution of other aspects of calcium metabolism in this population. In the 1960s, when dialysis was introduced, the constituents of the dialysate were arbitrarily determined to best match normal serum levels. Thus, ionized calcium levels were initially chosen at around 1.25 mmol/L to match the normal serum level. Because of impaired calcium absorption with resultant hypocalcemia, it soon became apparent that higher levels of dialysate calcium could be used to support the serum calcium level. Early studies of parathyroid hormone in the late 1960s showed that these higher dialysate calcium levels of 3.5 mEq/L (1.75 mmol/L) were also associated with lower parathyroid hormone levels.[316]

Another important and relevant development in the 1960s was the universal acceptance of aluminum compounds as the predominant phosphate binders. Aluminum was selected because it was “not absorbed” (actually, absorption was not detectable by the technology of that era) and seemed preferable to magnesium and calcium for a variety of reasons.[317]

In the 1970s, calcitriol was identified and synthesized, and it became available as a therapeutic agent. With its direct effect on gut absorption of calcium, the problems of hypocalcemia were ameliorated and the need for calcium loading via the dialysate were lessened. However, the traditional high calcium dialysate continued in most practices, with the goal being to maintain a high normal serum calcium using both dialysate and calcitriol in order to maximize PTH suppression. Phosphate control was achievable in most patients with the aluminum compounds, which we now know also directly inhibited PTH production and secretion.[318]

In the early 1980s, it became apparent that not only was aluminum absorbed from the gastrointestinal tract, but that it was also quite toxic.[319] Initially, aluminum toxicity was treated with deferoxamine, the iron-chelating agent. However, it quickly became apparent that deferoxamine caused infections with siderophilic organisms, particularly mucormycosis, which had an extraordinarily high mortality rate.[320] In the later 1980s, aluminum-based phosphate binders were gradually replaced by calcium-based phosphate binders and it was soon demonstrated that hypercalcemia occurred at a high rate, as a result of the combination of calcium-based phosphate binders, high calcium dialysate, and calcitriol use. In response to this marked increase in gut calcium

absorption from both the high oral calcium intake and the potent vitamin D metabolite, calcitriol, lower calcium dialysates began to be introduced. Other attempts to resolve this issue led to the use of intravenous, bolus dosing with calcitriol (which had much less effect on gut absorption than oral treatment) and lower calcium dialysates, generally 1.25 mmol/L, became the norm.[321]

With the concerns about aluminum and calcium, the pursuit of better phosphate binders has been a focus of research in the 1990s. Several are being studied and one, sevelamer HCl, has been released.[322] While these newer phosphate binders vary considerably in chemical characteristics, they do not contain calcium, magnesium, or aluminum and are, therefore, likely not to impact dialysis calcium concentrations directly. While they all appear safe, patient acceptability and effectiveness remain to be demonstrated.

While these historical developments in calcium/phosphate/PTH management were occurring, the bone disease that resulted was also evolving. In the first 25 years (until about 1985) the overriding concern was the suppression and prevention of bone disorders due to hyperparathyroidism. In the last 15 years, the appearance of adynamic bone disease, associated with low PTH, has been increasingly apparent and this is now the predominant form of osteodystrophy.[14] Speculation as to the cause of this lesion focuses on oversuppression of PTH due to calcium loading and/or the use of more potent vitamin D metabolites. In conjunction with this, the problem of metastatic calcification, especially vascular calcification, has assumed increasing importance and is clearly associated with both positive calcium and phosphate balance.[87,92]

Thus, the choice of dialysate calcium concentration has been determined largely by other aspects of calcium metabolism over the first 40 years of dialysis therapy. Since these other aspects of calcium metabolism remain problematic, the actual dialysate calcium concentration will continue to evolve and, of necessity, needs to remain flexible as this dynamic area of research continues to challenge us. Ideally, the dialysate calcium concentration should be individualized to meet specific patient needs, but this is not readily feasible economically at this time.

Studies of dialysate calcium concentration have been carried out for the entire time that dialysis therapy has been used. Such studies were initiated with the best of intentions and often with quite careful designs. Changes in other aspects of our knowledge of calcium metabolism generally made these studies obsolete or even unethical before they were completed. Those that were completed were often so compromised by other changes in patient care that their results could either not be interpreted or were of marginal relevance.

Several studies over the last 30 years have evaluated the PTH response to dialysate calcium and consistently found that PTH correlated inversely with dialysate calcium. In the early days of dialysis, these findings resulted in recommendations for higher dialysate calcium levels (usually 1.75 mmol/L) in order to suppress PTH. In more recent years some studies of adynamic bone disease have begun to recommend lower dialysate calcium levels (usually 1.00 to 1.25 mmol/L) in order to increase PTH and bone formation in such patients. Since other factors have also assumed importance in PTH regulation, it is not entirely clear what role dialysate calcium concentration will play in this regard in the future. Probably, at least as much attention should be paid to the potential adverse effects of calcium loading and metastatic calcification as to the potential benefits of PTH suppression by this means.

A variety of studies over the last 30 years have attempted to assess the effects of various dialysate calcium levels on morbidity, mortality, infections (in peritoneal dialysis patients), various bone markers, and bone mineral density. Since the studies were done at different periods in the history of dialysis and at times when different measures to control calcium and phosphate were practiced, it is essentially impossible to document or ascertain any clear conclusions from these studies. What is clear is that studies to assess dialysate calcium in the future may be conducted when other aspects of calcium, phosphate, PTH, and bone pathophysiology are well understood and characterized. If and when that occurs, it may be possible to design a trial that will be practical and meaningful.

### *Strength of the Evidence*

While the reasons for the recommendation of a 2.5 mEq/L dialysate calcium concentration appear clear from the historical record, there is little, if any, evidence to support this particular choice. Clinical experience, rather than outcome data, have really determined how we have come to this juncture. The difficulties, up to now, of obtaining outcome data on various dialysis calcium levels have been frustrated by all the other changes in our understanding and management of renal osteodystrophy. As noted above, once we have settled on a consistent approach to these issues it may be possible to return to a logically designed assessment of dialysate calcium concentration. For now, we must fall back on what appears to be a "best guess."

#### Limitations

While this is a "best guess" at what the dialysate calcium should be, there are many unanswered questions that remain to be settled before being completely comfortable with this recommendation. In conjunction with all the other maneuvers, we may decide that a somewhat lower calcium concentration allows better regulation of PTH and bone disease. We may also find that, even at a 2.5 mEq/L calcium level, excess calcium loading occurs and contributes to vascular disease and calciphylaxis.

On the other hand, it has been recognized that cardiac arrhythmia is more common in patients being treated with lower-calcium dialysates.[323] The prolongation of the QT interval, which is commonly seen during dialysis, is worse with lower calcium[324] and in other settings than dialysis, this electrocardiographic abnormality is often associated with fatal outcomes. Thus, there remain serious unresolved questions which are likely to influence the choice of dialysate calcium levels in the future and clinicians will need to keep abreast of these issues.

#### Clinical Applications

At this point in time, the most logical dialysate calcium concentration appears to be one of 2.5 mEq/L. With the use of calcium-containing phosphate binders and active vitamin D metabolites, this level of dialysate calcium is currently the most convenient in allowing flexible use of other therapies directed at treating the bone and parathyroid gland abnormalities of this patient population. Because of the rapid evolution of management of calcium disorders in these patients, no data exist to document that any particular calcium dialysate is safer, more effective, or associated with fewer complications. Some studies have shown an increase in cardiac arrhythmias with lower calcium dialysates, but no increase in mortality or morbidity has been shown to result.

There may be times when calcium dialysate concentration should be altered. A lower calcium dialysate concentration (eg, 1.5 to 2.0 mEq/L) might be considered when a low PTH level is associated with adynamic bone disease. In this setting, PTH will be stimulated and bone turnover increased. The intact PTH should be allowed to rise to at least 100 pg/mL (11.0 pmol/L) to avoid low-turnover bone disease. However, the physician will need to be wary of overstimulating PTH and producing high-turnover bone disease. Thus, if PTH values exceed 300 pg/mL (33.0 pmol/L), the dialysate calcium may need to be modified again. Dialysate calcium concentrations of 1.5 to 2.0 mEq/L, or even lower, may be used to treat hypercalcemia both in chronic dialysis patients and patients without kidney disease. Because such treatment will lead to marked bone demineralization, it should not be prolonged. It is the primary cause of hypercalcemia that should be sought and treated.

Similarly, higher calcium levels in dialysates may be useful to sustain calcium balance when it cannot be maintained with routine treatment. Treatment of "hungry bone syndrome" is perhaps the best example, but standard therapies for this problem are usually effective without having to adjust dialysate calcium. In the early days of dialysis, high calcium concentration dialysates (typically 3.5 mEq/L) were employed because the patient's calcium balance and calcium levels could not be sustained without them. Advances in vitamin D therapy have eliminated this need.

#### Recommendations for Research

There is a basic conflict in calcium pathophysiology that needs to be resolved in CKD patients, ie, the conflict between adequate suppression and control of PTH, and excessive calcium loading resulting in tissue injury. The resolution of this conflict will involve carefully designed trials

to assess basic issues currently being widely discussed.

(1) Prospective long term studies of calcium balance and the accelerated atherosclerosis of CKD patients need to be coordinated to find the proper calcium balance that does not worsen these problems in patients.

(2) The regulation of PTH remains a challenge. Studies need to be done to determine what level of PTH is best (in terms of osteodystrophy) in the dialysis population. Once that is determined, the best ways to achieve the desired result will need to assess the coordination of the various biochemical and other approaches to PTH control, including dialysate calcium level.

(3) An acceptable balance between adequate control of PTH/bone disease and avoidance of accelerated atherosclerosis needs to be determined. Studies to define this balance will be both difficult and tedious.

## GUIDELINE 10. $\beta_2$-MICROGLOBULIN AMYLOIDOSIS

**10.1 Screening for $\beta_2$-microglobulin amyloidosis, including measurement of serum levels of $\beta_2$-microglobulin, is not recommended. (OPINION)**

**10.1a No currently available therapy (except kidney transplantation) can stop disease progression of $\beta_2$-microglobulin amyloidosis or provide symptomatic relief. (EVIDENCE)**

**10.1b Kidney transplant should be considered to stop disease progression or provide symptomatic relief in patients with $\beta_2$-microglobulin amyloidosis. (EVIDENCE)**

**10.1c In patients with evidence of, or at risk for, $\beta_2$-microglobulin amyloidosis noncuprophane (EVIDENCE), high-flux dialyzers (OPINION) should be used.**

### Background

$\beta_2$-microglobulin amyloidosis (A$\beta_2$M) (also referred to as dialysis-related amyloidosis [DRA] or dialysis-associated amyloidosis) is a serious, debilitating complication affecting patients with end-stage renal disease. This disorder is characterized by amyloid deposits with $\beta_2$-microglobulin fibrils as the major protein, primarily affecting joints and periarticular structures. The clinical manifestations include carpal tunnel syndrome, spondyloarthropathies, hemarthrosis, and joint pain and immobility.[325,326] Late in the disease course, systemic deposition can occur principally in the gastrointestinal tract and heart.[327-329] While mortality from A$\beta_2$M is rare, the disease can cause significant morbidity and is a major cause of joint pain and immobility in patients on long-term dialysis. The disease is most commonly reported in patients undergoing long-term hemodialysis therapy, but has also been observed in patients treated exclusively by CAPD or prior to the initiation of dialytic therapy.[326,330-332]

$\beta_2$-microglobulin is a nonglycosylated polypeptide of 11,800 Da. The principal site of metabolism of $\beta_2$-microglobulin is the kidney.[333] In normal individuals, the serum concentration of $\beta_2$-microglobulin is less than 2 mg/L. However, $\beta_2$-microglobulin serum levels in dialysis patients are 15 to 30 times greater than normal. The pathophysiology of the disease is not clear, but most experts agree that the accumulation of $\beta_2$-microglobulin over time is important. The manifestations of A$\beta_2$M gradually appear over the course of years, between 2 and 10 years after the start of dialysis in the majority of patients (see below). In one series, 90% of patients had pathological evidence of A$\beta_2$M at 5 years.[334] However, many patients may have the disease pathologically, but do not manifest clinical symptoms. In addition, the clinical symptoms are often nonspecific, and easily mistaken for other articular disorders. All of these factors make A$\beta_2$M particularly difficult to diagnose clinically.

### Rationale

Given the significant morbidity that A$\beta_2$M causes in patients with end-stage renal disease, the Work Group focused on three major questions:

(1) What is the best diagnostic technique?

(2) What are the potential therapies that slow the progression, prevent, or symptomatically treat the disease?

(3) Is screening for the disease practical, and if so, when should it begin?

The "gold standard" diagnostic technique is a biopsy demonstrating positive Congo Red staining and immunohistochemistry for the presence of $\beta_2$-microglobulin. Thus, to answer the first question, alternative diagnostic techniques compared to biopsy as the "gold standard" were assessed. To answer question 2, studies evaluating potential therapies for A$\beta_2$M have aimed to reduce the serum level of $\beta_2$-microglobulin, remove or debulk the amyloid deposit, or reduce inflammation that may contribute to the development of the disease. Multiple clinical end points were evaluated in the search for therapies, including fractures, carpal tunnel syndrome, bone pain and mobility, and spondyloarthropathy. Although dialysis is not an exclusive cause of A$\beta_2$M as previously thought, it is plausible that differences in dialysis membranes may either (1) increase the removal of $\beta_2$-microglobulin and thus be a potential therapy; or (2) may cause increased inflammation and generation of $\beta_2$-microglobulin, and thus contribute to or exacerbate the disease process. Thus, in evaluating the potential contribution of dialysis membranes to A$\beta_2$M, multiple end-points were evaluated, including serum levels of $\beta_2$-microglobulin and clinical end-points. Lastly, in order to assess whether screening for the disease was practical, the answers to the preceding questions and the natural history of the disease were considered.

### *Strength of Evidence*

Because many patients with pathological evidence of the disease do not manifest clinical symptoms, and the disease progresses over several years, A$\beta_2$M is particularly difficult to diagnose or study. Ideally, appropriate clinical trials would require large numbers of patients followed for several years. Unfortunately, there are limited prospective trials. There were many available retrospective or case-control studies that fulfilled the evidence report inclusion criteria, but this design presents a particular problem in evaluating a slowly progressive disease due to changes in the dialysis procedure and medications over time. In addition, depending on how the cohort was defined (ie, pathological evidence, long-term dialysis patients, or those with clinical symptoms), there could be considerable bias. Thus, the overall strength of the evidence is weak. Nevertheless, some evidence-based Guidelines could be established from publications that meet the inclusion criteria established by the Work Group.

### *Diagnostic Tests*

To best answer the question of whether there are good alternative diagnostic tests to biopsy, an ideal design would be a direct comparison of these diagnostic techniques to pathological evidence of the disease by biopsy. However, of the 10 studies evaluating alternative diagnostic tests that met the inclusion criteria for evaluation,[335-344] only 3 utilized joint biopsy.[336-338] The rest compared the diagnostic technique with clinical symptoms, or presence of pathological evidence of the disease elsewhere (eg, carpal tunnel syndrome). Five studies on scintigraphy,[336,339-342] 4 studies of shoulder ultrasound,[337,338,343,344] and 1 study of MRI[335] were examined using the best available evidence. All of these studies reported that these alternatives worked well. However, most studies suffer from small sample size, lack of controls, and bias. The latter is usually in the form of predominantly enrolling patients with more severe forms of the disease, prohibiting the calculation of true sensitivity/specificity for these tests. Thus, the applicability of these studies to the general dialysis population is unknown. Furthermore, the ability to diagnose and differentiate $\beta_2$-microglobulin deposits from other causes of joint abnormalities will also be dependent upon the experience of the reader for each specific test. For example, the ability to diagnose A$\beta_2$M by MRI will be greatest with an experienced radiologist. It should also be noted that scintigraphy results may be affected by which carrier protein is labeled, and these are not readily available in the United States. Thus, despite the apparent usefulness of these various diagnostic tests in these studies, further confirmation is required, and biopsy remains the "gold standard." Based on a single study that looked at differences in biopsy sites, the sternoclavicular joint appeared to be the most sensitive location in assessing the pathological presence of A$\beta_2$M.[345]

### *Role of Dialysis Membrane*

To determine the effect of dialysis membranes on the incidence and severity of $\beta_2$-microglobulin, 21 studies evaluating the effect of one or more membranes on clinical, biochemical, and

**Table 29. Effect of Dialysis Membranes on the Development of Clinical or Radiographic Symptoms of $\beta_2$-Microglobulin Amyloidosis**

| Author, Year | Study Design | Follow-up | Membranes Used | N | Percentage (N) with A$\beta_2$M | Effect Size (95% CI)* | Direction of Effect† | Methodological Quality |
|---|---|---|---|---|---|---|---|---|
| Kuchle, 1996[346] | RCT | 72 months | Cuprophane | 12 | 67% (8) | 2.05 (0.37 to 3.73) | ⬆ | ● |
| | | | Polysulfone | 12 | 0% (0) | | | |
| Kessler, 1992[356] | Retro | 120-257 months | Cuprophane | 95 | 36% (34) | –0.54 (–1.16 to 0.07) | ⇔ | ○ |
| | | | PAN | 15 | 60% (9) | | | |
| Van Ypersele, 1991[363] | Retro | 5-17 years (median 5.5 years) | Cuprophane | 106 | 16% (17) | 0.68 (0.15 to 1.22) | ⬆ | ○ |
| | | | PAN | 115 | 5% (6) | | | |
| Brunner, 1990[352] | Retro | 108-204 months (median 132 months) | Cuprophane | 27 | 37% (10) | 0.28 (–0.36 to 0.92) | ⇔ | ○ |
| | | | PAN | 27 | 26%(7) | | | |
| Koda, 1997[364] | Retro | 94 months | Cuprophane | 571 | 5% (28) | –0.38 (–0.69 to –0.06) | ⬇ | ○ |
| | | | PMMA/PAN/PEPA/CTA | 248 | 9% (23) | | | |
| Schiffl, 2000[365] | Retro | 136±16 months | Cuprophane | 29 | 72% (21) | 0.87 (0.33 to 1.40) | ⬆ | ○ |
| | | | Polysulfone/PAN/PMMA | 60 | 35% (21) | | | |
| Mioli, 1994[366] | Retro | 66.5 months | Cuprophane | 37 | 27% (10) | 0.45 (–0.17 to 1.07) | ⇔ | ○ |
| | | | PAN/CR | 43 | 14% (6) | | | |
| Gonzalez, 1997[367] | Retro | 70 ±57 months (median ±SD) | Cuprophane | 63 | 41% (26) | 0.49 (0.02 to 0.95) | ⬆ | ○ |
| | | | CAPD | 49 | 22% (11) | | | |
| Benz,1988[330] | Retro | 44.4 months (mean) | Cuprophane | 90 | 17% (15) | 0.15 (–0.36 to 0.67) | ⇔ | ○ |
| | | | CAPD | 61 | 13% (8) | | | |

* Calculated by ECRI. Effect sizes are reported in the standardized metric of Hedges' d, which indicates a greater effect the further away d is from zero. If the 95% confidence intervals cross zero, the effect size is nonsignificant.

†The effect size summary indicates whether effect sizes were significantly positive or negative. A horizontal arrow indicates that the result was nonsignificant.

‡For explanation of symbols used, see *Methods for Analysis of Literature.*

***Abbreviations:*** *CAPD, continuous ambulatory peritoneal dialysis; CR, cuprammonium rayon; CTA, cellulose triacetate; PAN, polyacrylonitrile; PMMA, polymethylmethacrylate; RCT, randomized prospective controlled trial; Retro, retrospective, controlled trial; SD, standard deviation; $\beta_2$ ▯, $\beta_2$-microglobulin*

**Table 30. Summary of the Results of the Effect of Different Dialysis Membranes on β2-Microglobulin Serum Levels**

| Membrane | Long-Term Controlled Trials | Short-Term Controlled Trials | Retrospective Trials | Exploratory Meta-Analyses |
|---|---|---|---|---|
| Polysulphone | One trial: positive effect[346] | Two trials: positive effect[358, 361]<br>One trial: NS[362] | No trials | Mixed |
| PMMA | One trial: positive effect[350]<br>One trial: NS[347] | Two trials: NS[360, 362]<br>One trial: positive effect[358] | No trials | Mixed |
| PAN | One trial: NS[348] | Two trials: positive effect[361, 368] | One trial: positive effect[133]<br>One trial: NS[356] | Mixed |
| CAPD | One trial: positive effect[349] | No trials | Two trials: positive effect[353, 355]<br>Two trials: NS[354, 367] | Mixed |
| Hemophan | No trials | Two trials: positive effect[358, 360] | One trial: NS[351] | Mixed |

Positive effect = statistically significant effect, membrane of interest reported to have a lower $\beta_2$-microglobulin serum level than did cuprophane
Negative effect = statistically significant effect, membrane of interest reported to have a higher $\beta_2$-microglobulin serum level than did cuprophane
No effect = statistically significant, but no difference in $\beta_2$-microglobulin serum levels between the membrane of interest and cuprophane
NS = statistically nonsignificant results

radiological evidence of A$\beta_2$M were identified that fulfilled the inclusion criteria: 5 long-term, prospective studies,[346-350] 10 retrospective studies,[133,330,351-356] and 6 trials looking at the ability of different membranes to remove $\beta_2$-microglobulin from the blood over the course of 1 to 5 dialysis sessions.[357-362] None of these trials used any blinding. Unfortunately, of these 5 prospective trials, only 3 were randomized,[346,347,350] and only 1 of these looked at clinical signs and symptoms and had adequate follow-up.[346] Most studies evaluating various membranes have directly compared exclusive or near-exclusive use of cellulosic membranes such as cuprophane to noncellulosic, semi-synthetic, high-efficiency, or high-flux dialyzers. Several, but not all, studies have demonstrated a benefit of the noncellulosic membranes, with at least 1 clinical end-point (Table 29), but a meta-analysis could not be done comparing cellulosic versus other membranes due to heterogeneity. However, for the single end-point of prevalence of carpal tunnel syndrome, polyacrylnitrile membranes were superior to cuprophane membranes by meta-analysis.[352,356,363] The only prospective, randomized, controlled trial[346] found that patients dialyzed with polyacrylnitrile membranes had less carpal tunnel syndrome, fewer bone cysts, and decreased thickness by shoulder ultrasound compared to patients dialyzed with cuprophane.

