

**K/DOQI Clinical Practice Guidelines for Bone
Metabolism and Disease in Children
With Chronic Kidney Disease**

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Acronyms and Abbreviations

1 st PTH-IMA	First-generation parathyroid hormone immunometric assay
2 ^o HPT	Secondary hyperparathyroidism
AIs	Adequate intakes
AVN	Avascular necrosis
BCG	Bromocresol green method
BFR	Bone formation rate
BMC	Bone mineral content
BMD	Bone mineral density
CaR	Calcium-sensing receptors
CAPD	Continuous ambulatory peritoneal dialysis
CaXP	Calcium-phosphorus product
CCR	Creatinine clearance rate
CKD	Chronic kidney disease
CRF	Chronic renal failure
DBP	Vitamin D-binding protein
DEXA	Dual energy X-ray absorptiometry
DFO	Desferrioxamine
DOQI	Dialysis Outcomes Quality Initiative
DRI	Dietary Reference Intake
EBCT	Electron beam computed tomography
EEG	Electroencephalogram
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
GH, rhGH	Growth hormone, recombinant human growth hormone
ICMA	Immunochemiluminometric assay
IGF	Insulin-like growth factor
IRMA	Immunoradiometric assay
K/DOQI	Kidney Disease Outcomes Quality Initiative
MCV	Mean cell volume
MDRD	Modification of Diet in Renal Disease
MRI	Magnetic resonance imaging
NKF	National Kidney Foundation
PBM	Peak bone mass
PTH	Parathyroid hormone
QCT	Quantitative computed tomography
RDA	Recommended dietary allowance
RDI	Recommended daily intake
ROC	Receiver operating characteristics
SCFE	Symptomatic proximal femoral slipped epiphyses
SD	Standard deviation
VDR	Vitamin D receptor
VDRE	Vitamin D receptor element, vitamin D-responsive element

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

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Foreword

THE DISCIPLINE OF pediatric nephrology is unique and challenging because it encompasses the widest developmental stages of life, from *in utero* presentation of chronic kidney disease (CKD) through kidney failure presenting in early adulthood. CKD in our patients may arise from embryological disturbances, genetic mutations, acquired glomerulopathies and/or tubulopathies, systemic metabolic diseases, immune-mediated diseases, or those diseases that derive—in part—from lifestyle choices. The natural history of many of these diseases is being rewritten continually, as longevity for patients increases beyond that seen by our mentors before us. We see the influence of socio-demographic distributions on disease expression and severity, and the insufficiencies of organ availability for transplantation on disease chronicity.

In the pediatric population, body calcium balance remains markedly positive to support both somatic growth and bone mineral accretion. The *sine qua non* of pediatric CKD is the marked change in these two processes that leads to the devastating clinical disease that we term “osteodystrophy.” We have come to realize that the disorder encompasses marked disturbances in mineral homeostasis with chronic metabolic acidosis, secondary hyperparathyroidism (2° HPT), insufficiency of 1,25-dihydroxyvitamin D, and failure of linear growth in addition to extraskeletal disease. Thus, we have seen children, adolescents, and young adults with an as yet undefined cardiovascular

disease associated with calcium in incorrect places within the vasculature, similar to that seen in adult patients who develop CKD *de novo*. We recognize the pervasive nature of CKD, and perhaps a more subtle manifestation of its osteodystrophy, in abnormal neurological development of our youngest patients.

Although we were members of the committee for the preparation and publication of the National Kidney Foundation K/DOQI Guidelines for bone metabolism and disease in CKD in adults, we recognized that the subject in that population was filled with enough controversy that recommendations for children could not properly be placed within it. Therefore, the leaders of the K/DOQI process acceded to our request for a meeting in Chicago, in October 2002, to begin the arduous process of sorting through the literature to produce a pediatric-specific set of K/DOQI guidelines for bone metabolism and disease in CKD with our colleagues and committee members.

The task differed initially from the resultant guidelines seen here; but with very limited resources, and no external review of extant literature by a third party, we decided late in 2003 to follow the structure of the adult-based bone metabolism and disease guidelines instead. We owe great thanks to that group for their wisdom in allowing us to use some of their work, and adapt it where indicated for the aspects unique to pediatric osteodystrophy. It became rather clear, quickly, that the area of osteodystrophy in pediatric CKD is highly uninvestigated, and is a wonderful career-building opportunity for the generation of pediatric nephrologists who will follow the members of this writing committee.