Five long-term prospective controlled trials and seven retrospective studies addressed the effect of different dialysis membranes on serum $\beta_2$-microglobulin levels. The reported results from the studies and the results of the exploratory meta-analyses are summarized in Table 30. Due to the low number of trials for each membrane, and the heterogeneous nature of the results, summary effect sizes could not be calculated for most of the different membranes. Three out of four trials, including a high-quality, randomized, controlled trial, found that dialysis with polysulfone membranes removes more $\beta_2$-microglobulin from the serum than dialysis with cuprophane membranes. CAPD, Gambrane, Hemophan, PMMA, and EVAL membranes were all reported to remove more $\beta_2$ microglobulin from the blood during dialysis than dialysis with cuprophane membranes.

Two retrospective trials reported no significant difference in the prevalence of carpal tunnel syndrome in patients dialyzed with CAPD as compared to patients on hemodialysis with cuprophane membranes.[330,367] One retrospective trial reported that patients on CAPD had significantly lower rates of spondyloarthropathy and

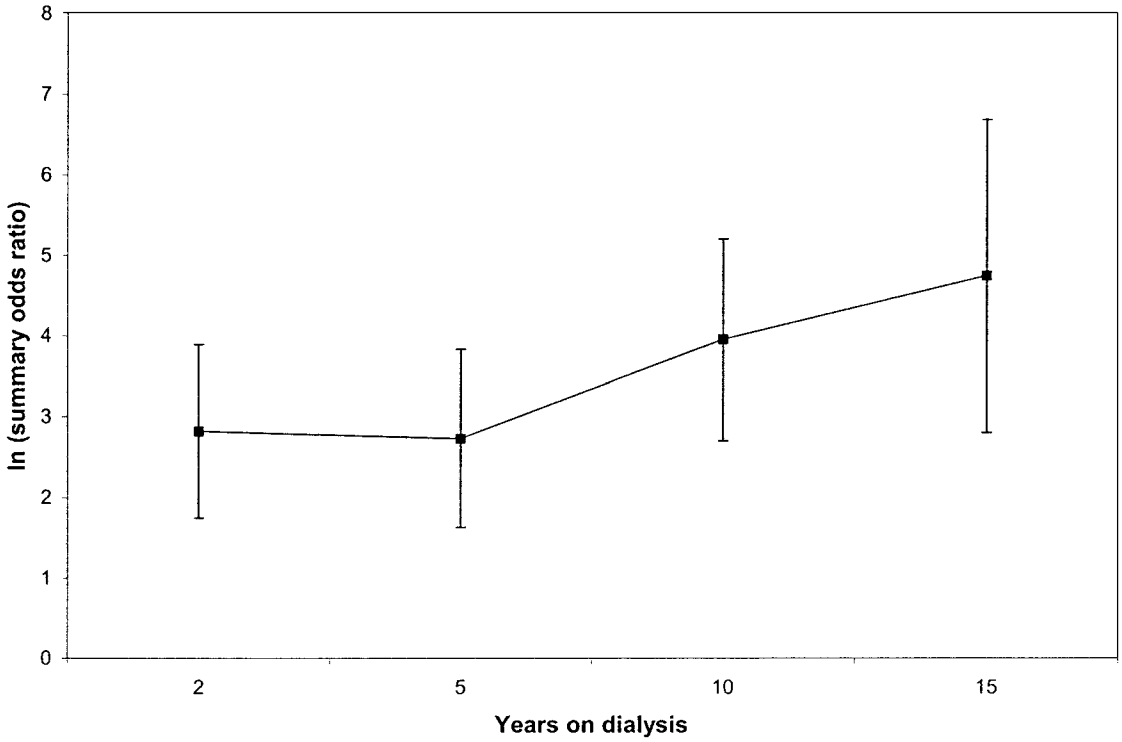



**Fig 13. Summary odds ratio of being diagnosed with A$\beta_2$M over time on dialysis.**

bone cysts than did patients on cuprophane hemodialysis.[367] CAPD was reported to result in lower $\beta_2$-microglobulin serum levels than did cuprophane hemodialysis. The low number and poor quality of the studies of CAPD must be kept in mind when interpreting these results.

### *Screening*

No studies that met the inclusion criteria of the Evidence Report addressed the question of how often, if ever, patients should be screened for A$\beta_2$M. An optimal approach to ascertaining when screening for A$\beta_2$M should begin would be to conduct a prospective cohort study in which a group of typical kidney failure patients were followed from the time that they commenced maintenance dialysis and were screened frequently for the onset of A$\beta_2$M. Only 1 study has approached this ideal trial design.[369] In this study, 15 patients were retrospectively followed for over 15 years on dialysis. The other 16 studies addressing this question are cross-sectional studies.[334,344,345,368,370-380] They are retrospective in that they selected groups of patients who had been on hemodialysis for some time (time on dialysis is retrospective), and then prospectively examined them for signs and symptoms of A$\beta_2$M (detection of the disease is prospective). A problem with this study design is that the incidence of A$\beta_2$M cannot be determined because it is unclear when exactly each patient began to develop A$\beta_2$M. Only prevalence of the disease can be determined from a cross-sectional trial. Another difficulty with this study design is that it may be inadvertently including a rather special group of patients—only those who remained on dialysis for long periods of time at the same center were included in the trial (ie, patients who died, received kidney transplants, or relocated were not included in the trial). Thus, the evidence is not optimal.

These study limitations not withstanding, a summary odds ratio of the prevalence of A$\beta_2$M was calculated using meta-analysis. An odds ratio of 1.0 indicates no cases; the larger the odds ratio, the more likely it is that all patients will have disease. After 2 years on hemodialysis, the summary odds ratio is 16.82 (95% CI, 5.75 to 49.17). After 5 years on hemodialysis, the sum-

mary odds ratio is 15.32 (95% CI, 5.12 to 45.83). After 10 years on hemodialysis, the summary odds ratio is 51.85 (95% CI, 15.11 to 177.86). After 15 years on hemodialysis, the summary odds ratio is 114.13 (95% CI, 16.49 to 789.96). The natural logarithm (ln) of the summary odds ratio is graphed versus time on dialysis in Fig 13. These results, in combination with considerations about the effectiveness of treatment for A$\beta_2$M, can be used to determine when screening for A$\beta_2$M should begin. However, for screening for A$\beta_2$M to be rational, there would need to be an effective therapy for the disorder.

### *Therapies*

Unfortunately, there are limited studies evaluating therapy, none of which are controlled and all of which have short term follow-up which, given the slow progression of the disease, may overestimate the efficacy of a specific therapy. Seven studies evaluated kidney transplant as a therapy,[351,381-386] two before and after transplantation.[383,384] As expected, kidney transplantation led to lower serum levels of $\mu_2$-microglobulin. In addition, joint mobility and bone pain improved, but X-ray findings and spondyloarthropathy did not improve, suggesting the deposits do not regress. Prednisone therapy improved bone pain and joint mobility, but only one small trial meeting criteria was available.[384] A study describing 11 patients who underwent surgical removal of amyloid deposits demonstrated improvement in joint mobility and bone pain, but follow-up was short.[387] Two other studies evaluated the use of $\beta_2$-microglobulin adsorbent columns run in series with standard dialysis.[388,389] These columns lowered serum levels of $\beta_2$-microglobulin, but clinical symptoms were not evaluated. Clearly these data are weak and should be considered preliminary due to small sample size and limited follow-up. In addition, none of the studies reported the use of any kind of blinding, resulting in substantial bias. Further complicating the interpretation of these studies is the variety of endpoints evaluated in the different studies. Thus, these studies would suggest that kidney transplantation is the only effective therapy to avoid the morbidity of A$\beta_2$M. However, given that a functional kidney transplant is a preferred therapy for kidney failure for a number of reasons, it is unlikely that transplantation will be prescribed only for the purpose of treating A$\beta_2$M. For this reason, the Work Group recommended that routine screening of patients for the presence of A$\beta_2$M not be done.

#### Limitations

The lack of quality studies in this field may be reflective of the slow progressive nature of the disease as well as the discordant relationship between clinical symptoms and pathological evidence of the disease. All of these factors produce significant limitations on the quality of the data. In addition, there was considerable bias in patient selection and very few studies had adequate and rigorous controls. Thus, the strength of the evidence supporting this Guideline is weak.

#### Clinical Applications

The Work Group agreed that A$\beta_2$M is a significant cause of musculoskeletal morbidity in dialysis patients. The Work Group also agreed that many of the available diagnostic techniques could demonstrate $\beta_2$-microglobulin amyloid, as could a clinical examination, although the true specificity and sensitivity of the available diagnostic test are unknown. The data evaluating dialysis membranes is of sub-optimal quality; however, the Work Group felt the data at least supported the observation that non-cuprophane membranes may slow the progression of the disease. The lack of conclusive data supporting the use of noncellulosic dialysis membranes or peritoneal dialysis, led the Work Group to—at this time—recommend that noncellulosic membranes be utilized only in patients who have a life expectancy on dialysis greater than 2 years, as this appears to be the earliest time-point that there is evidence for A$\beta_2$M. However, there may be reasons other than the prevention of, or slowing the progression of, A$\beta_2$M to use noncellulosic membranes such as issues associated with biocompatibility. Continued research into membranes or dialysis techniques that remove more $\beta_2$-microglobulin is needed. Routine screening for A$\beta_2$M is not recommended, as the only potential therapy is kidney transplantation and it is unlikely that transplantation will be prescribed only for the purpose of treating A$\beta_2$M.

### Recommendations for Research

Long-term studies of the role of various dialysis membranes and other novel therapies are clearly warranted. However, the overall mechanism of the pathogenesis of the disease also requires further research so that more specific therapies can be developed.

## GUIDELINE 11. ALUMINUM OVERLOAD AND TOXICITY IN CKD

**11.1 To prevent aluminum toxicity, the regular administration of aluminum should be avoided and the dialysate concentration of aluminum should be maintained at <10 μg/L. (EVIDENCE)**

**11.1a CKD patients ingesting aluminum should not receive citrate salts simultaneously. (EVIDENCE)**

**11.2 To assess aluminum exposure and the risk of aluminum toxicity, serum aluminum levels should be measured at least yearly and every 3 months in those receiving aluminum-containing medications. (OPINION)**

**11.2a Baseline levels of serum aluminum should be <20 μg/L. (OPINION)**

**11.3 A deferoxamine (DFO) test should be performed if there are elevated serum aluminum levels (60 to 200 μg/L); clinical signs and symptoms of aluminum toxicity (Table 31), or prior to parathyroid surgery if the patient has had aluminum exposure. (EVIDENCE) (Algorithms 6 and 7)**

**11.3a The test is done by infusing 5 mg/kg of DFO during the last hour of the dialysis session with a serum aluminum measured before DFO infusion and 2 days later, before the next dialysis session. (OPINION)**

**11.3b The test is considered positive if the increment of serum aluminum is ≥50 μg/L. (OPINION)**

**11.3c A DFO test should not be performed if the serum levels of aluminum are >200 μg/L to avoid DFO-induced neurotoxicity. (OPINION)**

**11.4 The presence of aluminum bone disease can be predicted by a rise in serum aluminum of ≥50 μg/L following DFO challenge combined with plasma levels of intact PTH of <150 pg/mL (16.5 pmol/L). (OPINION) However, the gold standard for the diagnosis of aluminum bone disease is a bone biopsy showing increased aluminum staining of the bone surface (>15% to 25%) using aluminum stain and often adynamic bone or osteomalacia. (EVIDENCE)**

### Background

Aluminum is widely present in nature, but most aluminum salts are quite insoluble. Moreover, only a tiny fraction of ingested aluminum is absorbed; this small amount is normally excreted by the kidney so that the body burden of aluminum does not increase. When there is a markedly reduced or absent kidney function, there is little or no ability to excrete aluminum and it can accumulate slowly. When aluminum is present in dialysate, it enters the body directly across the dialysis membrane, and the type of syndrome that develops depends on the rapidity and magnitude of aluminum accumulation. The various syndromes of aluminum toxicity were first identified in dialysis patients, but they can occur in both Stage 4 CKD patients and Stage 5 CKD patients not yet treated with dialysis. Because of their devastating nature and the difficulties in their management, it is essential that the clinical features of aluminum toxicity are known along with the biochemical methods for their recognition. These problems have become substantially less common with the reduced use of aluminum gels as phosphate binders and proper purification of dialysate; however, aluminum toxicity still occurs. It is necessary to consider the means for proper monitoring and the appropriate diagnostic procedures needed to identify the various syndromes of aluminum toxicity.

### Rationale

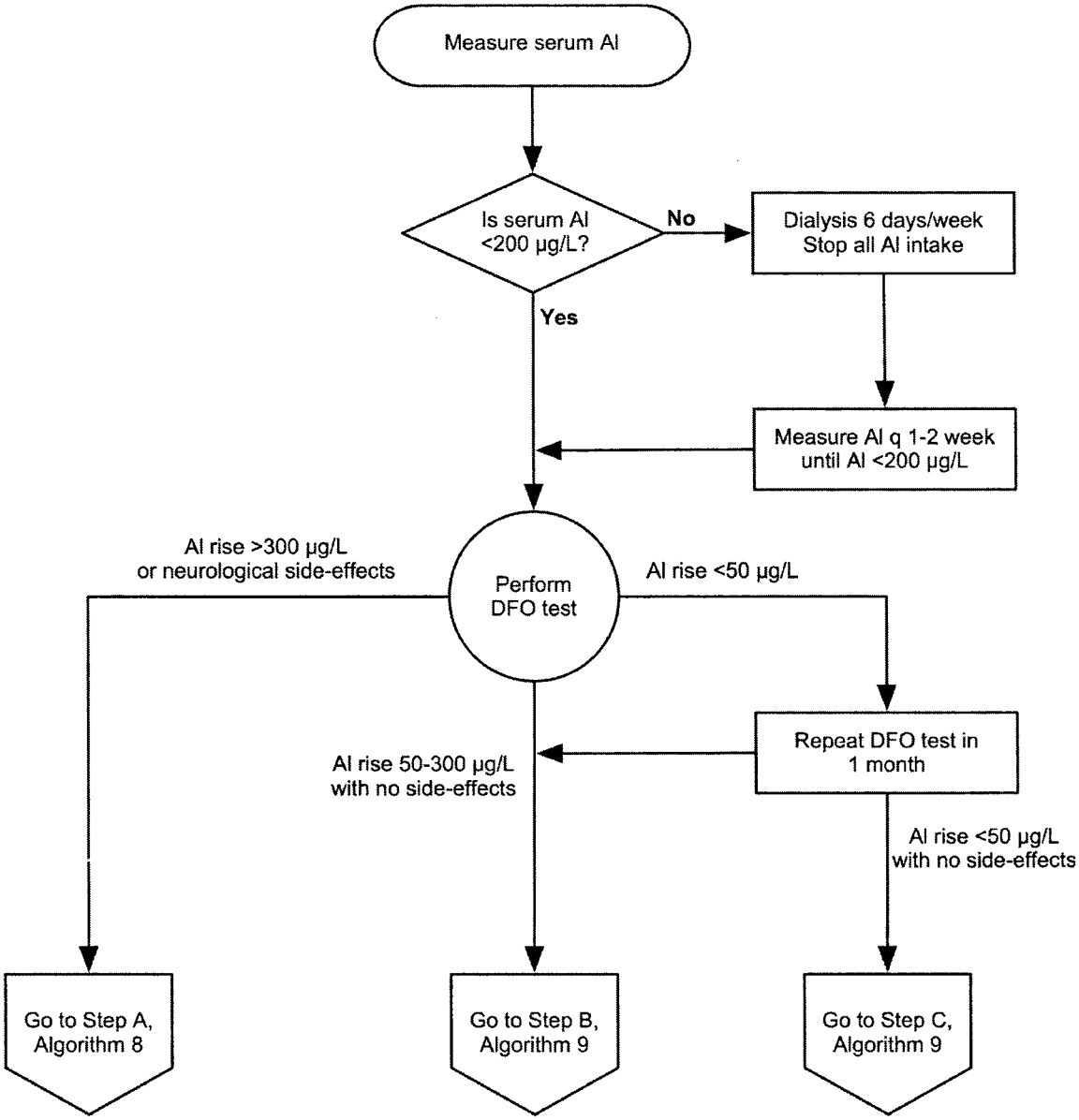
Aluminum toxicity occurs in dialysis patients or CKD patients with GFR <30 mL/min/1.73 $m^2$ (Stages 4 and 5 CKD) because aluminum that is absorbed from the gut or enters the body from dialysate or another parenteral route[390] is not

## Table 31. Aluminum-Related Disorders: Features, Causes and Considerations for Therapy

| Condition | Features (Clinical Diagnosis) | Causes | Management | Special Treatment |
|---|---|---|---|---|
| Acute Aluminum Neurotoxicity | Acute neurological syndrome with:<br>Altered consciousness<br>Seizures<br>Coma<br>Usually progresses to death | **1.** Dialysate Al >200 $\mu$g/L<br>**2.** HD patients with marked Al-loading ($P_{Al}$ >200 $\mu$g/L) treated with DFO, 20-40 mg/kg<br>**3.** Stage 4 & 5 CKD patients who ingest both Al-drugs ***plus*** a salt containing citrate[a] | Measure plasma Al<br>Stop all Al intake<br>Dialysate Al <5 $\mu$g/L<br>Daily dialysis<br>High-flux dialyzer<br>Follow algorithms for DFO testing & therapy | Standard Management ***plus***:<br>**Cause 2:** Stop DFO until $P_{Al}$ <200 $\mu$g/L<br>**Cause 3:** Withdraw all citrate[a] |
| Dialysis Encephalopathy | Subacute syndrome with:<br>Speech abnormalities<br>Defective spatial orientation<br>Altered consciousness<br>Seizures<br>Often intermittent and worsens transiently after dialysis<br>Usually slowly progressive | **1.** Dialysate Al >30-40 $\mu$g/L (with dialysate Al levels of 100-200 $\mu$g/L, symptoms appear sooner and progress more rapidly)<br>**2.** Rarely arises from Al ingestion alone, but ingestion of Al-containing agents can hasten its appearance | Measure plasma Al<br>Stop all Al intake<br>Dialysate Al <5 $\mu$g/L<br>High flux dialyzer<br>Follow algorithms regarding need for daily dialysis, DFO testing & therapy | Know level of plasma Al before doing DFO test<br>Specific electroencephalographic features can aid in the diagnosis (see text) |
| Aluminum Bone Disease | Insidious appearance of:<br>Bone pain<br>Fractures<br>Proximal muscle weakness<br>(Diagnosis by bone biopsy; prediction from DFO test result and intact PTH level) | **1.** Dialysate Al >30-40 $\mu$g/L (with higher Al levels, symptoms appear sooner)<br>**2.** Ingestion of Al-containing agents may hasten its development | Measure plasma Al<br>Stop all Al intake<br>Dialysate Al <5 $\mu$g/L<br>High flux dialyzer<br>Follow algorithms regarding need for daily dialysis, DFO testing & therapy | Know level of plasma Al before DFO test is done<br>May coexist with dialysis encephalopathy, particularly when dialysate Al >30-40 $\mu$g/L |
| Hypercalcemia | [Search may reveal other features of Al toxicity when hypercalcemia appears in the absence of either:<br>High intact PTH levels (e.g., when intact PTH >500 pg/mL), or<br>Vitamin D therapy] | **1.** Dialysate Al >30-40 $\mu$g/L<br>**2.** Ingestion of Al-containing drugs<br>Serum Ca can rise rapidly with use of Ca-based phosphate binders—probable manifestation of low bone turnover | Measure plasma Al<br>Stop all Al intake<br>Dialysate Al <5 $\mu$g/L<br>Follow algorithms regarding need for daily dialysis, high-flux dialyzer use, DFO testing & therapy | Hypercalcemia can dissipate rapidly with use of lower dialysate Ca (2.0-2.5 mEq/L) |
| Microcytic Anemia | When microcytosis present with:<br>No evidence of iron deficiency<br>No response to iron therapy | **1.** Dialysate Al >30-40 $\mu$g/L<br>**2.** Ingestion of Al-containing drugs<br>(uncommonly the only source of Al loading) | Measure plasma Al<br>Stop all Al intake<br>Dialysate Al <5 $\mu$g/L<br>Follow algorithms regarding need for daily dialysis, high-flux dialyzer use, DFO testing & therapy | Aluminum loading may increase requirements for erythropoietin but magnitude of this effect is not well documented |
| Aluminum Overload | Asymptomatic (by definition).<br>(Defined by analysis of bone Al content or by a specific but arbitrary rise of $P_{Al}$ after a DFO test) | **1.** Dialysate Al >20-40 $\mu$g/L<br>**2.** Ingestion of Al-containing drugs | Measure plasma Al<br>Stop all Al intake<br>Dialysate Al <5 $\mu$g/L<br>Follow algorithms regarding need for high-flux dialyzer use, DFO testing & therapy | May be subtle abnormalities on CNS testing<br>May respond to withdrawal of all exposure to Al<br>DFO treatment rarely needed |

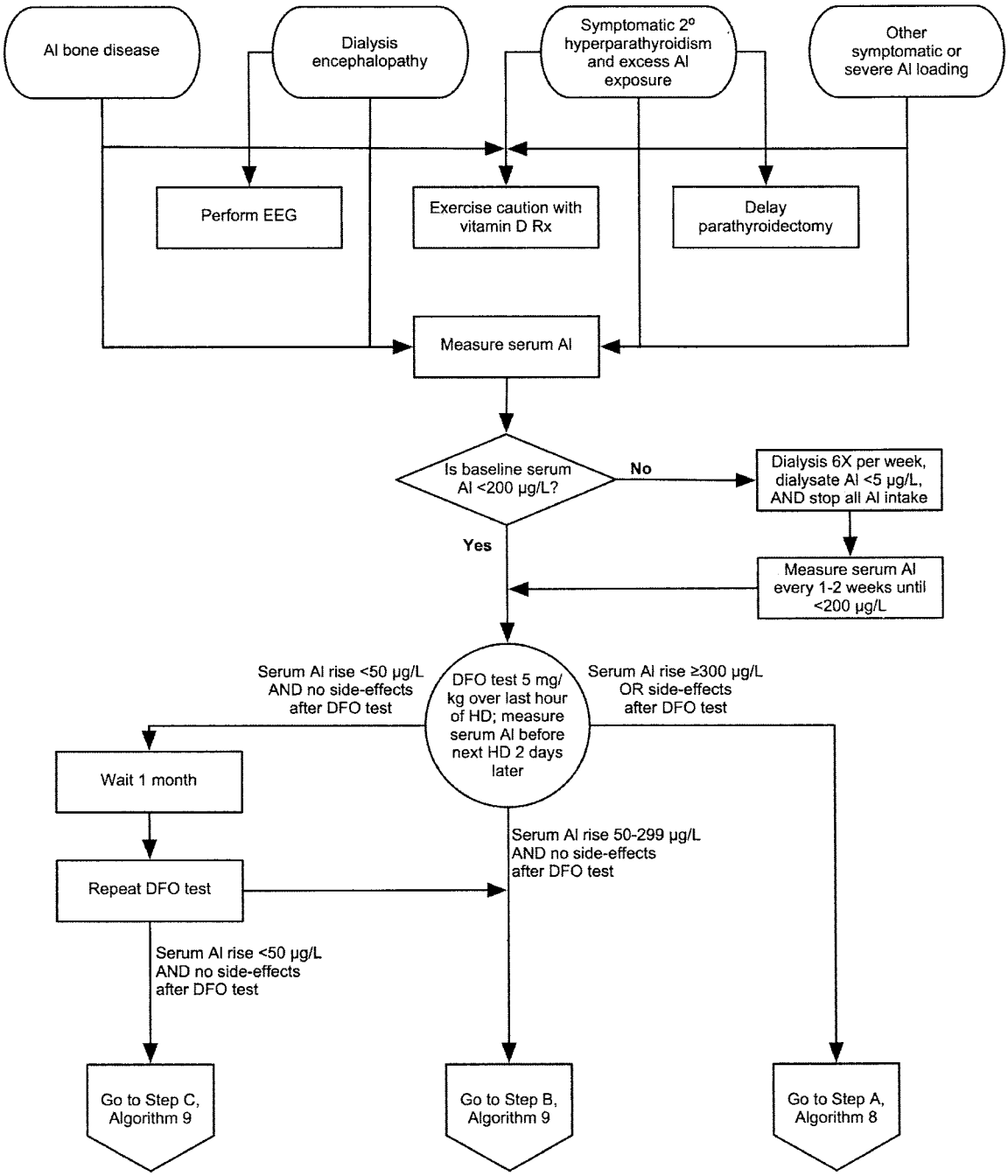
[a] Citrate source may be Bictra™, Shohl's solution, AlkaSeltzer™, calcium citrate, or excess intake of citrate-containing juices.

***Abbreviations**: $P_{Al}$, plasma aluminum; DFO, deferoxamine; CNS, central nervous system; HD, hemodialysis*




**Algorithm 6. Evaluation of aluminum neurotoxicity.**

excreted or is inadequately excreted by the diseased kidneys.[391,392] When aluminum accumulates in dialysis patients, it is only slowly removed by dialysis because 90% of aluminum is bound to plasma proteins (primarily transferrin[393,394]). The aluminum entering the body accumulates in various tissues, including bone, brain, parathyroid glands, and other organs.[395,396] Such accumulation of aluminum can produce toxicity with several distinct syndromes, depending on the rate and magnitude of aluminum loading. The first to be described was dialysis encephalopathy (or dialysis dementia).[397,398] Aluminum was then recognized as the cause of both "fracturing dialysis osteomalacia" (aluminum-related bone disease)[398-400] and a microcytic anemia developing without iron deficiency.[401-403] A fulminant variant of dialysis encephalopathy, termed "acute aluminum neurotoxicity," occurs with the sudden, marked elevation of serum aluminum levels and is commonly fatal.[404,405] These disorders are briefly described below. The




This algorithm is exclusive of acute Al neurotoxicity

**Algorithm 7. Evaluation of aluminum-related disorders: considerations for DFO test and subsequent DFO treatment.**

development and availability of a method to measure trace quantities of aluminum accurately in biological fluids and tissues[406] permits detection of these disorders, and this methodology provides a means to identify patients with increased body burden of aluminum (Table 31 and Algorithm 7).

***Acute aluminum neurotoxicity.*** Acute aluminum neurotoxicity is diagnosed based on clinical features and the elevation of plasma aluminum levels to 400 to 1,000 $\mu$g/L. It arises from aluminum contamination of dialysate, often to levels of 150 to 1,000 $\mu$g/L. As a rule, patients may become ill simultaneously in the same dialysis center. They develop agitation, confusion, myoclonic jerks, and major motor seizures; these symptoms are often followed by coma and death.[404,405] The syndrome can also develop in patients with Stages 3 to 4 CKD (GFR $<$30 mL/min/1.73 m$^2$) when they are given aluminum gels (to control hyperphosphatemia) *plus* sodium citrate (Bicitra™ or Shohl's solution) for the correction of metabolic acidosis.[407,408] Various citrate salts, including citric acid, sodium citrate, or calcium citrate, markedly enhance intestinal absorption of aluminum.[171,409,410] Acute aluminum neurotoxicity can also appear in patients with large aluminum body load soon after the start of treatment with DFO in doses of 20 to 40 mg/kg.[411,412] When acute aluminum neurotoxicity develops due to (1) very high dialysate aluminum levels or (2) the ingestion of both aluminum gels and citrate salts, most symptomatic patients have died.[404,405,407,408] When the syndrome appeared in aluminum-loaded patients given DFO, some patients died; however, others survived when DFO treatment was stopped for several weeks and restarted later using a lower dose.[411,412]

***Dialysis encephalopathy.*** Dialysis encephalopathy is an insidious disorder with symptoms generally appearing after patients have undergone dialysis for 12 to 24 months or even longer.[397,398] Initial symptoms include subtle personality changes and a progressive speech disorder, characterized by stuttering, stammering and hesitant speech, or even total inability to talk.[413] Motor disturbances include twitching, myoclonic jerks, and motor apraxia. Auditory and visual hallucinations, spatial disorientation, and paranoid behavior are common. These features can fluctuate widely and are characteristically worse shortly after dialysis. With time, the symptoms become persistent and worsen, seizures appear, and most untreated patients have died within 6 to 12 months after the onset of symptoms.[397] The only distinctive laboratory findings were substantial elevations of plasma aluminum, usually 150 to 350 $\mu$g/L. The electroencephalographic (EEG) findings differ from the generalized slowing noted with other causes of metabolic encephalopathy. The diagnosis of these neurological disorders rests on clinical suspicion, the finding of elevated plasma aluminum levels, and the EEG features. New cases of this syndrome disappeared after the initiation of water purification.

***Aluminum-related bone disease.*** Aluminum-related bone disease was first described in certain specific geographic areas of the United Kingdom and the United States[399,414]; there was a suspicion of aluminum toxicity because many patients developed clinical features of dialysis encephalopathy.[399,414] Epidemiological studies showed that this disorder—which presented with bone pain, a characteristic "waddling" gait, proximal muscle weakness and fractures[401]—was associated with dialysate aluminum levels above 100 $\mu$g/L.[400] The disorder was limited to certain geographical regions, and aluminum-contaminated dialysate was considered the only source of aluminum loading. Later, sporadic cases appeared in dialysis centers where elevated dialysate aluminum levels were never found,[415,416] and it was shown that small quantities of aluminum are absorbed from ingested aluminum gels.[417] Such sporadic cases of aluminum bone disease have become less common since the use of aluminum gels were stopped or their dosage reduced substantially.[14,418]

Patients with aluminum-related bone disease often exhibit hypercalcemia,[419,420] and PTH levels which are variably elevated, particularly with older C-terminal or mid-region PTH assays.[420,421] Some of these patients had radiographic features of subperiosteal erosions and, when parathyroidectomy was done, the clinical features worsened. Bone biopsies revealed typical aluminum-related bone disease, and the term *pseudohyperparathyroidism* was applied to such patients.[421] Other observations have documented the appearance or worsening of skeletal symptoms when patients with aluminum-related bone disease or alumi-

num loading had their PTH levels reduced by either parathyroid surgery[422] or by treatment with an active vitamin D sterol.[312,423]

Indirect methods to identify aluminum-related bone disease were sought. Plasma aluminum levels were elevated in afflicted patients, with values usually above 100 $\mu$g/L; however, similar levels were found in many patients lacking bone biopsy evidence of aluminum-related bone disease.[14,424] The DFO-infusion test, using DFO in doses of 20 to 40 mg/kg, was introduced to identify those with aluminum bone disease.[425,426] The results indicate that the rise in aluminum correlated better with the total bone aluminum content than with surface staining of aluminum[427,428]; and that the presence of bone surface staining for aluminum of >15% to 25% showed a close association with clinical symptoms and with bone biopsy features of reduced bone formation and even osteomalacia, the histological features of aluminum bone disease.[319,429,430]

Population studies suggested that the combination of the increment of plasma aluminum after DFO combined with intact PTH levels below 150 pg/mL (16.5 pmol/L) provided better sensitivity and specificity to predict aluminum bone disease than the DFO test alone.[426,431] Also, it was found that the sensitivity of the DFO test was reduced substantially in patients with no known exposure to aluminum for 6 months or longer.[431] Most information indicates that plasma aluminum levels only reflect recent aluminum intake.[432]

Problems arose with use of the DFO test. Isolated reports documented permanent visual loss from ophthalmological damage after one DFO test with a dose of 40 mg/kg.[433,434] Furthermore, as noted below under Treatment of Aluminum Toxicity, the use of DFO, 20 to 40 mg/kg, was associated with fulminant and fatal mucormycosis in an unacceptable number of dialysis patients.[435] As a consequence, there has been reluctance to use a DFO test using 40 mg/kg, and smaller doses have been evaluated.[436-438]

Prevention of aluminum toxicity is preferable to use of toxic methods for treatment, particularly with the mortality of the neurological disorders and high morbidity of the bone disease. Periodic monitoring of plasma aluminum levels and assessment of aluminum in dialysate are essential for its prevention.

***Strength of Evidence***

The evidence for the devastating neurological and skeletal disorders produced by contamination of dialysate with aluminum is compelling. However, these reports are not prospective, randomized trials. Obviously, such trials can never be done.

- **Plasma Aluminum Levels and Frequency of Monitoring.** Early studies of serum aluminum measurements in dialysis patients indicated that plasma aluminum levels reflect relatively recent exposure to aluminum.[395,439] The population studies based on a single measurement of serum aluminum provide no information on the optimal frequency to monitor serum aluminum levels. The purpose of monitoring plasma aluminum levels is: (1) to identify excessive aluminum intake or absorption in individual patients *or* (2) to aid in recognition of accidental contamination of dialysate with aluminum. The recent reported accidental events with aluminum contamination of dialysate were often detected because neurological symptoms appeared in dialysis patients;[405,440,441] deaths often occurred before the source was identified or corrected. Under these circumstances, dialysate aluminum levels were markedly elevated (>200 $\mu$g/L). Although the dialysate aluminum levels were high, dialysate monitoring may not be frequent enough to detect a problem, as water aluminum levels can vary from day to day. Twice yearly monitoring of plasma aluminum would be capable of detecting the slow accumulation of aluminum from oral absorption or from "modest" dialysate contamination (dialysate aluminum levels of 20 to 40 $\mu$g/L). Indirect evidence can be derived from studies showing the increment of plasma aluminum levels during the ingestion of aluminum gels or from studies of plasma aluminum levels after the withdrawal of aluminum gels. These studies suggest that serum levels change very slightly over 2 to 3 weeks of ingesting aluminum gels (when there is no intake of citrate). A prospective, controlled study in children and young adults undergoing peritoneal dialysis[442] with

measurements of aluminum levels at 2-monthly intervals, showed a slow increase of basal (or unstimulated) serum aluminum from 22.4 ± 30 μg/L to 57.8 ± 13 μg/L after 12 months with intake of aluminum hydroxide, 30 mg/kg BW, a dose considered "safe" in children with CKD[443]; this contrasts to serum aluminum decreasing from 21.6 ± 2.3 to 13.2 ± 1.3 μg/L in the group given only calcium carbonate.[442] In the Al-gel group, plasma aluminum levels had increased significantly by 4 months ($P < 0.05$), and the levels differed from the group not ingesting aluminum gels ($P < 0.05$). These studies showed that "safe" and "low" aluminum hydroxide doses failed to prevent significant rises in plasma intact PTH and alkaline phosphatase and worsening of hyperparathyroid bone disease on repeat bone biopsy after 13 months. Such data suggest that measuring plasma aluminum at 6-monthly intervals would be capable of detecting increased aluminum burden from oral aluminum gels.

- The changes in serum aluminum after withdrawal of aluminum gels provides information on how rapidly serum aluminum levels fall after they were known to be elevated. In 32 hemodialysis patients, plasma aluminum fell from 105 ± 21 μg/L to 34 ± 11 μg/L, 8 months after aluminum gels were stopped; the fall was slow with the magnitude of reduction being −67.3% ± 5.1% of "baseline" after 8 months.[203] In another study of individual serum aluminum values measured at 6-monthly intervals in 13 patients,[444] serum aluminum levels, ranging up to 66 μg/L while they received aluminum gels, fell below 20 μg/L at 6 months in all except 1 patient who "consumed large doses of $Al(OH)_3$."
- **Ingestion of Aluminum Gels and Aluminum Toxicity.** Is there a dose of aluminum gels that is effective and yet safe for long-term use? The safety of aluminum gels cannot be evaluated unless there is confidence that the dialysate contains no aluminum. The prevalence of aluminum-related bone disease has decreased markedly over the last 10 to 15 years in association with increased use of nonaluminum phosphate-binding agents in combination with purification of water used for dialysate.[14,418] A large population study of 289 patients reported that the cumulative dose of aluminum is a continuous variable predicting the risk of aluminum bone disease compared to other bone pathology, based on a difference of total intake of 1 kg of aluminum hydroxide (equal to 2 Alucap™ capsules thrice daily for 1 year).[59] One study of 17 patients with bone evaluated postmortem showed a close correlation ($r = 0.80$) between bone aluminum content and the cumulative intake of aluminum gels.[445] Another report of 92 dialysis patients undergoing bone biopsy also showed a close relationship between bone aluminum content and total intake of $Al(OH)_3$ ($r = 0.83$)[446]; moreover, bone aluminum levels were trivially elevated above normal in the dialysis patients who never ingested aluminum gels. In these reports,[445,446] the finding of aluminum bone disease was limited to patients with the greatest cumulative dose of aluminum gels; the latter is related to the duration of dialysis treatment. Among 253 Italian hemodialysis patients ingesting aluminum hydroxide, there was a relatively close association between serum aluminum levels and bone aluminum content; 93% of patients with serum aluminum levels above 60 μg/L had bone aluminum content above 60 μg/kg dry weight BW.[447] A study in children and young adults on CAPD[442] showed evidence of aluminum accumulation based on the result of a DFO infusion test (using 40 mg/kg BW), after only 1 year of consuming a "low dose" of aluminum gels; thus, the increment of serum aluminum rose from 58 ± 65 μg/L to 206 ± 153 μg/L. These data point to the risk of ingestion of aluminum gels, for any length of time. If aluminum gels are ingested, care must be taken to avoid the concomitant intake of any compound containing citrate because of the profound effect of citrate to enhance aluminum absorption.[409] Such intake is difficult to monitor since several over-the-counter preparations contain citrate (eg, AlkaSeltzer™ or Citracal™); they can be consumed

without any knowledge of those treating the patient.[317]

- **Monitoring Serum Aluminum and Recognition of Aluminum Toxicity.** One study reported monitoring serum aluminum twice yearly over the 4-year period, 1984-1987.[444] There were 1,193 Belgian dialysis patients in dialysis units with "negligible aluminum contamination of dialysate"; from 1986 onward, water aluminum concentrations were constantly below 3 $\mu$g/L. Data analysis involved individual measurements of serum aluminum rather than mean values for each patient. In a subset of 77 patients with bone biopsies, 31% demonstrated aluminum bone disease. With a cut-off serum aluminum of 60 $\mu$g/L, there was a sensitivity and specificity for detecting aluminum bone disease of 82% and 86%, respectively. Among the total group of patients, 6 were diagnosed with dialysis encephalopathy, based on clinical features and EEG abnormalities. The median serum aluminum was 121 $\mu$g/L (range, 15 to 462 $\mu$g/L) in patients with dialysis encephalopathy compared to 42 $\mu$g/L (range, 4 to 140 $\mu$g/L) in matched controls. Most patients had undergone dialysis for some time before these aluminum measurements were initiated.
- **DFO Infusion Test as a Predictor of Aluminum Bone Disease.** Because of side-effects with the DFO test using doses of 20 to 40 mg/kg BW,[433,434,448] such doses have been abandoned in favor of using lower doses.[436-438] DFO tests, both 10 mg/kg BW and 5 mg/kg BW, were given to 77 hemodialysis patients with bone biopsies; the patients came from European countries, North Africa, and South America. Both doses were given to 71 patients, with alternate order of giving the 2 doses. The indications for bone biopsy included a serum aluminum level above 60 $\mu$g/L or in those with serum aluminum below 60 $\mu$g/L, the presence of symptoms of osteodystrophy, radiological signs of osteodystrophy, or the need for calcitriol therapy or parathyroidectomy based on biochemical parameters. Based on a chemical aluminum content of bone $>$15 $\mu$g/g wet weight combined with positive aluminum staining ($>$0%), 57 patients were classified as having aluminum overload; 15 others were classified with aluminum bone disease (ABD) based on aluminum staining $>$15 % of bone surface *and* bone formation rate (BFR) reduced below normal. Using the DFO dose of 5 mg/kg BW, the combination of intact PTH $<$150 pg/mL (16.5 pmol/L) and an increment of serum aluminum $>$50 $\mu$g/L had a sensitivity of 87% and a specificity of 95% for detecting ABD. Use of the 10 mg/kg DFO dose provided no additional benefit.
- Several studies evaluated low doses of DFO but did not compare the results to findings on bone biopsy. The increment of serum aluminum was evaluated after 2 DFO tests, 30 mg/kg, and a total dose of 500 mg, in 22 hemodialysis patients: the lower dose was as efficacious in detecting evidence of aluminum overload as the higher dose.[449] Other reports utilized still lower doses of DFO: doses of 0.5, 2.5, and 5.0 mg/kg were each given to 5 patients with serum aluminum levels above 40 $\mu$g/L and the change in total and ultrafilterable aluminum measured after 44 hours.[437] The total and ultrafilterable aluminum rose with each dose, suggesting a reliable test value of even the lowest dose. Another study described repeated use of doses of 0.5 mg/kg, demonstrating significant chelation of aluminum with this so-called minidose.[438]

### Limitations

The evidence that aluminum is absorbed from aluminum hydroxide and other aluminum-containing compounds is indirect; however, the methodology for measuring true aluminum absorption using a stable isotope and mass spectroscopy is very expensive, has limited availability, and is likely to be done in very small numbers of patients. The close relationship between the cumulative aluminum intake and the skeletal accumulation of aluminum, along with the reduced prevalence of aluminum bone disease as the use of aluminum gels has decreased, provides only indirect—but convincing—evidence to recommend that aluminum gels not be used as phosphate binders, except for a very short periods of time.

The substantial reduction in prevalence of

aluminum bone disease, and the apparent disappearance of this problem in dialysis units where aluminum gels are not used as phosphate binders, makes this a problem that may be disappearing.

Prospective comparison of aluminum gels and calcium-based phosphate binders was done in a small numbers of patients and was limited to 1 year of therapy.[442] Also, the studies that showed the close correlation between the quantity of aluminum ingested and that present in bone at postmortem[445] or on biopsy[447] were not prospective studies.

### Clinical Applications

Awareness of the various manifestations of aluminum toxicity by all health-care providers will allow early recognition of aluminum loading and aluminum toxicity in CKD patients. This will permit the earlier diagnosis and treatment of the syndromes of aluminum toxicity, thereby leading to reduced morbidity and disability. Use of the recommended low dose for the DFO test will minimize any risk of side-effects from the test. Such better safety should lead clinicians to use the DFO test with more confidence in clinical conditions when it may be useful or necessary. Through proper monitoring of plasma aluminum levels and the interpretation of these values, there will be earlier recognition of aluminum loading, with a greater ability to prevent the occurrence of aluminum toxicity.

### Future Research

Longitudinal studies with the measurement of serum aluminum at 6-monthly intervals from the very outset of dialysis, combined with a subsequent DFO test and bone biopsy in randomly selected patients and others chosen because serum aluminum levels rise $>40$ $\mu$g/L, could provide information on the "peak" aluminum levels at which there may be a risk of aluminum loading or the development of aluminum bone disease.

Limited long-term trials with very low doses of aluminum gels, which remain the most "potent" of phosphate binders, would be useful. Such doses, however, almost certainly would need to be combined with another type of phosphate-binding agent.

Large, prospective, long-term trials with the use of "low doses" of aluminum gels as phosphate binders would be useful. Those who remain convinced that low doses of aluminum are safe (and there remain some with this viewpoint) should seem compelled to design such trials to prove the point. Whether low doses of aluminum gels might be effective and safe when they are given in combination with continued "minidoses" of DFO treatment[438] would be useful to consider for a prospective trial, particularly with the growing concern about potential risks of calcium-based phosphate binders.