As Co-Chairs, we owe a deep gratitude to our committee members. Each worked long hours, acceded to our many requests on short notice with a ‘can-do’ attitude, and worked in a collegial manner that allowed the project to succeed in a lofty manner.

With the successful completion of our task, we need to thank many of our colleagues who did not serve on the committee, but who taught us much from their science, and from their empathetic care of patients. We hope we acknowledged, by attribution within our text, their work and toil, and we take responsibility for any mistakes of omission in this regard. We thank the entire staff of the National Kidney Foundation for their excellent support, and especially that of Mr. Anthony Gucciardo and Ms. Donna Fingerhut, who were tireless in their pursuit of our goals. Drs. Gary Eknoyan

and Adeera Levin are to be commended for their spiritual input to our project (and ourselves) during its long course.

As you, the Reader, use these guidelines, you will be quick to see its flaws and weaknesses, as all such guidelines possess. We welcome your input directly through the National Kidney Foundation to those areas that need improvement, emendation, or removal in subsequent iterations of the work. Despite this caveat, we believe that regular attention to our patients’ osteodystrophy in a manner proscribed within the guidelines will lead to an improved outcome in every facet of the disease.

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Introduction

GROWTH AND DEVELOPMENT OF THE SKELETON

During childhood and adolescence, total skeletal calcium increases from approximately 25 g at birth to 900 g and 1,200 g in adult females and males, respectively. Attainment of optimal peak bone mass by young adulthood is thought to be the best protection against osteoporosis later in life.¹ Therefore, childhood and adolescence are particularly critical periods for the establishment of life-long bone health. While peak bone mass is strongly influenced by genetic factors, full genetic potential is attained only if nutrition, growth, physical activity, and metabolic and endocrine function are optimal in children. The clinical features of renal bone disease unique to childhood relate to distinctions between the growing and the fully-grown skeleton. The metabolic process of skeletal modeling throughout growth dictates that pediatric-specific recommendations for the management of the bone disease of CKD be developed.

BONE FORMATION

Formation of the skeleton occurs by two processes of ossification—intramembranous and endochondral. Intramembranous ossification is the direct mineralization of vascular connective tissue membrane in the plate-like bones of the skull, facial bones, mandible, and clavicle. The transformation of mesenchymal cells into osteoblasts and production of osteoid matrix convert the primitive mesenchyme into bone. In contrast, bones that involve joints and bear weight form by endochondral ossification. Endochondral bone formation is the result of ossification of an intermediate cartilage model that is derived from mesenchyme and represents the position and shape of the bone to be formed at that site. This provides a mechanism for the formation of bone during growth. In the long bones of the extremities, the primary center of ossification is located in the central portion of the cartilage model. Proliferation and hypertrophy of chondrocytes

and elaboration of matrix result in linear growth. Ossification proceeds toward the end of the bone and ultimately forms the growth plate (epiphyseal plate or physis) that is the predominant site of longitudinal bone growth. With continued maturation, the growth plate thins and eventually disappears with fusion of the epiphyseal and diaphyseal ossification centers. Epiphyseal union occurs at an earlier age in females than males. Knowledge about the appearance of various ossification centers in the carpal bones is used to determine a child's maturational age, or "bone age."

BONE MODELING

The shape and structure of bones are continuously modified and renovated by two different processes during growth: modeling and remodeling. Both processes result in the replacement of old bone tissue with new bone. The remodeling cycle of bone resorption and formation takes place throughout life and is vital for microdamage repair and maintenance of skeletal integrity. In contrast, modeling predominates during growth and promotes formation of new bone at locations different from the sites of bone resorption. This results in increased bone mass and modification of bone shape. For example, increases in cortical bone diameter of the diaphysis are due to concurrent bone formation on the periosteal (outer) surface and bone resorption on the endosteal (inner) surface. In contrast, as the bone grows in length, the wide metaphyseal region is converted to a narrow diaphysis through resorption of the periosteal surface and bone formation on the endosteal surface. Finally, long bones drift in a lateral direction during growth due to relatively greater resorption along the medial edge of the bone and formation along the lateral edge.