## GUIDELINE 12. TREATEMENT OF ALUMINUM TOXICITY (ALGORITHM 8 AND ALGORITHM 9)

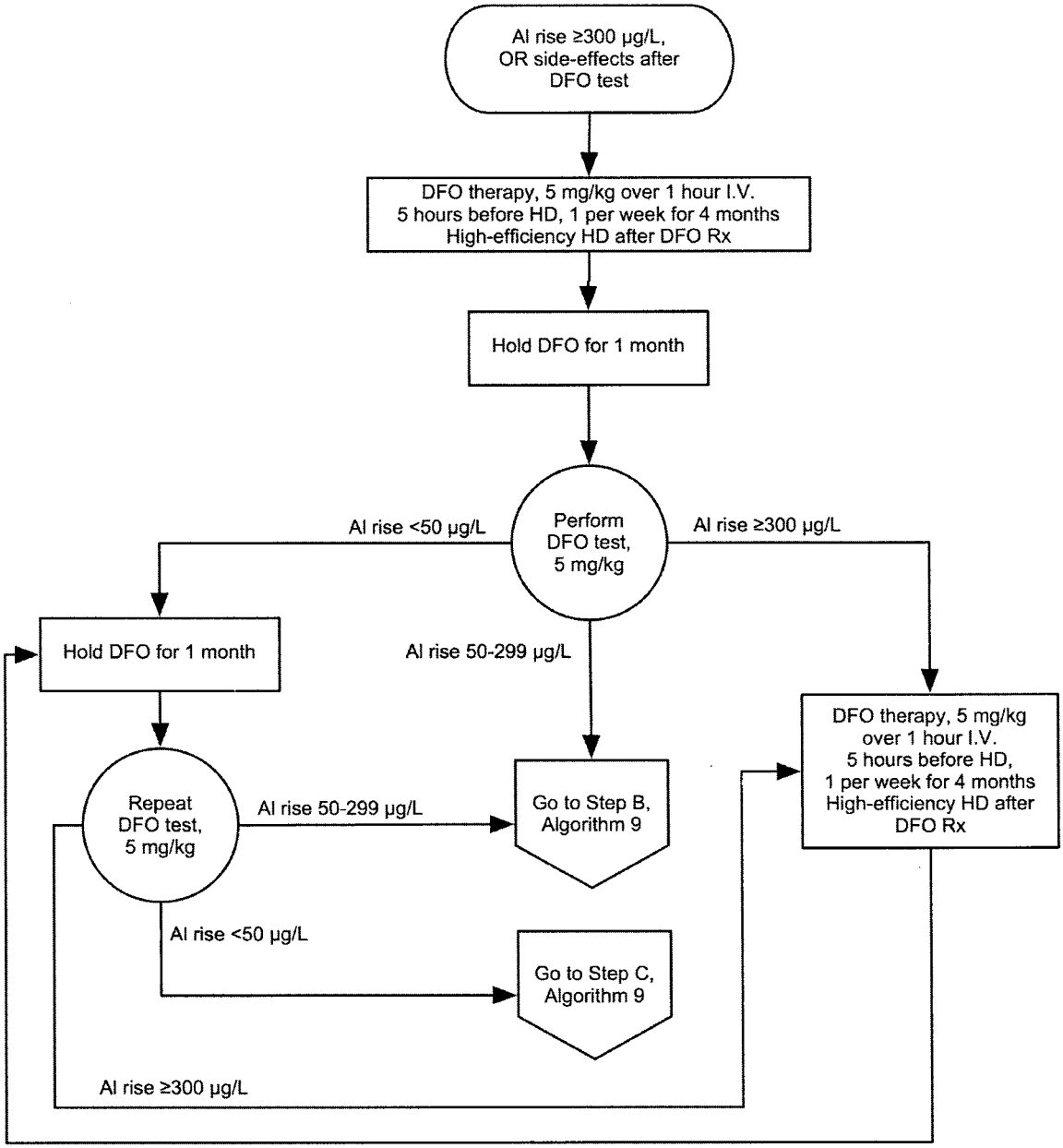
**12.1 In all patients with baseline serum aluminum levels $>60$ $\mu$g/L, a positive DFO test, or clinical symptoms consistent with aluminum toxicity (Guideline 11, Table 31), the source of aluminum should be identified and eliminated. (OPINION)**

**12.2 In symptomatic patients with serum aluminum levels $>60$ $\mu$g/L but $<200$ $\mu$g/L or a rise of aluminum after DFO $>50$ $\mu$g/L, DFO should be given to treat the aluminum overload. (See Algorithm 8 and Algorithm 9.) (OPINION)**

**12.3 To avoid DFO-induced neurotoxicity in patients with serum aluminum $>200$ $\mu$g/L, DFO should not be given until intensive dialysis (6 days per week) with high-flux dialysis membrane and a dialysate aluminum level of $<5$ $\mu$g/L and until the pre-dialysis serum aluminum level has been reduced to $<200$ $\mu$g/L. (OPINION)**

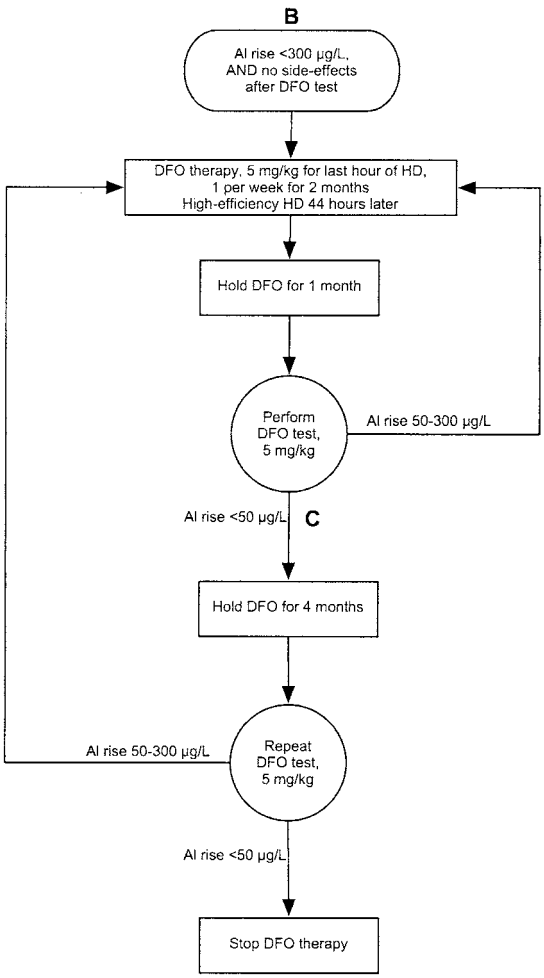
### Background

When dialysis encephalopathy and dialysis-related bone disease were first recognized, most patients had progressive disease with profound morbidity and very high mortality. The early cases arose, in large part, due to aluminum-contaminated dialysate. However, most patients were also receiving aluminum gels to control hyperphosphatemia, as it was then believed that little or none of the aluminum was absorbed. The first successful reversal of symptoms of dialysis




**Algorithm 8. DFO treatment after $P_{Al}$ rise ≥300 $\mu$g/L.**

encephalopathy were observed with DFO given in doses of 20 to 40 mg/kg for treating patients with aluminum-related bone disease. There was clinical and histological improvement; however, immediate side-effects affecting vision and mental status appeared in isolated patients, and there was concern about the use of DFO. More ominous was the appearance of rapidly progressive and fatal mucormycosis in dialysis patients who had been receiving DFO treatment. At about the same time, there was the introduction of calcium-based phosphate binders as well as widespread purification of water used for dialysate, so the prevalence of severe aluminum toxicity seemed to diminish. However, some aluminum toxicity still occurs and there remains a question of when and how chelation therapy with DFO should be used.




**Algorithm 9. DFO treatment after $P_{Al}$ rise between 50 and 300 $\mu$g/L.**

## Rationale

### *Beneficial Effect of DFO Treatment on Aluminum Bone Disease and Other Features of Aluminum Toxicity*

Long-term DFO treatment reduces the surface-stainable aluminum on trabecular bone.[430,450-453] This is associated with an increase of bone formation rate,[430,450-452] and symptoms of proximal muscle weakness and bone pain commonly improve.[450,454,455] Isolated reports have shown improved neurological symptoms in patients with dialysis encephalopathy.[456-460] In these reports, DFO doses have varied from 1 to 6 g[430,454] or, expressed in relation to body weight, 30 to 40 mg/kg BW per treatment.[451,452,461] The treatment was given once weekly in some trials,[430,455] and with each dialysis (thrice weekly) in others.[451,452,461] In 1 study,[430] the reduction of stainable aluminum and improved bone formation rates were substantially less in patients with an earlier parathyroidectomy than in those with intact parathyroid glands. Treatment with DFO was associated with improvement of anemia in some, but not all, patients.[453,461,462]

### *Side-Effects of DFO Treatment*

Two serious problems associated with DFO therapy are: (1) the precipitation of acute aluminum neurotoxicity and (2) the development of mucormycosis, which is commonly fatal.

***Precipitation of acute aluminum neurotoxicity.*** When DFO is given to patients with very high serum aluminum levels (>200 $\mu$g/L), acute and fatal aluminum neurotoxicity has been precipitated[411,412]; this presumably occurs because aluminum is rapidly mobilized from various tissue stores.

***Fatal mucormycosis in dialysis patients receiving DFO.*** In experimental infections with *Mucor* species, DFO administration markedly augments the growth and pathogenicity of the mucormycosis.[463,464] When DFO is given, it chelates iron to form feroxamine; the latter has a molecular weight of 714 Da and several dialysis treatments are needed to clear it from the circulation. Certain species of *Mucor*, with very low pathogenicity, exist widely in nature and are found on skin and mucous membranes; feroxamine enhances their growth and pathogenicity, thereby promoting the development of fatal disseminated or rhinocerebral mucormycosis in hemodialysis patients given DFO.[320,435,465] Most afflicted patients had received DFO, 20 to 40 mg/kg BW, once or thrice weekly, with standard dialysis membranes (usually cuprophane) employed. The shortest reported duration of treatment before infection appeared was 3 weeks.[435]

***Methods to avoid serious side-effects. In patients exposed to high dialysate aluminum levels or with high plasma aluminum levels (>120 µg/L), the following scheme is recommended to reduce the risk of acute neurotoxicity:***

The very first dose of DFO is withheld until serum aluminum levels are substantially reduced after total withdrawal of aluminum exposure—both from dialysate and from ingesting aluminum-containing drugs. With serum aluminum levels

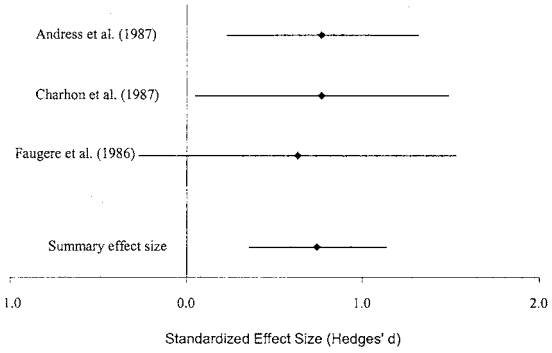



**Fig 14. Individual study and summary effect sizes for the effect of DFO therapy on bone formation rate.**

>200 μg/L, daily hemodialysis should be done using high-flux membranes and dialysate aluminum concentration <5 μg/L. The first "low dose" DFO test (5 mg/kg) should be done only after 4 to 6 weeks of such treatment, with increment of plasma aluminum determining the timing of subsequent DFO treatments. If the increment of aluminum is high (>300 μg/L), DFO treatments should be given via a peripheral vein, 5 hours before the next dialysis that uses a high-flux membrane; this allows for rapid removal of the DFO-aluminum complexes from the circulation and minimizes the duration of patient exposure to high concentrations of the DFO-aluminum chelate (aluminoxamine).

If the increment of plasma aluminum after the first DFO test is <300 μg/L and no neurological or ophthalmological symptoms appear, the DFO can be given over the last hour of dialysis, with the next dialysis done using a high-flux dialyzer, 44 hours later. The dose of DFO should be 5 mg/kg, with an expanded interval between treatments of 3 to 4 dialysis procedures using a high-flux hemodialysis membrane; this allows for more complete clearance of feroxamine from the circulation, reducing the risk of mucormycosis. Intravenous iron should be avoided while DFO is being given to limit the formation of feroxamine.[435,463]

***Management of aluminum overload without symptoms.*** The proper management of aluminum overload in the absence of symptoms is not established. There have been "consensus" viewpoints that aluminum overload be treated with DFO[466]; however, there are no data to support this recommendation. When CKD Stage 5 patients with aluminum overload and high plasma aluminum levels have aluminum gels withdrawn and they undergo dialysis with aluminum-free dialysate (<5 μg/L), plasma aluminum levels fall substantially and progressively.[203,442,444] Small numbers of patients with histomorphometric features of aluminum bone disease but without any musculoskeletal symptoms were treated as above; after 1 year, repeat bone biopsies showed a reduction of surface stainable aluminum and a rise in bone formation rate consistent with reversal of aluminum bone disease.[467,468] The exception was 2 patients who had previously undergone parathyroidectomy; in these 2 patients, there was a modest reduction of surface-stainable aluminum but bone formation rate did not improve to normal.[468] These data suggest that DFO therapy may not be needed for the treatment of asymptomatic patients.

### *Strength of Evidence*

**Beneficial Effects of DFO Therapy.** Several trials with DFO therapy showed a reduction of surface aluminum staining,[430,451-454] and an increase in bone formation rate,[430,451,452,454] after treatment periods of 8 to 12 months. Meta-analysis of 4 trials that provided data on aluminum staining and 3 trials with bone formation rate are shown in Figs 14 and 15, respectively. The doses used were variable, ranging from 20 to 40 mg/kg; there are no data to indicate a benefit of thrice-weekly treatment compared to once weekly. All these trials utilized standard dialysis membranes (probably cuprophane). The data on improvement of neurological features of dialysis encephalopathy involve many reports of small

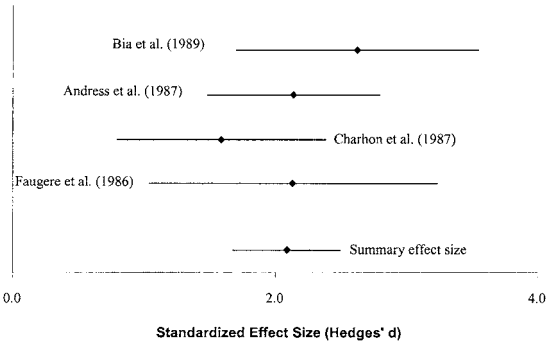



**Fig 15. Individual study and summary effect sizes for the effect of DFO therapy on bone surface aluminum stain.**

numbers of patients who received such treatment.[456-460,469-471]

Data on the most efficient means to clear DFO-bound aluminum from the circulation include dialysis using a high-flux membrane[472] or hemoperfusion with a charcoal filter[473]; these remove aluminum more rapidly than standard dialysis using cuprophane membranes. A crossover study compared: (1) the combination of charcoal perfusion combined with standard dialysis; (2) dialysis using a high-flux membrane; and (3) standard dialysis. The hemoperfusion/hemodialysis combination had a small advantage over the high-flux dialyzer,[474] and standard dialysis was inferior to both. In this study, the removal of feroxamine (the DFO-iron complex) was far greater with either the high-flux dialyzer or the hemoperfusion/hemodialysis combination than with the standard cuprophane dialyzer. Other studies showed that either intraperitoneal or intramuscular administration of DFO was effective in augmenting aluminum removal in patients undergoing peritoneal dialysis.[475,476] The intramuscular administration of DFO, as it is sometimes given in hematological disorders, may provide a convenient method 4 to 5 hours before dialysis when an intravenous route is not available.[476]

Experience with the "safe" long-term treatment with DFO is derived from an outbreak of marked aluminum loading due to aluminum contamination of water used to prepare the dialysate solution. A 6-month course of "low-dose" DFO treatment was used in 42 patients exposed to high dialysate aluminum.[477] After neurological symptoms first appeared, but before the diagnosis of aluminum intoxication was made, 11 patients had died. Forty-two other patients were followed. All aluminum gels were stopped, a new reverse-osmosis system was installed, and an alternate water source was used (dialysate Al $<2$ $\mu$g/L). The initial basal aluminum levels were $506 \pm 253$ $\mu$g/L (mean $\pm$ SD; range, 104 to 1,257 $\mu$g/L); hemodialysis was done for 4 hours, 6 days per week; charcoal hemoperfusion was combined with the dialysis weekly. (High-flux dialysis membranes, which had similar clearance of DFO-stimulated aluminum as hemoperfusion, were not available.) After 4 weeks, the frequency of dialysis was reduced to thrice weekly with hemoperfusion once weekly.

After 6 weeks of such "intensive hemodialysis/hemoperfusion," the basal serum aluminum fell from $506 \pm 253$ $\mu$g/L to $121 \pm 46$ $\mu$g/L (mean $\pm$ SD). The first DFO infusion test (5 mg/kg) was given during the last hour of dialysis; the increment of plasma aluminum was 300 $\mu$g/L in 11 patients, 7 of whom developed neurological symptoms (headache, hallucinations, or myoclonic jerks) and 2 developed ophthalmological symptoms (transiently blurred vision) after the DFO test; 30 patients had increments of plasma aluminum $<300$ $\mu$g/L, only 3 of whom had developed neurological symptoms. These 3 symptomatic patients and the 11 patients with a post DFO aluminum increment $<300$ $\mu$g/L received DFO treatment given via a peripheral vein 5 hours before starting a hemodialysis/hemoperfusion session (Group 1). The other 27 patients (Group 2) received DFO (5 mg/kg) during the last hour of dialysis with a hemodialysis/hemoperfusion session done 44 hours later. The DFO treatments were given weekly in all patients. After 4 months, DFO was stopped for a 4-week "washout," and the DFO test was repeated. If the basal plasma aluminum was $<60$ $\mu$g/L and the increment after DFO was $<50$ $\mu$g/L, the DFO treatment was stopped (2/14 of Group I and 8/27 of Group 2). If the basal serum aluminum level or the increment exceeded these limits, DFO treatment was continued weekly for an additional 2 months. There have been no comparisons of different doses of DFO, although crossover studies with single infusions and small short-term studies suggest that doses lower than 5 mg/kg may be useful.

Throughout this 6 months of DFO treatment, no neurological or ophthalmological symptoms appeared and the baseline plasma aluminum gradually fell, as did the increment after DFO. There were significant increments in the mean cell volume (MCV) of RBCs and a modest rise in plasma intact PTH levels in both groups.[478]

**Mucormycosis and DFO Treatment.** Numerous case reports have described fulminant, fatal cases of systemic or rhinocerebral mucormycosis in dialysis patients being treated with DFO for aluminum toxicity,[320,435,465,479,480] while reports of mucormycosis among dialysis patients not receiving DFO are unusual.[391] An international registry collected 59 cases of mucormycosis among dialysis patients[435]; among these, 78% had been treated with DFO for aluminum or iron

overload. In this report, the mortality was 91%, the disorder was the disseminated or rhinocerebral variety in 75% of the cases, and a diagnosis of mucormycosis was made only at autopsy in 61%. Experimental infections with mucormycosis in animals demonstrated that DFO, and in particular feroxamine, augmented the pathogenicity of certain species of *Mucor* and prevented effective treatment with amphotericin B.[463,464,481] Increased susceptibility to mucormycosis was found to occur because of persistence of significant concentrations of feroxamine, the iron chelate with DFO, in ESRD patients given DFO. Such feroxamine is rapidly excreted by the kidneys of hematology patients treated with the drug, and mucormycosis has been very rare among DFO-treated hematology patients with normal kidney function.[391] The clearance of feroxamine by a standard dialyzer is quite low, and 3 to 4 dialysis treatments may be required to clear this substance from the blood.[474]

With proper water purification and reduction in the intake of aluminum gels, the incidence of aluminum bone disease and other features of aluminum toxicity has decreased substantially. Over the same period, there have been trials utilizing much lower doses of DFO to treat aluminum toxicity. Also, there appeared to be fewer cases of mucormycosis in 1986 through 1989 as the DFO usage decreased. For a recent review of mucormycosis, an attempt was made to locate cases that had occurred over the last 10 years; in communications with various individuals in Belgium, Spain, Portugal, and the United States with interest in aluminum toxicity and use of DFO, no recent cases of mucormycosis associated with DFO therapy could be identified.[482]

Attention has been given to methods that utilize DFO in a manner that reduces its risk. By reducing the time between the administration of DFO and the next dialysis, and by doing the dialysis with a highly permeable membrane, both feroxamine and the aluminum chelate, aluminoxamine, are removed more effectively.[472] Hemoperfusion with a sorbent cartridge has also been very effective[474]; however, such cartridges are not presently available in the United States. In addition, there has been a reduction of the DFO dose from 20 to 40 mg/kg to 5 to 10 mg/kg, with the DFO dose given 4 to 6 hours before the next dialysis, along with the use of a high-flux or highly permeable dialysis membrane and/or the use of a sorbent system.[477] Also, DFO should only be given every 7 to 10 days,[477] with 3 to 4 dialysis procedures between each dose of DFO.[477] With attention to prevention of aluminum toxicity by curtailing the administration of aluminum-containing drugs and attention to proper water purification, the incidence of aluminum toxicity is now much lower than it was 10 to 15 years ago. It has not been possible to identify patients who have developed mucormycosis when these newer protocols have been followed.

#### Limitations

The trials showing beneficial effects of DFO treatment on bone biopsies and symptoms of aluminum bone disease were done several years ago when symptomatic aluminum bone disease was common, and most used DFO in doses of 20 to 40 mg/kg BW. Despite this, the numbers of patients in prospective trials was relatively small; also, because of the severity of the disorder and poor prognosis in untreated patients, there were no controlled trials. In a small trial of asymptomatic patients found to have biopsy evidence of aluminum bone disease, there was reduced surface staining of aluminum and increased bone formation when all exposure to aluminum was eliminated.[468] There is evidence in one trial that the use of DFO in a dose of 5 mg/kg is effective in lowering basal serum aluminum. The largest trial represented acute marked aluminum loading, and neurological rather than skeletal disease was the major risk. Fourteen patients who were not treated died, and there was only 1 death (due to hyperkalemia) among 42 patients who followed the recommended protocol.[405] Small studies suggest that doses of DFO as low as 1 mg/kg and 0.5 mg/kg can raise the ultrafilterable aluminum in plasma, so such aluminum can be removed by dialysis, but there are no long-term data documenting the effectiveness of such low doses.

With regard to the safety of using low doses of DFO, the reduced frequency of its administration to once weekly, and use of high-flux dialyzers to minimize the increased susceptibility to mucormycosis, the evidence is only indirect. It has not been possible to find any cases of mucormycosis with this schema. If no new cases of fatal mucormycosis appear, this will be presumptive evi-

dence of the effectiveness of the preventive measures.

The management of dialysis patients with "asymptomatic aluminum loading" has not been carefully evaluated, and the recommendation of treating such patients with DFO[466] has not been critically evaluated. There was a small number of dialysis patients with elevated plasma aluminum levels and histological features of aluminum bone disease, who had repeat biopsies approximately 12 months after all aluminum was withdrawn.[467,468] The close association between the reduction of surface stainable aluminum and the improvement of bone formation and mineralization rate[468] is consistent with a "cause and effect" relationship. Whether such patients would have had greater improvement after receiving DFO treatment is uncertain. The lack of improvement of bone formation in the patients with earlier parathyroidectomy[468] is consistent with failure of bone histomorphometry to improve in DFO-treated patients with symptomatic aluminum bone disease.[430]

#### Clinical Applications

The proper and early identification and treatment of aluminum toxicity, even that occurring accidentally via unusual contamination of dialysate or water, is now possible and safe using the low doses of DFO that are recommended. Although prevention of aluminum toxicity is greatly preferred, the early recognition and initiation of aggressive treatment might reduce the very high mortality associated with acute aluminum neurotoxicity when patients are seen in the early phases and treated with daily, high-efficiency dialysis until it is safe to begin DFO treatment. A clinician's fear of using DFO, based entirely on problems that occurred with use of DFO in doses of 20 to 40 mg/kg, should give way to the timely use of DFO when it is needed using a "safe" dose of 5 mg/kg, followed by dialysis using a high-efficiency dialysis membrane. These precautions are designed to minimize any risk of side-effects of the DFO treatment.

#### Recommendations for Research

With the great reduction of incidences of aluminum toxicity, large clinical trials to evaluate its treatment are not likely to occur or to be possible. Some nephrologists still believe that certain "low doses" of aluminum gels are indeed both safe and effective to control serum phosphorus levels. It would be well to establish long-term, prospective trials in such patients to assess the safety of the treatment in comparison to other nonaluminum-based phosphate binders. There is little doubt that aluminum-based phosphate binders are more potent and effective in binding dietary phosphate, in comparison to similar doses of other phosphate-binding agents.[144]

Very small and uncontrolled trials indicate that it is possible to give aluminum-based binders combined with very small doses of DFO ($<$1 mg/kg), and the investigators reported a slow, gradual reduction of plasma aluminum levels during such treatment.[438] Others have shown that DFO in doses of 0.5 to 1.0 mg/kg increases the ultrafilterable (and hence the dialyzable) level of plasma aluminum in dialysis patients with elevated plasma aluminum levels.[437] These data provide the background for a potential prospective trial that could test the safety and effectiveness of aluminum gels combined with repeated, very low doses of DFO in comparison to other nonaluminum-based phosphate binding agents.

Investigators with interest in aluminum toxicity and its treatment need to collect additional series and cases where the DFO is given in "low" doses of 5 mg/kg BW or even less. Recognizing whether cases of mucormycosis will be seen with such doses and use of high-efficiency dialyzers is also needed.

In a population with substantial numbers of patients with aluminum overload and minimal symptoms, controlled trials comparing total aluminum withdrawal with DFO treatment would be worthwhile to prove the advantage of DFO treatment over total withdrawal of exposure to aluminum.

## GUIDELINE 13. TREATMENT OF BONE DISEASE IN CKD

**The therapeutic approach to bone disease in CKD is based on its specific type. As such, this Guideline encompasses 3 parts: Guideline 13A deals with high-turnover and mixed bone disease; Guideline 13B with osteomalacia; and Guideline 13C with adynamic bone disease.**

## GUIDELINE 13A. HYPERPARATHYROID (HIGH-TURNOVER) AND MIXED (HIGH-TURNOVER WITH MINERALIZATION DEFECT) BONE DISEASE

**13A.1 In CKD patients (Stages 3 and 4) who have plasma levels of intact PTH >70 pg/mL (7.7 pmol/L) (Stage 3) or >110 pg/mL (12.1 pmol/L) (Stage 4) on more than 2 consecutive measurements, dietary phosphate intake should be restricted. If this is ineffective in lowering plasma PTH levels, calcitriol, (EVIDENCE) or 1 of its analogs [alfacalcidol (EVIDENCE) or doxercalciferol (OPINION)] should be given to prevent or ameliorate bone disease. (See Guideline 8A.)**

**13A.2 In CKD patients (Stage 5) who have elevated plasma levels of intact PTH (>300 pg/mL [33.0 pmol/L]), calcitriol (EVIDENCE) or 1 of its analogs (doxercalciferol, alfacalcidol, or paricalcitol) (OPINION) should be used to reverse the bone features of PTH overactivity (ie, high-turnover bone disease), and to treat defective mineralization. (See Guideline 8B.)**

### Background

Numerous studies have shown that high-turnover bone (encompassing both osteitis fibrosa and mixed uremic osteodystrophy) is often associated with serum levels of intact PTH of over 400 pg/mL (44.0 pmol/L), though high-turnover lesions may be seen at lower intact PTH levels and low-turnover bone disease may occur at serum levels of intact PTH above 400 pg/mL (44.0 pmol/L).

### Rationale

The understanding of bone disease in CKD has evolved dramatically over the years. The recognition that hyperparathyroidism is a complication of kidney failure actually predated, by many years, the initiation of dialysis treatment. Early studies of osteodystrophy focused largely on understanding the pathophysiology and the prevention of hyperparathyroidism. The development of increasingly more precise and specific PTH assays permitted more careful studies of the calcium and PTH interaction and the importance of phosphate in this interaction.

#### *Strength of Evidence*

- **Bone Histology Studies.** Initial bone histological studies in the 1960s and 1970s demonstrated the heterogeneity of bone abnormalities. Generally, 2 patterns were described: osteomalacia and osteitis fibrosa. Osteomalacia, characterized by large amounts of unmineralized osteoid, strongly resembled the picture seen in severe vitamin D deficiency. With the demonstration of the critical role of the kidney in vitamin D metabolism, it was thought that the synthesis of the active form of vitamin D would provide the answer to this abnormality. Osteitis fibrosa, in contrast, had been long identified with primary hyperparathyroidism in the general population and the features seen in dialysis patients were quite typical of what had been described in that setting—increases in osteoclasts, osteoblasts, osteocytes, and fibroblasts resulting in abnormal bone resorption, abnormal bone formation, and marrow fibrosis. It was assumed that suppression of PTH would resolve that problem. Ultimately, 2 other histological lesions were described: (1) the adynamic form, characterized by suppressed bone formation with various degrees of bone resorption; and (2) mixed uremic osteodystrophy, with various degrees of mineralization defect and hyperparathyroid bone changes. Mixed uremic osteodystrophy can also be considered a variant of hyperparathyroid bone disease. In summary, there is a continuous spectrum of abnormalities from low-turnover, adynamic bone lesions at one extreme to the high-turnover, osteitis fibrosa lesions at the other.
- **PTH Studies.** Early studies evaluating PTH were compromised by the imprecise nature of early assays, which measured the carboxy-terminal portion of this 84-amino-acid polypeptide. The C-terminal assays were particularly flawed in kidney failure, because of the accumulation of fragments that are normally excreted by the kidney.

Subsequently, an amino-terminal assay was more accurate in reflecting high values, but was less effective in discriminating low values. In recent years, the "intact" PTH assay has proven superior to previous assays. Correlations with bone histology, largely carried out over the past decade, have shown it to be better predictive of pathological findings, and to be the best "noninvasive" marker of bone turnover.

Because of the difficulty and expense of obtaining bone biopsies, most clinical studies of osteodystrophy have utilized the levels of PTH, particularly intact PTH, as a marker for bone turnover. Thus, the newer vitamin D analogs have largely obtained FDA approval for use in the control of intact PTH and do not have adequate data to document their effect on bone histology. Limited data do exist to show that features of hyperparathyroid bone disease (osteitis fibrosa) are improved by both oral and parenteral calcitriol. Since intact PTH levels correlate with bone turnover, it was assumed that avoidance of very high or very low intact PTH levels would prevent either the hyperactive osteitis fibrosa or the hypoactive adynamic disorder, though no convincing outcome studies proved this. Indeed, it has been shown recently that the intact PTH assays measure not only PTH-(1-84) but also large C-terminal fragments, some of which antagonize the effects of PTH-(1-84) on bone.

### Limitations

See the corresponding section in Guidelines 8A and 8B.

### Recommendations for Research

Studies are needed to evaluate the changes in bone histology, PTH, and its fragments with the available vitamin D analogs and other therapeutic approaches.

## GUIDELINE 13B. OSTEOMALACIA

**13B.1 Osteomalacia due to aluminum toxicity should be prevented in dialysis patients by maintaining aluminum concentration in dialysate fluid at $<10$ $\mu$g/L and avoiding the use of aluminum-containing compounds (including sucralfate). (OPINION)**

**13B.2 Aluminum overload leading to aluminum bone disease should be treated with deferoxamine (DFO). (See Guidelines 11 and 12.) (OPINION)**

**13B.3 Osteomalacia due to vitamin $D_2$ or $D_3$ deficiency or phosphate depletion, though uncommon, should be treated with vitamin $D_2$ or $D_3$ supplementation (see Guideline 7) and/or phosphate administration, respectively. (OPINION)**

**13B.3a If osteomalacia due to vitamin D deficiency fails to respond to ergocalciferol or cholecalciferol, particularly in patients with kidney failure (Stage 5), treatment with an active vitamin D sterol may be given. (OPINION) (See Guideline 8B.)**

**13B.3b Doses of phosphate supplementation should be adjusted upwards until normal serum levels of phosphorus are achieved. (OPINION)**

### Background

As aluminum accumulates on bone surfaces, it impairs bone formation, leading to either osteomalacia or adynamic bone disease. Since this was recognized and aluminum exposure curtailed, osteomalacia has largely disappeared. However, patients may still be seen with this problem and its diagnosis and treatment need to be understood. If osteomalacia is found in the absence of aluminum, it is often related to preexisting tubular defects of phosphate depletion or vitamin $D_2$ or $D_3$ deficiency.

### Rationale

In the late 1970s, it was documented that osteomalacic bone changes occur in patients with CKD Stage 5 secondary to aluminum intoxication. The clinical manifestations of such lesions are bone pain, fractures, and deranged mineral homeostasis. When marked aluminum loading occurs, brain abnormalities develop which, if untreated, are usually lethal. Treatment with a chelating agent, DFO, dramatically improves patients both clinically and histologically. The avoidance of aluminum has largely eliminated

aluminum-related osteomalacia as a clinical problem in the dialysis population. Occasionally, dialysis patients may present with osteomalacia not associated with aluminum intoxication. This may be due to vitamin D deficiency, drugs (inducers of cytochrome P450 pathways), alcohol, calcium and/or phosphate deficiency, or other toxins.

### *Strength of Evidence*

There is compelling evidence of the role of aluminum in the development of osteomalacia. For detailed discussion, see the corresponding sections in Guidelines 11 and 12.

#### Limitations

Due to the severe clinical outcome of osteomalacia and other complications resulting from aluminum toxicity, no placebo-controlled studies are possible.

#### Clinical Application

A DFO challenge test (see Guidelines 11 and 12) can often identify aluminum overload, but is not specific for the presence of bone lesions. A firm diagnosis of bone aluminum accumulation and its associated histological derangements requires a bone biopsy (see Guideline 12). Treatment approaches to nonaluminum-related osteomalacia need to be tailored according the underlying causative agent (removal of the toxin or supplementation of the missing factors such as vitamin D and/or phosphate). Treatment should be continued until clinical indicators of osteomalacia, such as bone alkaline phosphatase activity in serum, normalize.

#### Research Recommendations

Aluminum accumulation in bone has become much less frequent with cessation of use of aluminum-containing phosphate binders. Unfortunately, the binders which have largely replaced aluminum have not proven completely satisfactory. Studies need to be conducted to determine whether there is a threshold of kidney function below which aluminum-based phosphate binders might be acceptable, and whether there are other substances besides citrate that increase intestinal aluminum absorption. Most importantly, studies evaluating the efficacy and safety of nonaluminum-containing and calcium-based binders are needed.

## GUIDELINE 13C. ADYNAMIC BONE DISEASE

**13C.1 Adynamic bone disease in stage 5 CKD (as determined either by bone biopsy or intact PTH <100 pg/ml [11.0 pmol/L]) should be treated by allowing plasma levels of intact PTH to rise in order to increase bone turnover. (OPINION)**

**13C.1a This can be accomplished by decreasing doses of calcium-based phosphate binders and vitamin D or eliminating such therapy. (OPINION)**

#### Background

Adynamic bone disease has become increasingly frequent since it has become possible to suppress PTH with calcium and potent vitamin D analogs. In certain dialysis centers, it has become the most common bone disorder. The degree to which it increases morbidity and mortality is unknown, but the limited available data increasingly raise concerns about these issues. The main concerns are related to the inability of bone to contribute to mineral homeostasis in the absence of kidney function and the risk of hip fracture.

#### Rationale

With the use of high-dose calcium salts for phosphate binding, and more frequent and aggressive vitamin D treatment, adynamic bone lesions have become increasingly common in histological studies. Typically associated with low PTH levels, the disease has been ascribed to oversuppression of PTH, either with the aggressive use of vitamin D, chronic positive calcium balance, or following parathyroidectomy. It is also seen in association with aging and diabetes, 2 conditions known to predispose to osteoporosis in the general population. Data on bone mass (bone densitometry) and on fracture in dialysis patients increasingly suggest that the adynamic lesion is not without clinical consequences.

While low blood levels of intact PTH strongly suggest the presence of adynamic bone, a high PTH level does not exclude this possibility. His-

tological studies have found adynamic bone despite PTH values well above 400 pg/mL (44.0 pmol/L). This may be related to limitations of the PTH assay due to accumulation of inhibitory PTH fragments. Thus, bone biopsy may be required to establish or rule out the diagnosis of adynamic bone disease even when the level of PTH is at or above target levels.

Accumulating data suggest that the adynamic histology is not benign. A 4-fold increase in hip fracture risk has been found in the dialysis population compared to the general population. Age, duration of dialysis, female sex, and diabetes appear to confer an increased risk for fracture. In 1 study, an increased risk of hip fracture occurred in dialysis patients with lower PTH levels. An increased risk of vertebral collapse fracture has been found in association with a reduced DEXA measurement and low PTH values. An unanswered question is how adynamic bone lesions and osteoporosis are related. Many of the risk factors noted for adynamic bone disease also predispose to osteoporosis in the general population. In addition, low bone turnover is seen in the majority of osteoporotic subjects who do not have kidney disease. Finally, the aging of the dialysis population results in a population that would be expected to be at high risk for osteoporosis. While osteodystrophy and osteoporosis have generally been defined as distinct entities, they are likely to exist together in kidney failure (Stage 5). Recent advances in treatment of osteoporosis, which utilize PTH administration to stimulate bone formation, further strengthen this association.

The relatively inert, adynamic bone does not modulate calcium and phosphate levels appropriately. With this regulatory function impaired, calcium is neither released from nor taken up by the bone normally. One result is that minimal calcium loading often leads to marked hypercalcemia. In addition, with the failure of the bone to accrue calcium, other tissues become vulnerable to its accumulation in the form of metastatic calcification, with calciphylaxis being the most dreaded result. Curiously, early descriptions of calciphylaxis in dialysis patients noted its association with hyperparathyroidism and parathyroidectomy was often curative. More recently, such patients have had low PTH levels and, when assessed, bone biopsy evidence of adynamic histology. Treatment of this condition has been particularly frustrating, but measures to improve bone turnover appear promising.

### *Strength of Evidence*

Calcium kinetic studies clearly show that in patients with adynamic bone disease, decreased calcium accretion with similar intestinal calcium absorption occurs as in patients with high bone turnover. This predisposes the patients to hypercalcemia and risks of calcification. There are no controlled studies on treatment of adynamic bone disease, though its consequences are troublesome. Recommendations on therapy can be based only on the current understanding of the pathogenetic mechanisms of the bone abnormalities.

Bone densitometry and its relationship to fracture has only begun to be defined in end-stage kidney disease patients, though data continue to suggest that bone density is reduced and it is clear that fracture rates are markedly increased. In the general population, there is a strong association between decreased bone density and fractures, both of which are improved by current therapies. The most recently described therapy for osteoporosis, intermittent bolus PTH infusions, is extremely effective in regards to both these outcomes. It seems very possible that these and other measures used in osteoporosis may be of benefit to patients with adynamic bone disease.

#### Limitations

Much of the data described above suggest a relationship between low PTH, bone mass, and low bone turnover in the dialysis population with fracture as a foreseeable outcome. Similar data and outcomes are noted in osteoporosis. Correction of these factors clearly improves the outcome in that disorder. However, there are no fracture or bone mass intervention trials in dialysis patients.

#### Clinical Application

Adynamic bone is treated by increasing bone turnover through an increase in PTH. This can best be accomplished by lowering doses of calcium-based phosphate binders and vitamin D or entirely eliminating such therapy. The lowering of dialysate calcium (1.0 to 2.0 mEq/L) has also been suggested as a possible approach. The 1

published study of this therapy (in peritoneal dialysis patients) did lead to a substantial increase in the number of patients with marked PTH elevation; however, this approach must be considered experimental at this point.

### Research Recommendations

The long-term safety of lower dialysate calcium concentration for treatment of adynamic bone disease, that is the risk of development of osteoporosis, needs to be carefully studied. Moreover, agents with a potential to increase bone turnover (eg, PTH) or newer vitamin D analogs need to be studied as candidates for treatment of adynamic bone disease. Manipulation of the calcium receptor with either calcilytics (which stimulate PTH release) or calcimimetics (which suppress PTH, but increase the amplitude of PTH cycling) may also become important therapeutic agents. Trials with some of these approaches are already underway, while others are planned for the future.

## GUIDELINE 14. PARATHYROIDECTOMY IN PATIENTS WITH CKD

**14.1 Parathyroidectomy should be recommended in patients with severe hyperparathyroidism (persistent serum levels of intact PTH >800 pg/mL [88.0 pmol/L]), associated with hypercalcemia and/or hyperphosphatemia that are refractory to medical therapy. (OPINION)**

**14.2 Effective surgical therapy of severe hyperparathyroidism can be accomplished by subtotal parathyroidectomy, or total parathyroidectomy with parathyroid tissue autotransplantation. (EVIDENCE)**

**14.3 In patients who undergo parathyroidectomy the following should be done:**

**14.3a The blood level of ionized calcium should be measured every 4 to 6 hours for the first 48 to 72 hours after surgery, and then twice daily until stable. (OPINION)**

**14.3b If the blood levels of ionized or corrected total calcium fall below normal (<0.9 mmol/L or <3.6 mg/dL corresponding to corrected total calcium of 7.2 mg/dL), a calcium gluconate infusion should be initiated at a rate of 1 to 2 mg elemental calcium per kilogram body weight per hour and adjusted to maintain an ionized calcium in the normal range (1.15 to 1.36 mmol/L or 4.6 to 5.4 mg/dL). (OPINION)** ***A 10-mL ampule of 10% calcium gluconate contains 90 mg of elemental calcium.***

**14.3c The calcium infusion should be gradually reduced when the level of ionized calcium attains the normal range and remains stable. (OPINION)**

**14.3d When oral intake is possible, the patient should receive calcium carbonate 1 to 2 g 3 times a day, as well as calcitriol of up to 2 $\mu$g/day, and these therapies should be adjusted as necessary to maintain the level of ionized calcium in the normal range. (OPINION)**

**14.3e If the patient was receiving phosphate binders prior to surgery, this therapy may need to be discontinued or reduced as dictated by the levels of serum phosphorus, and some patients may require phosphate supplements. (OPINION)**

**14.4 Imaging of parathyroid glands with $^{99}$Tc-Sestamibi scan, ultrasound, CT scan, or MRI should be done prior to re-exploration parathyroid surgery. (OPINION)**

### Background

Hyperparathyroidism is a common complication of chronic kidney disease that results in significant morbidity and warrants monitoring and therapy throughout the course of kidney disease. The cornerstones of the treatment of hyperparathyroidism include dietary phosphate restriction, the use of phosphate binders, correction of hypocalcemia, and the use of vitamin D sterols. While the majority of patients can be

controlled in this way, medical therapy is not always successful in achieving adequate control of secondary hyperparathyroidism. Accordingly, some patients require surgical parathyroidectomy to correct the problem. Hyperparathyroidism is currently most often assessed using measurements of intact PTH. These assays can be supplemented with measurements of markers of bone metabolism or imaging techniques, as the clinical circumstances indicate. Newer assays which are more specific for the intact PTH 1-84 molecule have been developed, and are becoming available, but warrant further study of their clinical utility.

### Rationale

While medical therapy is often effective for the control of hyperparathyroidism, surgical therapy can provide effective reductions in the serum levels of PTH. In general, it is felt that surgical parathyroidectomy is indicated in the presence of severe hyperparathyroidism associated with hypercalcemia, which precludes further approaches with medical therapy, and/or hyperphosphatemia which also may preclude medical therapy with vitamin D sterols. In these circumstances, surgical ablation of the parathyroid glands can provide effective therapy. The efficacy of surgical parathyroidectomy is well documented.[483-489] An additional indication for surgical parathyroidectomy is the presence of calciphylaxis with PTH levels that are elevated (>500 pg/mL [55.0 pmol/L]), as there are several reports of clinical improvement in patients with calciphylaxis after such therapy. It is important to emphasize, however, that not all patients with calciphylaxis have high levels of PTH, and parathyroidectomy—in the absence of documented hyperparathyroidism—should not be undertaken.

There are many variations on the procedure performed to accomplish surgical parathyroidectomy, which include subtotal or total parathyroidectomy, with or without implantation of parathyroid tissue (usually in the forearm). All of these methods can result in satisfactory outcomes, and no one technique appears to provide superior outcomes.[483-489] Accordingly, the choice of procedure may be at the discretion of the surgeons involved. It is important to emphasize that if reimplantation of parathyroid tissue is considered, that a portion of the smallest parathyroid gland, ie, one less likely to have severe nodular hyperplasia, should be reimplanted. Total parathyroidectomy probably is not the procedure of choice in patients who may subsequently receive a kidney transplant, since the subsequent control of serum calcium levels may be problematic in such patients.

It would be helpful if noninvasive assessments of parathyroid function or of parathyroid mass were available that could predict whether medical therapy would be helpful. There is insufficient evidence at the present time to support this approach, although there are some preliminary suggestions that this might be helpful.[490] Parathyroid imaging is not usually required, preoperatively, although it may be helpful in cases where re-exploration is required, or for recurrent hyperparathyroidism.[491-493] Of the methods used, $^{99}$Tc-sestamibi with or without subtraction techniques appears to have the highest sensitivity, although MRI, CT, and ultrasound have also been regarded to be useful.[490-492,494-502]

### *Strength of Evidence*

The indications for surgical parathyroidectomy are not well defined and there are no studies to define absolute biochemical criteria which would predict whether medical therapy will not be effective and surgery is required to control the hyperparathyroidism. There has been some suggestion that those patients with large parathyroid mass might fail attempts at medical therapy and, therefore, assessments of parathyroid mass with ultrasonographic or radionuclide techniques could conceivably be useful as a predictor of efficacy of medical therapy. Unfortunately, there is insufficient evidence to support this at the present time.