In conclusion, bone growth during childhood and adolescence involves the complex coordination of varied cell activities on specific bone surfaces. Cartilage proliferation, bone modeling, and epiphyseal closure are under the direct influence of a variety of hormones and growth factors, such as growth hormone (GH), thyroid hormone, estrogen, testosterone, parathyroid hormone (PTH), vitamin D, and insulin-like growth factors (IGF).² Each of these factors may be

Table 1. Signs and Symptoms of Bone Disease in Children with CKD

Metabolic Abnormalities
Hypocalcemia
Hyperphosphatemia
Hormonal Abnormalities
Altered vitamin D metabolism
Secondary hyperparathyroidism
Radiographic Abnormalities
Subperiosteal resorption
Osteosclerosis
Bone Disease
Linear growth failure
Delayed skeletal maturation and epiphyseal closure
Slipped epiphyses
Skeletal deformities resembling vitamin D-deficient rickets (Knee genu valgum & genu varus, ankle valgus)
Avascular necrosis
Spontaneous tendon rupture
Meniscal tears
Bone pain
Fractures
Proximal Myopathy
Progressive muscle weakness, waddling gait
Extraskeletal Calcification
Soft-tissue calcification of blood vessels, lung, kidney, myocardium, coronary arteries, and cardiac valves
Ocular Disease
Band keratopathy
Corneal calcification
Dermatological Disease
Pruritis
Skin ulceration and soft-tissue necrosis

disordered in CKD, with important effects on bone structure and maturation.

CLINICAL MANIFESTATIONS OF BONE DISEASE IN CHILDREN WITH CKD

Renal osteodystrophy is an early, universal, and pervasive consequence of CKD that may develop prior to any clinical manifestations of renal failure. The clinical manifestations of renal bone disease seen in adults may also appear in childhood. However, the effects of abnormal bone and mineral metabolism on endochondral ossification during growth result in complications in the epiphyseal region that are unique to the children with CKD. The clinical signs and symptoms of bone disease in children with CKD

are summarized in [Table 1](#), highlighting those seen exclusively during growth and development.

GROWTH RETARDATION AND SKELETAL MATURATION DELAY

Growth retardation is a frequent feature of CKD in children. Skeletal maturation is usually delayed commensurate with the growth deficit. In the 2002 North American Pediatric Renal Transplant Cooperative Study Annual Report, growth status is described in over 5,000 children and adolescents with CKD Stages 2-4. Use of age- and gender-specific standard deviation (SD) scores revealed that more than one-third of patients had a height SD score of less than -1.88

(3rd percentile). Height deficits were observed across all ages, from infants through adolescents; however, the SD score deficits were greatest among the children with early-onset and long-standing CKD. Nevertheless, significant height deficits were also observed in children with mild to moderate CKD. Among children with an estimated glomerular filtration rate (GFR) of 50-75 mL/min/1.73 m² (Stages 2-3), 22% had a height SD score of less than -1.88; among children with an estimated GFR of 25-50 mL/min/1.73 m² (Stages 3-4), 38% had a height SD score of less than -1.88.

The growth retardation and delayed maturation in children with CKD is multifactorial. Potential contributing factors include prior steroid therapy, chronic metabolic acidosis, anorexia, inadequate nutrient (vitamins, trace minerals) and caloric intake, hyposthenuria and sodium depletion, inadequate insulin-like growth factor I (IGF-I) availability due to increased serum levels of IGF-binding protein 3 (IGFBP-3), inadequate testosterone and estrogen production during puberty, and bone disease, including severe rachitic-like lesions. The contribution of renal bone disease to growth failure is unclear; however, treatment with 25(OH) vitamin D₃ therapy in children with CKD resulted in improved growth.³

MUSCULOSKELETAL DEFORMITIES

Clinical manifestations of the bone disease associated with CKD in children generally involve the musculoskeletal system. Nonspecific symptoms such as bone pain, muscle cramps with repetitive motion activities, and a decrease in normal muscle functions used in activities of daily living may be seen in children with CKD. Fractures may occur in children with CKD with deformed bones subjected to the trauma of normal childhood activities. The evaluation and treatment of orthopedic complications are discussed in greater detail in Guideline 3.

During childhood and adolescence, bony deformities may develop, most commonly involving rapidly growing bones of the extremities. Vitamin D deficiency in CKD results in skeletal deformities resembling vitamin D-deficient rickets, such as a rachitic rosary, widening of the metaphysis, frontal bossing, craniotabes, ulnar deviation, and pes varus. Histologically, there is disorganization in the growth plate and subjacent

metaphysis. The hypertrophic zone of the growth plate demonstrates an increase in cell number and loss of the normal columnar cell pattern. The disordered cartilage is resorbed and no longer provides adequate scaffolding for bone deposition. The subjacent metaphyseal fibrosis may interfere with vascularization and maturation of the growth plate.