The type of surgery performed has been variable and, while subtotal parathyroidectomy or total parathyroidectomy with or without autotransplantation have all been shown to be successful, there are no comparative studies. Efficacy and recurrence rates are all comparable. There is some concern that total parathyroidectomy may not be suitable for patients who will receive a kidney transplant since the control of serum calcium levels may be difficult following kidney transplantation.

While some advocate parathyroid imaging for

**Table 32. Frequency for Measurement of Serum Levels of Total $CO_2$**

| CKD Stage | GFR Range (mL/min/1.73 m²) | Frequency of Measurement |
|---|---|---|
| 3 | 30-59 | At least every 12 months |
| 4 | 15-29 | At least every 3 months |
| 5 | <15 | At least every 3 months |
| | Dialysis | At least every month |

re-exploration surgery and have shown it to be useful in some cases, others do not feel that it is necessary. There are no studies comparing the results with and without preoperative imaging.

An alternative to surgical removal of parathyroid glands has recently been introduced in which parathyroid tissue is ablated by direct injection of alcohol into the parathyroid gland under ultrasound guidance. Additional long-term studies with this technique are needed to evaluate its role in long-term therapy.[503]

### Limitations

In the absence of firm criteria for surgery, the use of different operations, the use of parathyroidectomy in limited, selected groups of patients, limited follow-up, and heterogeneity of the patients studied, it is difficult to provide conclusive guidelines to address this complication of CKD.

### Clinical Applications

Clearly, hyperparathyroidism is a frequent complication of CKD which requires monitoring and therapy. Many cases can be managed with phosphate control, calcium supplementation, and the use of vitamin D sterols. Some, however, fail these measures and therefore, surgical ablation becomes an option which can effectively control the overactivity of the parathyroid, although recurrence rates are high.

### Recommendations for Research

The monitoring and control of hyperparathyroidism remains a difficult problem and further information is needed in several areas. Correlations of PTH values with bone histology are necessary in the current era. New assays of PTH need to be evaluated for their clinical utility. The appropriate target values for PTH that are achieved by medical therapy need to be defined and related to bone histology. The appropriate target values for PTH during the course of CKD at various stages of kidney dysfunction need to be defined. Comparative studies of medical and surgical therapy would be of interest. Novel approaches to the control of hyperparathyroidism will be forthcoming.

## GUIDELINE 15. METABOLIC ACIDOSIS

**15.1 In CKD Stages 3, 4 and 5, the serum level of total $CO_2$ should be measured.**

**15.1a The frequency of these measurements should be based on the stage of CKD as shown in Table 32. (OPINION)**

**15.2 In these patients, serum levels of total $CO_2$ should be maintained at ≥22 mEq/L (22 mmol/L). (EVIDENCE) If necessary, supplemental alkali salts should be given to achieve this goal. (OPINION)**

### Background

A fall in serum total $CO_2$occurs during the course of CKD.[504] An overt acidosis is present when the estimated GFR is below 30 mL/min/1.73 $m^2$ in a large proportion of patients,[478] and it progresses such that most patients on maintenance dialysis have an acidosis.[505]

### Rationale

Classical studies in humans demonstrated the powerful effect of chronic metabolic acidosis, induced experimentally or resulting from chronic kidney disease, on the loss of bone mineral.[506-509] Experimental studies performed largely in animals fed excess mineral acid, or bone organ cultures exposed to varying pH environments, have investigated mechanisms whereby chronic metabolic acidosis alters bone composition. Chronic metabolic acidosis produces a change in the ionic composition of bone, with net reductions in apatite, sodium, and potassium.[510] Cellular functions within bone are changed by chronic metabolic acidosis, such that matrix gene expression associated with osteoblastic activity is inhibited,[511] while osteoclastic activities are increased.[512] Additionally, the trophic effects of the growth hormone IGF-1 axis on bone growth and structure is blunted in chronic metabolic acidosis.[513] Chronic metabolic acidosis reduces the kidney proximal tubule synthesis of

**Table 33. Frequency of Measurement of Calcium, Phosphorus, PTH and Total $CO_2$ after Kidney Transplantation**

| Parameter | First 3 Months | 3 Months to 1 year |
|---|---|---|
| Calcium | Every 2 weeks | Monthly |
| Phosphorus | Every 2 weeks | Monthly |
| PTH | Monthly | Every 3 months |
| Total $CO_2$ | Every 2 weeks | Monthly |

One year after transplantation, the frequency of measurements should follow the recommendations of Table 14,15, Guideline 1, depending on the level of kidney function.

$1,25(OH)_2D_3$,[514] and may thereby limit calcium absorbed from the diet. Chronic metabolic acidosis alters the homeostatic relationships between blood ionized calcium, PTH, and $1,25(OH)_2D_3$ such that bone dissolution is exaggerated.[515,516]

Bone fractures are a relatively common manifestation of chronic metabolic acidosis.[517] Recent studies utilizing dynamic histomorphometry have demonstrated a reduction in bone mineral density,[518,519] and in bone formation rates. However, histomorphometric analyses of bone in patients with forms of chronic metabolic acidosis are quite limited, and remain controversial. Linear growth in children is reduced by chronic metabolic acidosis.[520] Chronic metabolic acidosis contributes, in part, to the osteodystrophy in patients with chronic kidney disease.[53]

### *Strength of Evidence*

There is scant evidence, in patients with kidney disease on maintenance dialysis, that either amelioration or improvement of osteodystrophy occurs through elimination of chronic metabolic acidosis per se. One study in 21 patients on maintenance dialysis found that, after 18 months of observation, a group with acidosis (total $CO_2$ = 15 mmol/L) had progression of secondary hyperparathyroidism biochemically and on bone biopsy, when compared to the absence of worsening in the control group (total $CO_2$ = 24 mmol/L), all of whom still had some degree of secondary hyperparathyroid bone disease.[521] Additionally, a cross-sectional study of 76 patients studied with percutaneous, transiliac bone biopsy demonstrated that those with a normal biopsy result had a serum bicarbonate level of 23 mmol/L while those with either mild or advanced mixed osteodystrophy had serum bicarbonate levels below 20 mmol/L.[53] It appears that the absence of acidosis renders therapy of osteodystrophy with a vitamin D metabolite more effective.[522] Also, in children with renal tubular acidosis, normalization of serum bicarbonate is one component of the return of normal growth parameters.[520]

### Clinical Applications

Measurement and monitoring of the serum levels of total $CO_2$ is warranted in patients with CKD Stages 3, 4, and 5,[478] or in patients on maintenance dialysis. Steps to keep the measured serum levels of $CO_2$ above 22 mmol/L are warranted for improvement in bone histology, and to ameliorate excess protein catabolism.[523] The clinician is reminded that the use of exogenous alkali salts containing citrate may increase the absorption of dietary aluminum in patients with CKD,[521] both before dialysis and in those treated with dialysis[524]; therefore, citrate alkali salts should be avoided in CKD patients exposed to aluminum salts.

### Recommendations for Research

Areas for future research into the effects of chronic metabolic acidosis and osteodystrophy should include a fuller understanding of the calcium-vitamin D-PTH and the growth hormone-IGF-1 axes in humans with CKD at the level of bone. The role of newer therapeutic agents for osteoporosis, such as bisphosphonates, selective estrogen-receptor modulators, or isoflavones in patients with CKD, with or without chronic metabolic acidosis, remains unknown and deserves exploration.

## GUIDELINE 16. BONE DISEASE IN THE KIDNEY TRANSPLANT RECIPIENT

### 16.1 Serum levels of calcium, phosphorus, total $CO_2$ and plasma intact PTH

**should be monitored following kidney transplantation. (OPINION)**

**16.1a The frequency of these measurements should be based on the time following transplantation, as shown in Table 33. (OPINION)**

**16.2 During the first week after kidney transplantation, serum levels of phosphorus should be measured daily. Kidney transplant recipients who develop persistently low levels of serum phosphate (<2.5 mg/dL [0.81 mmol/L]) should be treated with phosphate supplementation. (OPINION)**

**16.3 To minimize bone mass loss and osteonecrosis, the immunosuppressive regimen should be adjusted to the lowest effective dose of glucocorticoids. (EVIDENCE)**

**16.4 Kidney transplant recipients should have bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DEXA) to assess the presence or development of osteoporosis. (OPINION)**

**16.4a DEXA scans should be obtained at time of transplant, 1 year, and 2 years post-transplant. (OPINION)**

**16.4b If BMD t-score is equal to or less than −2 at the time of the transplant or at subsequent evaluations, therapy with parenteral amino-bisphosphonates should be considered. (OPINION)**

**16.5 Treatment of disturbances in bone and mineral metabolism is determined by the level of kidney function in the transplant recipient as provided in Guidelines 1 through 15 for CKD patients. (OPINION)**

### Background

Kidney transplantation is an effective modality for therapy of end-stage kidney disease; while successful kidney transplantation reverses many problems of uremia which are not corrected by dialysis therapy, osteodystrophy (disorders of bone remodeling and modeling) persists. Ninety to one hundred percent of kidney transplant patients have histological evidence of osteodystrophy[525,526] and osteopenia (reduction of bone mass)[527] following transplantation. Most importantly, the loss of bone mass in the early post-transplant period produces osteopenia and osteoporosis (bone mass reduction more than 2 standard deviations below young adult peak bone mass according to the World Health Organization).[528] In addition, a sizable number of patients suffer from avascular necrosis (AVN), usually in the first 2 years following transplantation.[527]

#### *Hypercalcemia*

Hypercalcemia following kidney transplantation is common and is usually due to hyperparathyroidism that persists from the preceding period of chronic kidney disease. Restoration of kidney function partially reverses the resistance to the calcemic action of PTH and restores calcitriol production, with consequent hypercalcemia from increased intestinal calcium absorption and the effects of PTH on kidney calcium transport and bone turnover. The hypercalcemia generally resolves as the parathyroid gland hypertrophy is reversed in the presence of sufficient kidney function. However, in 1% to 5% of transplant recipients, abnormal PTH secretion persists, causing hypercalcemia that may require parathyroidectomy.

#### *Hypophosphatemia*

Hypophosphatemia occurs in 50% to 80% of patients in the first 3 months after kidney transplantation and is due to hyperphosphaturia.[529-544] By 3 months after transplant, 0% to 26% of patients will be hypophosphatemic[541-544] and by 1 year after transplant, it can be expected that <5% of patients will still be hypophosphatemic.[542-544] The hyperphosphaturia is multifactorial in origin and is related to persistent hyperparathyroidism,[156,529,537,538,541,545-551] immunosuppressive and diuretic drugs, reduced intestinal absorption of phosphorus,[530,534,535,537,540,552-554] and possibly the existence of a phosphaturic substance, like phosphatonin, which is present in the serum of kidney transplant patients.[530,539,545,546,555,556] This phosphaturic substance promotes phosphate loss via the nephron, independent of parathyroid hormone (PTH). In patients without CKD or kidney transplant,

hypophosphatemia can lead to extrarenal complications such as osteopenia, osteomalacia,[557-561] rhabdomyolysis, impaired cardiac contractility, cardiac arrhythmias, respiratory failure, neurological complications, hemolytic anemia, and leukocyte dysfunction.[562-565] For these reasons, it is important to determine whether treatment of hypophosphatemia should be undertaken in kidney transplant patients.

### *Metabolic Acidosis*

Metabolic acidosis following kidney transplantation may be present due to a variety of causes. Skeletal buffering of excess protons contributes to the abnormalities in calcium and phosphorus metabolism and the disorders of bone remodeling seen following kidney transplantation. Correction of the acidosis may assist in the general resolution of the electrolyte abnormalities and a lessening of the forces producing post-transplant osteoporosis.

### *Hyperparathyroidism*

After successful kidney transplant, biochemical evidence of hyperparathyroidism can persist in many patients.[557,566-572] Persistent hyperparathyroidism has negative effects upon bone mineralization and may also worsen skeletal complications such as osteopenia and rates of bone fracture.[557,569] Persistent hyperparathyroidism is potentially a risk factor for hypercalcemia, hypophosphatemia, worsening of bone disease, and possibly acute tubular necrosis after kidney transplant.[571,572] Because this increased risk may be injurious to patients, the Work Group felt that a review of this area and treatment recommendations were in order.

## Rationale

### *Hypercalcemia*

With the restoration of kidney function following transplantation, the parathyroid glands that may have hypertrophied during the period of CKD must involute. Until this is complete, patients are at risk for hypercalcemia due to hyperparathyroidism. Failure of the parathyroid glands to involute sufficiently to decrease PTH secretion to levels appropriate for calcium homeostasis in the post-transplant period is an indication for parathyroidectomy. This is observed in about 1%-5% of transplant recipients.

### *Hypophosphatemia*

Associated with restoration of kidney function following transplantation, high rates of urinary phosphate excretion are observed that often lead to the development of hypophosphatemia. The cause of the phosphaturia is a reduction in the tubular maximum (Tm) for phosphate in the proximal tubule. Multiple factors contribute to this dysregulation of tubular phosphate transport which may in part be due to decreased levels of a type II sodium-dependent phosphate transport protein (NaPi2) in the brush-border membrane. The regulatory influences that would produce such a situation include PTH, glucocorticoids, and phosphatonin. The latter is a newly discovered hormonal regulator of phosphate transport that is responsible for hypophosphatemia in cases of oncogenic osteomalacia and autosomal dominant hypophosphatemic rickets (ADHR). Phosphatonin is normally processed by subtilisin-like proprotein convertases and degraded by endopeptidases including the product of the gene PHEX that is responsible for the disease, X-linked hypophosphatemia. In this genetic osteomalacia, mutations in PHEX lead to failure of phosphatonin degradation and severe hypophosphatemia due to decreased levels and inhibition of NaPi2 activity in the proximal tubule. Similarly, following kidney transplantation high levels of phosphatonin may occur and contribute to the hypophosphatemia observed.

### *Hyperparathyroidism*

Biochemical evidence of hyperparathyroidism may persist in a large number of patients after successful kidney transplant.[547-551,573-579] The increases in PTH are believed to be due to a large glandular mass of parathyroid cells that develops during CKD and persists after kidney transplant.[547-551,557,566-579] Kidney transplantation can have beneficial effects upon hyperparathyroidism by reversal of hyperphosphatemia and production of 1,25-dihydroxyvitamin $D_3$ by the renal allograft.[156,542,580,581] PTH levels tend to decline over time as the hyperplastic parathyroid glands undergo involution.[582,583]

There are many longitudinal studies of the behavior of PTH levels after kidney transplantation. The PTH levels decline rapidly after transplant, then decline at a slower rate,[547-551,573-579,582,583] generally decreasing by 50% within 14 days of trans-

plant. Within approximately 3 to 6 months after successful transplant, it can be anticipated that 50% of patients with serum creatinine <2.0 mg/dL (177 nmol/L) will have normal levels of intact PTH.[547,579,584] Most reports indicate that intact PTH levels usually return to near normal by 1 year after transplant.[542,547-550,579-581,584-590] However, PTH levels can remain above normal, presumably due to persistent parathyroid hyperplasia, as evidenced by other reports. One group found 50% of patients with PTH levels above normal at 24 months after transplant.[543] In a long-term study, 21% of transplant patients had significant biochemical hyperparathyroidism up to 15 years after transplantation,[591] but this presumably relates to low levels of kidney function.[156,575]

Persistent elevations in the levels of PTH have been associated with a longer duration of dialysis prior to kidney transplant,[592] along with high levels of PTH[156] and high values of serum calcium at the time of transplantation.[568,593] There are conflicting studies regarding the importance of vitamin D receptor genotype upon the persistence of hyperparathyroidism after transplant. One study found that patients with BB genotype had lower PTH levels post-transplant,[577] but another noted lower PTH levels in patients with bb genotype for vitamin D receptor.[578]

Some kidney transplant patients will require parathyroidectomy to alleviate hyperparathyroidism. In general, most studies indicate a prevalence rate of approximately 5% for kidney transplant patients who will require parathyroid surgery, but the prevalence rate varies from 1%-20% among different transplant centers.[575,576,584,587,592,594-599] Parathyroid surgery may be indicated for persistent hypercalcemia in transplant patients (particularly if serum calcium is ≥11.5 mg/dL [2.87 mmol/L]).[595,596] Other indications for parathyroidectomy after kidney transplant include calciphylaxis, rapidly worsening vascular calcification, symptomatic hyperparathyroid bone disease, and the development of spontaneous fractures in the presence of hyperparathyroidism.[575,576,584,587,588,592,594-599] One group advocates waiting at least 1 year post-transplant to see if there is spontaneous regression of hyperparathyroidism.[597] There is no consensus on the proper parathyroidectomy operation that should be performed, with some authors advocating subtotal parathyroidectomy and others advocating total parathyroidectomy with autotransplantation of parathyroid tissue.[575,576,584,587,592,594-596]

Previous studies comparing the predictive value of C-terminal PTH assays have shown that the results are not always indicative of an elevated N-terminal PTH assay.[549,550,557,558,578,581,600-602] PTH levels are not always indicative of the rate of bone turnover in kidney transplant patients.[557,558,581,600-602] In fact, PTH levels may have limited value for the assessment of bone turnover in kidney transplant patients. In a study of 4 patients with PTH levels >100 pg/mL (100 ng/L), 3 had normal bone turnover.[601] Several studies that have used bone biopsies to document bone turnover have shown that kidney transplant patients with osteopenia may have several bone histological patterns that are not due to hyperparathyroidism. These bone biopsy findings describe a low-turnover bone lesion[557,600] similar to osteoporosis, persistent hyperparathyroidism,[551,578,602,603] and even osteomalacia.[581] Previous studies have indicated a relatively high prevalence of increased bone turnover in kidney transplant patients. However, a more recent cross-sectional study of bone biopsy findings in kidney transplant patients, with an average of 5.4 years after transplant, noted low bone turnover in 46% of patients.[558] Mineralization lag time was prolonged in approximately 88% of patients undergoing bone biopsy. PTH levels were not always indicative of the rate of bone turnover.

### *Osteopenia/Osteoporosis and Fractures*

Osteopenia is nearly a uniform finding in the late post-transplant period (longer than 2 years post-transplant).[525,604] Older studies underestimated the severity of osteopenia, since they were performed when osteopenia was not generally present at the time of transplant.[525,526] Pretransplant osteitis fibrosa and pre-existing osteodystrophy, associated with high bone turnover rates or osteomalacia, were the prevalent forms of bone disease at the time of these studies, and osteopenia was not commonly associated with chronic dialysis therapy.[605] In recent studies, osteopenia due—in part—to the adynamic bone disorder has become more prevalent in CKD, and represents a significant component of bone disease at the time of kidney transplantation.[23,559]

High rates of trabecular bone fracture complicate solid organ transplantation (kidney, liver,

heart, lung, and pancreas). Vertebral bodies, ribs, and hips are the sites most often affected. These fractures represent major stumbling blocks to the post-transplant rehabilitation that would otherwise be expected. Fractures add tremendously to the costs of health care for these patients. The causes of the increased fracture risk in the kidney transplant population is an osteodystrophy associated with rapid reductions in bone mass during the first 2 years post-transplant. Kidney transplantation is characterized by various pretransplant osteodystrophies, but the main pathophysiological issue is a rapid loss of bone mass in the early post-transplant period. The cause of this early post-transplant bone loss is unknown, and its pathophysiological mechanism has not been accurately characterized. However, there is a growing consensus that—similar to other clinical situations in which glucocorticoids are used therapeutically—their use is the major factor producing decreased osteoblast function and loss of bone mass. Further worsening of osteopenia occurs up to 2 years post-transplant, and fractures occur during the entire post-transplant period. Transplant recipients should be monitored for this rapid loss of bone mass. DEXA is the clinical standard for measurement of BMD,[528] and patients should be monitored for changes in their bone mass on a regular basis following kidney transplantation. If osteoporosis is identified by changes in BMD, therapy should be initiated.

The nature of osteodystrophy prior to transplantation has changed in the last decade. As a result, more patients are osteopenic at the time of transplant due to the adynamic bone disorder. At the same time, the rapid bone loss that occurs following transplantation has not been prevented. Therefore, post-transplant fracture rates remain high, and post-transplant osteodystrophy (which is often an osteoporosis) with fractures and osteonecrosis are major causes of morbidity associated with long-term post-transplant survival.

High rates of fracture also complicate cardiac, liver, pancreas, and lung transplantation to even a greater degree than in kidney transplantation. The chronic illnesses leading to these organ transplants often produce osteopenia secondary to inactivity or immobilization. Associated with the immediate post-transplant period, there is a very significant bone loss resulting in a major reduction in BMD within the first 6 months following the operation. High rates of fracture complicate the first 2 years of the post-transplant period. The cause of the rapid loss of bone mass associated with organ transplantation has been attributed to the use of glucocorticoid and immunosuppressive therapy as contributing factors.[606-611]

### *Strength of Evidence*

#### *Hypophosphatemia*

The Work Group did not identify any double-blind, randomized, placebo-controlled trials (highest-quality evidence) regarding treatment of hypophosphatemia in kidney transplant patients. There were 2 prospective trials on the effect of phosphate supplementation. One study reported a single group pre-treatment versus post-treatment[156]; this study included transplant patients with serum phosphorus $<3.5$ mg/dL. This was a very short-term study of only 15 days' duration. These patients had been transplanted for an average of 41 months, and they had normal kidney function. Patients received oral neutral phosphate in a dosage of 750 mg BID, and they were restudied after 2 weeks of therapy. Phosphate supplements tended to decrease serum calcium, increase serum phosphorus, increase levels of PTH, and decrease serum levels of 1,25-dihydroxyvitamin D. Very few patients increased their serum phosphorus level to 4.5 mg/dL (1.45 mmol/L). The authors contended that phosphate administration after kidney transplantation may worsen hyperparathyroidism, and that if phosphate supplements are used, concomitant calcitriol administration may be of value to maintain calcitriol levels and avoid worsening of hyperparathyroidism.

Another randomized, controlled trial studied transplant patients who were hypophosphatemic after transplant (serum phosphorus 0.93 to 2.34 mg/dL [0.30 to 0.76 mmol/L]).[532] Patients were randomized to receive either neutral sodium phosphate or sodium chloride for 12 weeks. Within 2 weeks, the phosphorus-supplemented group increased serum phosphorus levels, but by week 12 of the study, both groups had average phosphorus levels of approximately 2.5 mg/dL (0.81 mmol/L). At the beginning of this study, muscle phosphorus content was below normal in both

**Table 34. Commercially Available Preparations for Phosphate Supplementation.**

| Preparation/Supplement | Phosphorus/Phosphate Content |
|---|---|
| Fleets Phospho-Soda Liquid | 12.45 mEq/mL phosphate; 4.15 mmol/mL phosphorus |
| K-Phos Tablets | 500 mg potassium phosphate; 114 mg phosphorus |
| k-Phos MF Tablets | 155 mg potassium phosphate; 250 mg sodium phosphate |
| K-Phos Neutral Tablets | 155 mg potassium phosphate; 852 mg dibasic sodium phosphate; 130 mg monobasic sodium phosphate |
| K-Phos No. 2 Tablets | 250 mg phosphorus; 305 mg potassium phosphate; 700 mg sodium phosphate |
| Neutra-Phos Powder | 1.25 g packet = 250 mg phosphorus |
| Neutra-Phos K Powder | 1.45 g packet = 250 mg phosphorus |
| Phosphate-Sandoz Tablets | 500 mg phosphorus |

groups. By week 12 of the study, the phosphate-supplemented group had slightly higher muscle ATP content than the sodium chloride-treated group. The phosphate-treated group also tended to have higher levels of plasma bicarbonate. PTH levels declined in both groups.

A third study treated 10 kidney transplant patients with oral calcium carbonate (1,000 mg/day) and either dihydrotachysterol (0.37 mg/day) or oral calcitriol (0.60 $\mu$g/day).[540] All patients had serum creatinine levels <2.0 mg/dL (177 mmol/L), had been transplanted for 0 to 44 months (average, 14 months), and all patients were already using oral phosphate supplements. With calcium and vitamin D analogs, the phosphate supplement dosage decreased from 8.0 g/day to 4.6 g/day and the serum phosphorus remained in the range of 2.7 to 3.1 mg/dL (0.87 to 1.00 mmol/L). Serum calcium increased from 9.3 mg/dL (2.32 mmol/L) to 10.0 mg/dL (2.50 mmol/L) and PTH values declined by 30% to 40% from initial values. The renal fractional excretion of phosphorus declined.

The Work Group also recognizes that, in patients without CKD or kidney transplantation, it is common practice to provide oral phosphate supplements when the serum phosphorus declines below 1.0 mg/dL (0.32 mmol/L).[562-565] A serum phosphorus level <1.5 mg/dL (0.48 mmol/L) is commonly defined as severe hypophosphatemia and phosphate supplementation with either oral or intravenous compounds would be recommended in non-CKD patients.[562-565]

Upon review of the literature, it appears that there is no clear consensus as to the level of serum phosphorus that should prompt phosphate supplementation in CKD patients with kidney transplant. The Work Group found that the overall literature regarding phosphate supplementation was not entirely clear. A recent review of this subject has suggested that phosphate supplementation is indicted if the serum phosphorus level declines below 2.5 mg/dL (0.81 mmol/L) in patients with kidney transplant.[612]

Based upon review of the available literature, the Work Group recommends that kidney transplant patients with serum phosphorus levels <1.5 mg/dL (0.48 mmol/L) should receive oral phosphate supplements to achieve a serum phosphorus level of 2.5 to 4.5 mg/dL (0.81 to 1.45 mmol/L). CKD kidney transplant patients with serum phosphorus levels of 1.6 to 2.5 mg/dL (0.52 to 0.81 mmol/L) may often require oral phosphate supplements with a desired serum phosphorus target range of 2.5 to 4.5 mg/dL (0.81 to 1.45 mmol/L). The Work Group further recommends that, when phosphate supplements are administered, serum phosphorus and serum calcium levels should be measured at least weekly. If serum phosphorus levels exceed 4.5 mg/dL (0.81 mmol/L), then the dosage of phosphate supplements should be decreased.

PTH levels should be determined and the patients should be examined for evidence of persistent hyperparathyroidism if oral phosphate supplements are required to maintain serum phosphorus levels >2.5 mg/dL (0.81 mmol/L) more than 3 months after kidney transplant. These

patients may require the use of oral calcium supplements, and possible coadministration of vitamin D analogs.

Beyond 3 months after kidney transplant, the levels of PTH, calcium, and phosphorus should be measured at a frequency that is commensurate with the level of GFR (see Guideline 1). Table 34 lists some of the available preparations for phosphate supplementation.

### *Osteopenia/Avascular Necrosis and Fractures*

The nature of the osteodystrophy following kidney transplantation is not well established. Histological studies have been reported in fewer than 200 patients. An Italian study[525] identified 3 histological patterns: low bone turnover lesions similar to osteoporosis; persistent osteitis fibrosa; and osteomalacia. Others[525] described persistent osteodystrophy and osteopenia in a high percentage of transplant patients at 1 year post-transplant, but failed to establish the relationship between histomorphometry and clinical symptomatology. Lesions with a very low rate of bone formation have been described in patients with avascular necrosis.[527] Recent studies have described a high prevalence of low bone turnover, osteoporosis, and osteomalacia following kidney transplantation.[558] Studies of BMD have established a rapid decrease in bone mass following kidney transplantation with a nadir around 6 months that tends to slow or recover by 1 year.[557] The osteodystrophy of CKD has evolved significantly since some of the above studies were performed. The prevalence of osteomalacia has diminished. A new form of osteodystrophy, adynamic bone disorder (also known as "adynamic bone disease" or "low-turnover bone disease") independent of aluminum intoxication, has become common in the patients with Stage 5 CKD.[613] The impact of kidney transplantation on this form of pretransplant osteodystrophy has not been carefully elucidated.

A study of 20 patients with mild osteitis fibrosa prior to transplant demonstrated that all the patients sustained a major post-transplant loss of bone mass by 6 months.[557] The loss of bone mass was characterized by a marked decrease in mineral apposition and bone formation rate, resulting in major prolongation of mineralization lag time and formation periods while there was a reduction of the elevated pretransplant rate of bone resorption to normal. This correlated with a decrease in bone densitometry assessed by dual-photon absorptiometry and a persistent decrease in BMD at 18 months, in addition to the reductions seen at 6 months. Thus, these patients developed osteoporosis and an adynamic bone disorder but the course of patients with adynamic bone disorders prior to transplant was unknown. Others have confirmed these findings, but with the added finding that osteomalacia was present more often than expected.[558] A study using DEXA demonstrated, in 34 kidney transplant recipients, that bone mineral content and BMD were decreased 7% and 5%, respectively, by 5 months.[559] These authors also noted a 3% reduction in spine BMD at 3 months which was progressive to 5 months post-transplant. Large cross-sectional studies of BMD post-transplant demonstrate that bone loss continues for the first 2 years, reaching reductions of 10% at 12 months and 16% at 24 months compared to the normal population.[604]

The clinical impact of the osteodystrophy and bone loss is a marked increase in the fracture rate associated with kidney transplantation from 0.009 fractures per patient per year pre-transplant to 0.032 post-transplant.[614] Peripheral bone fractures affected 10% to 15% of kidney transplant recipients, and a similar percentage of the patients sustained vertebral fractures.

Persistent hyperparathyroidism is a factor that could play a role in the osteopenia that develops after kidney transplantation. Osteopenia has been described in patients with primary hyperparathyroidism.[615] It is unclear whether persistent hyperparathyroidism is a major factor contributing to early bone loss before involution of hypertrophic parathyroid glands.[530] Osteitis fibrosa is less frequent but still observed in post-kidney-transplant bone biopsies.[526,557,558,582] Recent studies demonstrate that the severity of pretransplant hyperparathyroidism predicted the magnitude of the change in vertebral bone mineral density.[616]

Glucocorticoid (eg, prednisone) therapy is a major factor in the development of osteopenia. Glucocorticoids have been shown to have a variety of effects on calcium metabolism which are likely to decrease bone mass.[617,618] These include increases in urinary calcium and phosphate excretion, direct and indirect (via interference with vitamin D metabolism) inhibition of intestinal calcium absorption, and suppression of osteo-

blast and enhancement of osteoclast function.[618-621] Data from noninvasive techniques document a suppression of serum osteocalcin and urinary hydroxyproline during a short course (12 weeks) of high-dose prednisone therapy (mean dose, 34 mg/day) in patients with Graves' ophthalmopathy.[619,622] Other studies have concluded that cumulative and maintenance doses of prednisone correlated inversely with bone volume and bone turnover following kidney transplantation,[558] but this remains a controversial issue.

Using the methodology for study selection described earlier in these Guidelines, the Work Group identified 5 studies examining 302 patients that studied the relationship between immunosuppressant-steroid combinations and bone mineral density (BMD).[561,623-626] Four studies used DEXA as the method for measuring BMD, while 1[624] used dual-photon absorptiometry. Four studies were controlled trials,[561,623,625,626] while 1 was a case-control study.[624] Three of the five studies were retrospective[561,624,625]; the other 2 were prospective, randomized, controlled trials.[623,626] These studies all examined different patient populations and different interventions, and this did not allow the Work group to do any specific synthesis or meta-analysis of the results. The evidence review comprised a qualitative literature review of these studies.

Three of the controlled trials[561,625,626] compared a variety of immunosuppressant and steroid combinations. No new studies looked at the same drug combinations. In the only prospective trial,[626] the authors compared single, double, and triple therapy. They found that cyclosporine monotherapy led to improved BMD compared to cyclosporine plus prednisone, or cyclosporine plus prednisone and azathioprine. This group did not note any statistically significant differences in BMD between the double and triple therapy groups over 18 months.[626] One retrospective study found no differences in BMD between groups receiving cyclosporine versus azathioprine plus prednisone in the 7 to 15 years after transplant.[625] Another retrospective study compared patients who had received $<10$ mg of prednisone per day to those receiving $>10$ mg prednisone per day.[561] At the end of 1 year, DEXA measurements of BMD had improved slightly in the low-prednisone group versus the high-prednisone group, and the inter-group difference was statistically significant ($d = 1.409$, 95% CI, 0.92 to 1.02, Hedges' d test for standard effect sizes).

In a study conducted on children, using a controlled design, the authors calculated the change in BMD over a 1-year period when patients were switched from prednisone to deflazacort, or continued taking prednisone, both in conjunction with cyclosporine and azathioprine or mycophenolate.[623] Thus, although the only intended inter-group difference was the type of glucocorticoid given, the use of mycophenolate rather than azathioprine in 5 patients in the prednisone group may have affected results. Both groups showed declining BMD over the 1-year period. No statistically significant differences were found in BMD measurements between the 2 groups over the 1-year period of the study.

Immunosuppressive therapy may have an impact on bone remodeling. Transplant recipients routinely receive cyclosporine A or tacrolimus. These immunosuppressive agents are used in high doses in heart and liver transplantation, and may be associated with worse osteopenia than is observed following kidney transplantation, in which lower doses of these agents are generally used. Cyclosporine's major effect on bone cells in vitro is to inhibit osteoclastic bone resorption,[627] possibly by decreasing the formation of mature osteoclasts.[628] Effects of cyclosporine A in vivo appear to differ from its actions in vitro. The effects of cyclosporine A on bone modeling have been studied in rats.[629-631] This series of studies demonstrated that cyclosporine A produced osteopenia through stimulating resorption, and that elevated osteocalcin levels were related to increased bone turnover. There are major difficulties translating these results to the human post-transplant situation, but they indicate a major need to carefully analyze post-transplant osteodystrophy mechanistically for combined effects of corticosteroids and cyclosporine A. They appear to demonstrate one reason that bone resorption is higher than expected for the major decrease in bone formation that occurs following transplantation. On the other hand, a study of cyclosporine A in kidney transplant patients suggests that it reduces the incidence of avascular necrosis (AVN) by permitting a lower dose of steroids.[632] However, this study was flawed by the use of historical controls. The effect of cyclo-

sporine A to increase osteocalcin levels, which has been observed in post-transplant osteodystrophy in general, may be additive to the low-turnover osteodystrophy produced by glucocorticoids. Also, the nephrotoxic effects of cyclosporine and tacrolimus may lead to secondary hyperparathyroidism when glomerular filtration rates drop to the range of 40% to 50% of expected.[633]

### *Avascular Necrosis (AVN)*

AVN is a well-recognized complication of kidney transplantation. It usually begins at the weight-bearing surface of the femoral head with collapse of surface bone and cartilage. With time, the area of collapse spreads to involve a large proportion of the femoral head. Pain is severe and patients are often unable to bear weight on the involved hip. Other weight-bearing joints are also frequently involved.[634] Speculations about the mechanism for this development mostly focus on the observation that fat cells are present in increased numbers and intraosseous pressure is high. This has led to the theory that the proliferation of fat cells causes the high intraosseous pressure with subsequent interference with perfusion of the bone.[634] Glucocorticoid dosage[635] and prior dialysis[527] appear to be important in the development of AVN. Patients on maintenance dialysis for longer duration prior to transplantation are more likely to develop AVN.[527] No mention is made in this report of the particular type of bone disease that these patients had, though, with longer duration of dialysis, both osteitis fibrosa and osteomalacia are increased in frequency.[18,636]

Using the methodology described previously, the Work Group identified 7 studies dealing with the relationship between immunosuppressant and glucocorticoid therapies, and avascular necrosis.[632,637-642] All 7 studies varied either the dosage of glucocorticoids or glucocorticoid-immunosuppressant combination. These 7 studies enrolled a total of 1,471 patients. Most of the patients were from 3 retrospective trials[632,641,642]; thus, the bulk of patient data comes from lower-quality studies. Five controlled studies compared high- versus low-dose glucocorticoids.[638-642] In all 5 of these studies, the glucocorticoids were given in conjunction with azathioprine. Both prednisone and prednisolone were used in these studies, but no distinction was made for the purpose of this analysis. These 5 studies reported different dosage of glucocorticoids, but all compared "high dose" versus "low dose." Such data did not allow the Work Group to determine the "best" dose of glucocorticoid.

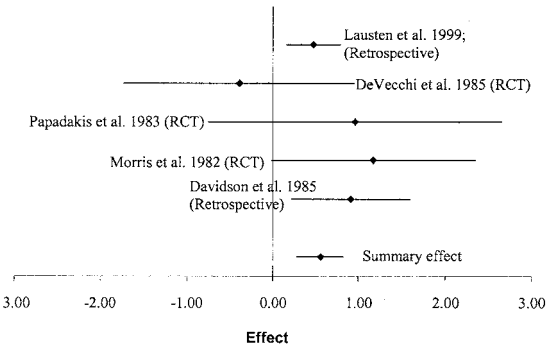



**Fig 16. Effect sizes and 95% CI of RCTs and retrospective studies reporting incidence of necrosis.**

Based on these 5 studies, a meta-analysis indicated that high-dose glucocorticoids plus azathioprine resulted in significantly more cases of avascular necrosis than did an azathioprine plus low-dose glucocorticoid combination ($P < 0.001$, Hedges' d test, odds ratio calculated according to the method of Hasselblad and Hedges[38]). The results are graphically depicted in Fig 16. These results were then confirmed using the log-odds ratio method (odds ratio = 2.74, 95% CI, 1.69 to 4.44, $P < 0.001$).

To further facilitate interpretation of these results, a statistical analysis in the form of a binomial effect size display was performed. This analysis indicated that patients taking high-dose glucocorticoids have at least a 1.5-fold greater risk of avascular necrosis than those taking low-dose glucocorticoids.

The Work Group also noted that, of the studies presented, cyclosporine was part of the treatment regimen in only 2 studies.[632,637] Thus, caution must be used in applying these observations to the currently used immunosuppressant regimens, which often include cyclosporine or other calcineurin inhibitors.

### *Therapy for Post-Transplant Osteodystrophy*

Therapy with replacement of gonadal steroid hormones for estrogen-deficient and testosterone-deficient patients should be seriously considered

following transplantation. These are effective therapies for increasing bone mass in patients with osteoporosis, although their use following transplantation has not been adequately studied. However, patients with kidney disease often have gonadal hormone deficiencies that are untreated.

A major group of drugs to consider in the therapy of post-transplant bone loss is the bisphosphonates. These drugs have the unique capacity to bind to bone surfaces for prolonged periods.[643] They primarily inhibit osteoclastic bone resorption. Etidronate, the bisphosphonate available in the United States until the release of pamidronate and alendronate, unfortunately inhibits bone formation as well as resorption, when given continuously. Recent reports document that intermittent administration of etidronate maintains the antiresorptive effect. In addition, these reports[644] delineate a possible benefit in terms of bone mass and fracture prevention in osteoporosis. Etidronate therapy post-transplant has been a failure both in the prevention of BMD loss, and in preventing fractures.[645,646]

Aminohydroxypropylidene (APD), or pamidronate, has been used in patients receiving steroids, and bone mass was well preserved.[647] There are limited data on the use of APD in disorders other than Paget's disease. In Paget's disease, the effects of APD following a single injection are sustained for months. The use of APD in kidney and heart transplant patients with BMD as the endpoint have recently been reported with promising preliminary results in the prevention of BMD changes at 6 months and 1 year.[648,649] A small, randomized study of transplant recipients treated in the early post-transplant period[648] demonstrated that the control subjects lost 6.4% of BMD at 12 months compared to no loss of BMD in the pamidronate group.[646]

Alendronate has recently been carefully studied in osteoporosis.[650] Women receiving alendronate experienced progressive increases in BMD at all skeletal sites including the spine, femoral neck, and trochanter. In addition, in 1 study, the drug resulted in a 2.5% increase in total body BMD. Alendronate produced a 48% reduction in the proportion of women with new vertebral fractures and a reduction in the loss of height in the vertebral bodies. It appears that alendronate may progressively increase bone mass in the spine, hip, and total body, and reduce the incidence of vertebral fractures in patients with osteoporosis. The drawback of alendronate therapy is that it is only available in an oral form in the United States, and it has to be taken very carefully to avoid esophageal irritation.[651]

Another inhibitor of resorption, calcitonin, holds promise. This naturally occurring hormone has been studied extensively. With documented efficacy in the treatment of Paget's disease, malignant osteolysis, and high-turnover osteoporosis,[652] this agent has also been shown to protect bone mass in conventional osteoporosis[653] A recent report[654] even describes long-term effects (1 year) after short-term therapy (6 to 8 weeks). Finally, clinical trials with calcitonin glucocorticoid-treated patients have shown promise.[655] Calcitonin acts by inhibiting osteoclast action,[656] although others have presented in vitro data showing that calcitonin may also stimulate osteoblast function.[657] Until recently, calcitonin's use has been limited by the need to give it by injection. The development of the nasal route of administration has considerably improved patient acceptance.[658] In addition, side-effects and toxicity, known to be low, are even less by this route than by injection. Bioavailability is also excellent with the intranasal preparation, showing 50% to 100% of the availability of the intravenous route.[659] Animal studies have documented low toxicity and demonstrated a bone effect limited to suppression of osteoclastic activity without deleterious effects on bone formation.[660] A small, randomized trial of nasal calcitonin (200 IU) compared to oral clodronate (800 mg/dL; a bisphosphonate not available in the United States) in patients in the late post-transplant period, demonstrated equal efficacy in increasing bone mass compared to a control "no treatment" group that had no significant change in BMD.[661]

The common diuretics used post-transplant, thiazides and furosemide, have differing effects on bone and calcium metabolism. The thiazides have been described to counteract the adverse effect of steroids on calcium metabolism.[662] However, furosemide—commonly used for control of hypertension and edema—causes calciuria and may potentially accelerate bone resorption. One study has demonstrated that thiazides decreased calcium loss in the urine and increased gut calcium absorption in patients receiving steroids.[662]

Other studies (in subjects not receiving steroids) have shown decreased bone resorption[663] and a reduction in the prevalence of age-related hip fracture.[664] Thiazides are associated with metabolic abnormalities (eg, hyperlipidemia, hypokalemia) also seen with steroids and, thus, they aggravate the steroid side-effects related to accelerated atherosclerosis. As a result, caution should be exercised with the use of thiazides in transplant recipients.

### Limitations and Clinical Applications

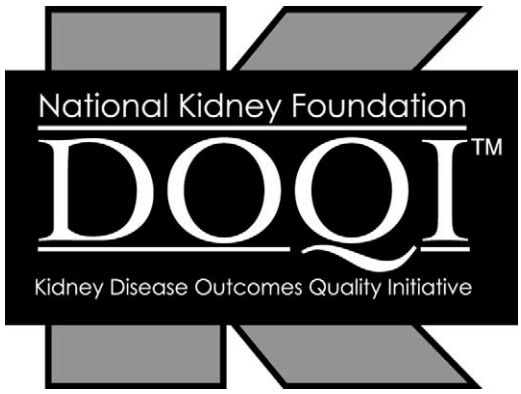
There is no FDA-approved therapy for post-transplant osteodystrophy. Therefore, recommendations for use of therapeutic agents approved for osteoporosis in the post-transplant situation is based on a small number of clinical trials in small numbers of patients and extrapolation from the nontransplant and kidney disease settings. The appropriate management of calcium and phosphate homeostasis in the post-transplant setting begins with a continuation of the principles and practices contained in the Guidelines for patients with chronic kidney disease and ESRD.

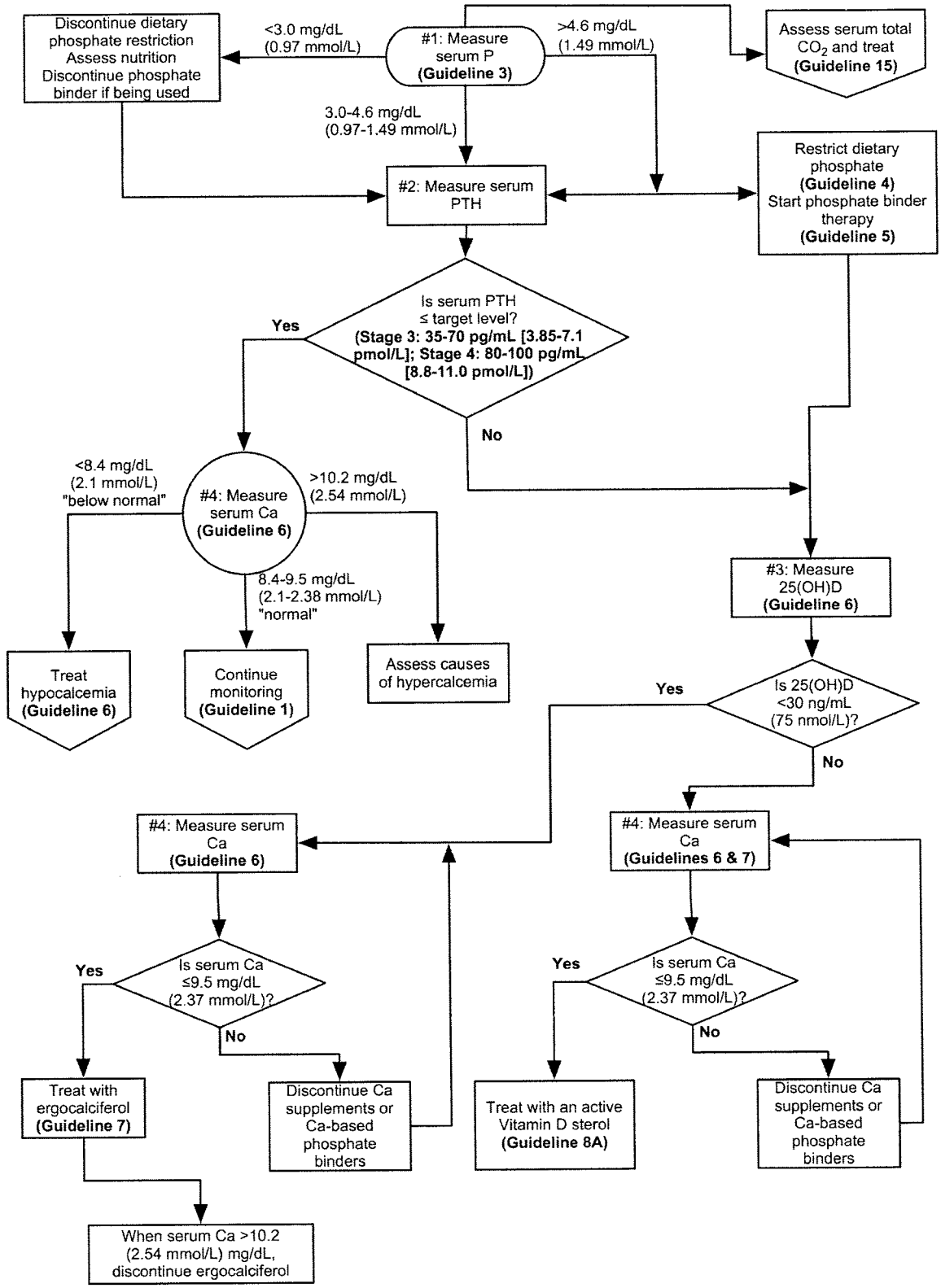
### Recommendations for Research

Much research is needed into all aspects of post-transplant osteodystrophy, including its pathogenesis and treatment. Most of the recommendations for management of post-transplant osteodystrophy require additional clinical trials. Clinical trials comparing alternative potentially beneficial therapies, alone or in combination, should be conducted in this important population.

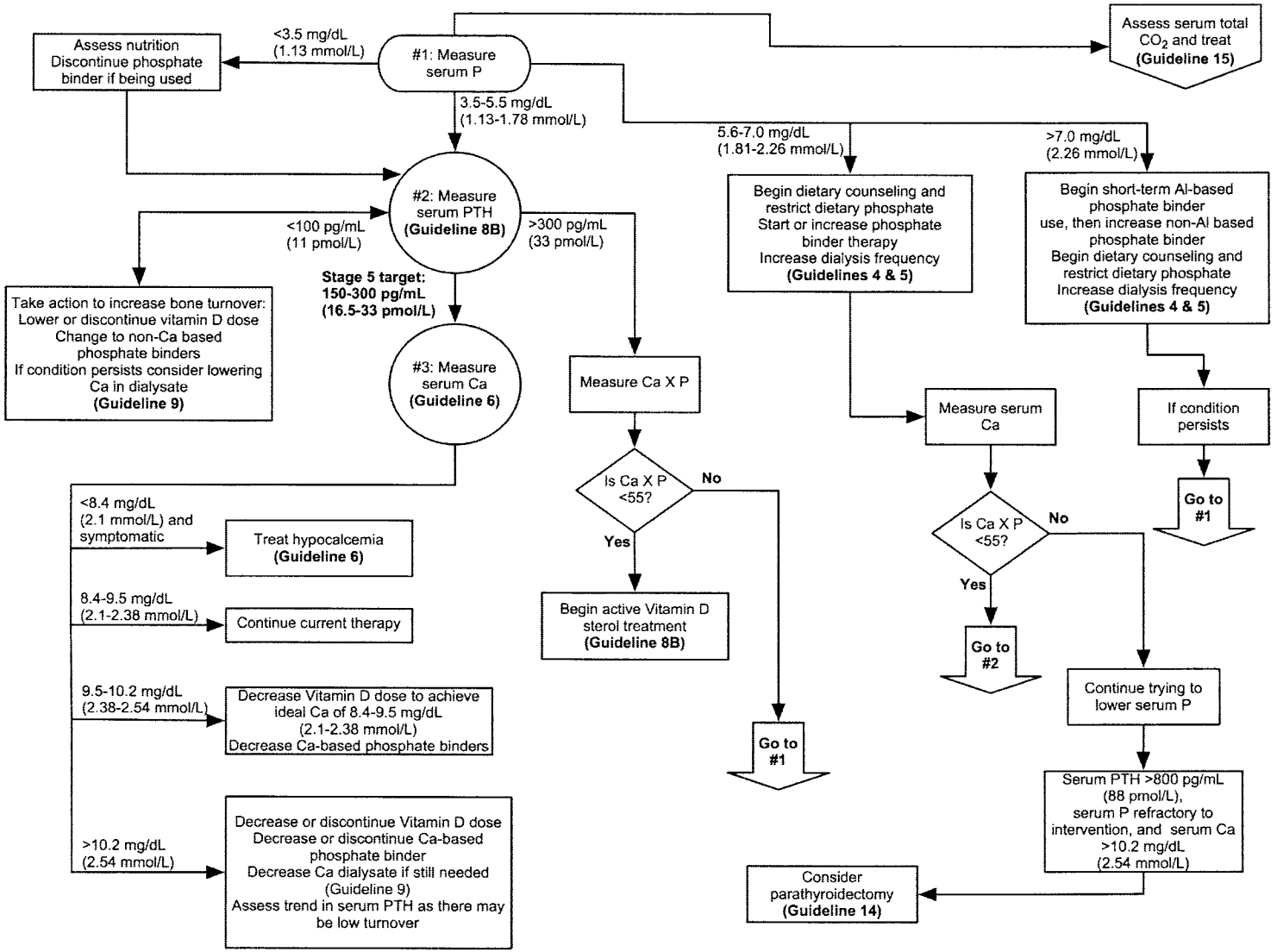
# The Overall Approach to the Management of Bone Metabolism and Disease in CKD Patients

The K/DOQI Bone Metabolism and Disease Guidelines (1 through 16) address individual issues of bone metabolism and disease in CKD patients. The approach to the problems of these patients is not easily amenable to a protocol, as all of the variables involved (levels of calcium, phosphorus, vitamin D, PTH, and total $CO_2$) affect each other. The following 2 algorithms allow for an integrated approach for the care of bone metabolism and disease in CKD patients in Stages 3 and 4 (Algorithm 10) and in CKD patients Stage 5 (Algorithm 11). However, it should be emphasized that the care of CKD patients with bone disease requires frequent assessment of the various parameters underlying the derangements in bone metabolism and bone disease, and frequent evaluation of the therapies as detailed in Guidelines 1 through 16 are necessary.






**Algorithm 10. CKD Stages 3 and 4.**




**Algorithm 11. CKD Stage 5 (on dialysis).**

# BIOGRAPHICAL SKETCHES OF WORK GROUP MEMBERS

**Kline Bolton, MD, FACP,** is Professor of Medicine at the University of Virginia in Charlottesville, where he is Chief of the Division of Nephrology and Director of the Nephrology Clinical Research Center, Kidney Center and Renal Operations. He has received special honors from organizations ranging from the American Society for Clinical Investigation to the International Society of Nephrology. He has published many articles in journals ranging from the *American Journal of Kidney Diseases* and *Kidney International* to *Immunologic Renal Diseases*, and contributed to numerous text books, including the *Textbook of the Autoimmune Diseases* and the *Textbook of Nephrology*. He is Chairman of the Renal Physicians Association Work Group on *Appropriate Preparation of Patients for Renal Replacement Therapy*. His research interests are in refining the epitope(s) involved in causing Goodpasture's syndrome, treating glomerulonephritis, and disease management of CKD and ESRD.

**Jack W. Coburn, MD, FACP**, (*Work Group Vice-Chair*), is Professor of Medicine at the UCLA School of Medicine. In addition to serving as a staff physician at the West Los Angeles VA Medical Center, where he had previously been the Chief of the Nephrology Section, Dr. Coburn is an attending physician at Cedars-Sinai Medical Center, Los Angeles, Brotman Medical Center, Culver City, and Century City Hospital, Los Angeles, and a visiting physician at UCLA Medical Center. A recipient of the Alumni Achievement Award from the University of Redlands and the Lifetime Achievement Award for Research in Vitamin D from the 9th Annual Vitamin D Workshop, he has served past and present as a long-time member on several editorial boards including the *American Journal of Nephrology*, *Kidney International*, and the *American Journal of Kidney Diseases*, and has over 450 published scientific papers, reviews, and editorials to his credit. Dr. Coburn is on the Medical Advisory Boards of Bone Care International, R & D Laboratories and Amgen, Inc., and has also consulted with Genzyme Corporation.

**Glenn M. Chertow, MD, MPH**, is Assistant Professor of Medicine in Residence at the University of California, San Francisco (UCSF) and Director of Clinical Services in the Divisions of Nephrology at Moffitt-Long Hospitals and UCSF-Mt. Zion Medical Center. He serves as Medical Director of the Dialysis programs at both sites. Dr. Chertow's research interests are focused on epidemiology, health services research, and clinical trials in acute and chronic kidney disease. He has written numerous papers on end-stage renal disease, acute renal failure, mineral metabolism, nutrition, and costs and outcomes of dialysis therapy. He is currently Associate Editor of the *Journal of Renal Nutrition*, and on the Editorial Board of *Journal of the American Society of Nephrology*. He serves on the Board of Directors of the TransPacific Renal Network (Network #17) and has been active in numerous volunteer positions with the National Kidney Foundation, American Kidney Fund, and American Society of Nephrology. He was Vice Chair of the Work Group that developed the K/DOQI Clinical Practice Guidelines for Nutrition of Chronic Renal Failure. Dr. Chertow has received research support from, and has served as an advisor to, Amgen, Inc., Genzyme, Inc., and GelTex Pharmaceuticals, Inc.

**Keith A. Hruska, MD,** is the Ira M. Lang Professor of Medicine at Barnes-Jewish Hospital at Washington University School of Medicine and a Professor of Medicine at Washington University School of Medicine, where he also completed a fellowship in the Renal Division. He was previously the Director of the Renal Division at the Jewish Hospital of St. Louis. Dr. Hruska's areas of research and special interest include renal osteodystrophy, mineral homeostasis and bone cell signal transduction, and he has received special honors from the American Association of Physicians. He has served as the principal investigator in several long-term studies and has been published well over 200 times. Dr. Hruska is on the Medical Advisory Board of Bone Care International and has received funding or compensation from it as well as AlloSource, Creative BioMolecules, Inc., and Monsanto/Pharmacia.

**Craig B. Langman, MD,** is a Tenured Professor of Pediatrics at Northwestern University Medical School and Head of Nephrology and Mineral Metabolism and Director of Dialysis at

Children's Memorial Medical Center in Chicago. Dr. Langman's research has focused on the anatomical, biochemical, and clinical expression of inherited or acquired disorders of calcium, phosphorus, and vitamin D metabolism in infants, children, and adolescents, and he has pioneered the use of noninvasive testing to assess bone cell function in children. Dr. Langman has had more than 125 articles in his discipline published and serves on the Editorial Advisory Boards of *Advances in Renal Replacement Therapy* and *Pediatric Endocrinology*. He previously served on the Editorial Advisory Board of *Pediatric Nephrology*. Dr. Langman has been President of the American Board of Pediatrics sub-board of Pediatric Nephrology, the American Society of Pediatric Nephrology, and the Council of American Kidney Societies. He has served on the work group for the K/DOQI Clinical Practice Guidelines for Nutrition of Chronic Renal Failure as well as on the Scientific Advisory Board and the Public Policy and Executive Committees of the Council of Pediatric Urology and Nephrology Committees of the NKF and on the Growth Advisory Board of the North American Pediatric Renal Transplant Cooperative Study. Dr. Langman is on the Academic Advisory Board of Total Renal Care, Inc, and has been a consultant for many pharmaceutical laboratories, health-care companies, and health-care-related foundations, including Merck USA, Roche Pharmaceuticals, Abbott Laboratories, and the Oxalosis and Hyperoxaluria Foundation.

**Hartmut Malluche, MD,** is Professor of Medicine and Chief of the Division of Nephrology, Bone and Mineral Metabolism at the University of Kentucky Medical Center, Lexington, KY., where he is also the Robert G. "Robin" Luke Chair in Nephrology. Dr. Malluche is on the Active Scientific Staff at the Shriner's Hospital for Crippled Children, Lexington Unit, Lexington, KY. He has been a Scientific Reviewer for the National Institutes of Health (NIH) and an advisor to the Food & Drug Administration's Division of Cardio-Renal Drug Products Meeting. Dr. Malluche is an ex-officio member of the General Clinical Research Committee, and he is the University of Kentucky Institutional Representative for the American Society of Clinical Investigation. He is also a member of the Educational Review Committee for the Department of Preventative Medicine and Environmental Health. Dr. Malluche has been a visiting professor at universities throughout Europe and the United States and is a frequent guest speaker within the academic and health-care communities. He is a member of numerous professional societies, including the American Society of Nephrology, the International Society of Nephrology, the American Physiological Society, and the European Dialysis and Transplant Association (EDTA). He has served as a member of the Editorial Board of the *American Journal of Kidney Diseases* and *Nephron* and is the American Editor of *Clinical Nephrology*, in addition to having been published over 400 times. Dr. Malluche has received several grants from the NIH and other organizations including the Veterans Administration.

**Kevin J. Martin, MB, BCh, FACP,** is Professor of Medicine and Director of the Division of Nephrology at Saint Louis University School of Medicine, St. Louis, MO. He has also served as the Chief of the Nephrology Section at John Cochran Veterans Administration Hospital, St. Louis, MO. Dr. Martin completed a fellowship and an advanced research fellowship in the renal division of the Washington University School of Medicine, St. Louis, MO, as well as fellowships with the National Kidney Foundation of Eastern Missouri and Metro-East. He is on the Executive Committee of the Department of Internal Medicine at St. Louis University and was Chairman of the NIH General Medicine B Study Section and the Endocrinology Study Section of the Veterans Administration, and has been both a board member and President of the NKF of Eastern Missouri and Metro-East. Dr. Martin is a member of the American Federation for Clinical Research, the American Society of Nephrology, the International Society of Clinical Investigation, American Society of Nephrology and the NKF. He is on the Editorial Board of the *American Journal of Physiology* and has over 150 publications. Dr. Martin has been a consultant to Amgen, Inc., and Abbott Laboratories, and has also received funding from Genzyme Corporation.

**Shaul G. Massry, MD,** (*Work Group Chair*) is Professor Emeritus of Medicine, Physiology and Biophysics, at the Keck School of Medicine, University of Southern California. He has received honorary doctorates from several universities across Europe and is an honorary member

of many professional societies worldwide, including the Italian, Polish, Bulgarian, Hungarian, Czechoslovakian, Indian, and Israel Societies of Nephrology. He is also an honorary member of the Belgian, Polish, Russian, and Bulgarian Academies of Science as well as the Royal College of Physicians of Ireland, Thailand, and London. In addition to the NKF's David Hume Memorial Award and the Distinguished Scientific Achievement Award from the American Heart Association, Greater Los Angeles Affiliate, Dr. Massry has been the recipient of numerous other awards from universities and societies throughout the world, including the first Leo Ambard Gold Medal from the University of Strasbourg. Dr. Massry has served as the Editor-in-Chief of several journals including *Nephron*, and the *American Journal of Nephrology*, and is a reviewer for many other journals. He is a past President of the NKF and past Chairman of the NKF's National Medical Advisory Board, and has served with other organizations such as the NIH, the International Society of Nephrology, the American Heart Association, Greater Los Angeles Affiliate, and the International Society of Nutrition and Metabolism in Renal Disease. Dr. Massry has been a frequent guest speaker at national and international meetings and a visiting professor at many universities across the globe, and he has an extensive list of publications to his credit. Dr. Massry is a consultant to Genzyme Corporation and has participated in Advisory Board Meetings of Abbott Laboratories and Amgen, Inc.

**Linda McCann, RD, CSR, LD,** is Nutrition Services Manager at Satellite Dialysis Centers, Inc., Redwood City, CA. She is also Chairperson of the Dietitian Advisory Board for Genzyme Corporation and a Nutrition Consultant for Baxter Healthcare Corporation. Ms. McCann is a member of the American Dietetic Association (ADA) and the ADA Renal Practice Group, for which she served as Chairperson of the Standards of Practice Committee and a Test Writer and Reviewer in Renal Specialization. In addition to serving on the Volunteer Development Committee and the Editorial Board of *Advances in Renal Replacement Therapy* for the NKF, she is also on the NKF Council on Renal Nutrition, where she has been Nominating Committee Chairperson, and on the Editorial Board of the *Journal of Renal Nutrition*. Ms. McCann is on the Editorial Board of *Dialysis and Transplantation*, and has been published numerous times in a variety of publications. She is also a frequent guest lecturer in both the health-care and business sectors. Ms. McCann has received the Award of Distinguished Achievement from the CRN of Northern California, was honored as a Recognized Renal Dietitian (RRD) by the NKF Council on Renal Nutrition, and has twice been the recipient of the NKF's Distinguished Service Award. In addition to Baxter and Genzyme, she has also consulted for Abbott Laboratories.

**James T. McCarthy, MD,** is Staff Consultant, Division of Nephrology and Internal Medicine, for the Mayo Clinic and Mayo Foundation, Rochester, MN. He is affiliated with Mayo Health System clinics and hospitals in Minnesota, Wisconsin, and Iowa, and Mayo Foundation Mayo Clinics in Scottsdale, AZ and Jacksonville FL. Dr. McCarthy is the Medical Director of the Mayo-Austin Hemodialysis Unit, and Physician Liaison at Immanuel St. Joseph's Hospital, Mankato, MN. He is also the Chair of the Mayo Health System (MHS) 1999 Core Goal Work Group, a member of the MHS Regional Operations Committee, a member of the Board of Directors at Immanuel-St. Joseph Hospital, and a member of the Clinical Practice Innovation Review Committee, a Subcommittee of the Mayo-Rochester CPC. Dr. McCarthy belongs to the American Society of Nephrology, the International Society of Nephrology, the Renal Physicians Associations, and the NKF. He has been principal investigator on a number of research studies and has been published over 150 times in different journals and publications. Dr. McCarthy is also a member of the Scientific Advisory Boards of MinnTech Corporation and Nx-Stage, and has received research grants from Schein Pharmaceuticals, GelTex Pharmaceuticals, Bayer Corporation, Amgen, and Luitpoldt Pharmaceutical.

**Sharon M. Moe, MD,** is Associate Professor of Medicine at Indiana University School of Medicine and Director of Nephrology and Assistant Dean for Research Support at Wishard Memorial Hospital. She is also affiliated with the Richard L. Roudebush Veterans Association Medical Center. Dr. Moe is on the Board of Directors of the NKF of Indiana and a member of the American Society of Nephrology. Dr. Moe is

currently a member of the editorial board for the *American Journal of Kidney Diseases.* Her areas of research and special interests are bone and mineral metabolism including $\beta$2-microglobulin amyloidosis, immunomodulatory effects of vitamin D, and mechanisms of vascular calcification. She has received the NIH K24 award for musculoskeletal diseases in dialysis patients and the VA merit award on $\beta$-2-microglobular amyloidosis. Dr. Moe has been a consultant for Genzyme Corporation, Amgen, Inc., and Bone Care International, and has received grants from Genzyme, Amgen, and Abbott Laboratories.

**Isidro B. Salusky, MD, FAAP,** is Professor of Pediatrics at UCLA School of Medicine, Program Director of the UCLA General Clinic Research Center, and Director of the Pediatric Dialysis Program. He has a long-standing interest in the fields of growth and nutrition in children with renal failure that has ranged from experimental models to patients treated with maintenance dialysis. Dr. Salusky has done extensive work to characterize the syndromes of renal osteodystrophy in children with chronic renal failure undergoing regular dialysis and postrenal transplantation. He has had more than 150 papers published and is active in many professional societies. During the course of his research, Dr. Salusky has obtained funding from the NIH as well as other nonprofit and commercial organizations. He is a consultant for Genzyme Corporation, Bone Care International, and Abbott Laboratories.

**Donald J. Sherrard, MD,** is Professor of Medicine and the Chief of Veteran Affairs (VA) Nephrology at the University of Washington Medical School. Dr. Sherrard also completed a fellowship in nephrology at the University of Washington. His areas of research and special interest include calcium and bone as well as chronic renal failure, and he has received a Training Grant from the NIH. Dr. Sherrard has received funding from and consulted with Amgen, Inc., Abbott Laboratories, and Geltex Pharmaceuticals.

**Miroslaw Smogorzewski, MD,** is Associate Professor of Medicine at the University of Southern California School of Medicine. He is affiliated with the USC Ambulatory Health Center, LAC+USC Medical Center, the USC Healthcare Consultation Center, and the USC University Hospital. Dr. Smogorzewski completed a fellowship in Renal Medicine at Hammersmith Hospital in England and a fellowship in Nephrology at the LAC+USC Medical Center. His chief research interests include heart hypertrophy in chronic renal failure, signal transduction, and cystolic calcium in uremia, the role of parathyroid hormone as a uremic toxin, and metabolic derangement in phosphate depletion, and his main clinical interests are in kidney and renal transplantation and nephrology. In addition to being published many times, Dr. Smogorzewski has also collaborated on the editing of nephrology textbooks He is a member of the American Society of Nephrology, the International Society of Nephrology, and the European Dialysis and Transplant Association.

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