The growth plate in children with CKD is vulnerable to injury; the hypertrophic zone is most vulnerable to shearing injuries. Morphological studies on the epiphyses have demonstrated a dense fibrous tissue that disrupts the connection between the epiphyseal plate and the metaphysis.⁴ These abnormalities, along with hyperparathyroid erosions of bone, result in an increased risk for slipped epiphyses (physiolysis) and genu valgum. Possible sequelae of slipped epiphyses include severe varus deformity, osteonecrosis, chondrolysis and degenerative joint disease. The orthopedic approach to correction of extremity deformities in children with CKD often requires an osteotomy. It is clinically recognized that healing of the bone after such a procedure proceeds poorly in the face of severe secondary hyperparathyroidism (2° HPT). Therefore, it is urged that biochemical control of the hyperparathyroidism be accomplished prior to performance of the osteotomy to enhance success of the procedure.

BONE MINERAL ACCRETION AND PEAK BONE MASS

The impact of CKD on peak bone mass is not known. However, increased bone resorption on the periosteal and endosteal surfaces due to 2° HPT may compromise bone microarchitecture, density, and dimensions. Biopsy studies in adults with kidney disease have demonstrated a 40% reduction in cortical bone mass⁵; therefore, it is likely that CKD during childhood compromises bone mineral accretion and results in inadequate peak bone mass.

As outlined in these guidelines, the management of bone disease in children with CKD requires careful monitoring for skeletal complications in the growing child, and strategies to optimize bone mineral accretion. In addition, dual-energy X-ray absorptiometry (DXA) is subject to several limitations that limit its usefulness in children. These include the inadequacy of

pediatric reference data across varied maturational stages, ethnic groups, and gender groups in healthy children, and difficulties in the interpretation of DXA results in children with impaired growth, altered body composition, or delayed maturation due to childhood illness.

OVERVIEW OF PRIOR PEDIATRIC K/DOQI GUIDELINES: IMPACT OF RENAL FUNCTION, GROWTH HORMONE, AND NUTRITION ON THE MANAGEMENT OF BONE DISEASE IN CHILDREN WITH CKD

Prior K/DOQI Pediatric Work Groups have published recommendations regarding the assessment of renal function in children with CKD, the indications and monitoring of growth hormone therapy, and the unique nutritional needs of these children. These guidelines impact the management of bone disease in CKD and are summarized here.

Estimation of GFR in Children with CKD

Among children, the Schwartz and Counahan-Barratt formulae provide clinically useful estimates of GFR.^{6,7}

Growth and Nutrition in Children on Dialysis

Scheduled, interval measurements of growth and nutrition parameters should be obtained to

provide optimal care of the nutritional needs of children on dialysis.

Supplemental nutrition support should be considered when a patient is not growing normally (i.e., does not have a normal height velocity) or fails to consume the Recommended Dietary Allowances (RDA) for protein and/or energy. Supplementation for the oral route is preferred followed by enteral tube feeding.

Recommendations for the Use of Recombinant Human Growth Hormone (rhGH) for Children Treated with Maintenance Dialysis

Treatment with rhGH in children with CKD should be considered under the following conditions:

Children who have (a) a height for chronological age more negative than 2.0 SD; or (b) a height velocity for chronological age SD more negative than 2.0 SD; (c) growth potential documented by open epiphysis; and (d) no other contraindications for GH use.

Prior to the consideration of the use of rhGH, there should be correction of (a) insufficient intake of energy, protein and other nutrients; (b) acidosis; (c) hyperphosphatemia (the level of serum phosphorus should be less than 1.5X the upper limit for age); and (d) 2° HPT.

GUIDELINE 1. EVALUATION OF CALCIUM AND PHOSPHORUS METABOLISM

1.1 Serum levels of calcium, phosphorus, alkaline phosphatase, total CO₂, and PTH—measured by a first-generation immunometric parathyroid hormone assay (1st PTH-IMA)—should be measured in all patients with CKD Stages 2 through 5. The frequency of these measurements should be based on the stage of CKD (Table 2). (OPINION)

1.1.a Patients with known tubulopathies in Stage 1 CKD should have serum phosphorus levels measured at least yearly.

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 (Guidelines 4-10), is a transplant recipient (Guideline 17), or is a patient being treated with rhGH (Guideline 11).

1.2.a The target range of serum PTH, in the various stages of CKD, are denoted in Table 3. (OPINION)

affected. The onset of the disorder is detectable about the time 50% of kidney function is lost.^{8,9} 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,^{10,11} patients with CKD should be monitored for imbalances in calcium and phosphate homeostasis, and for 2° HPT, by determination of serum calcium, phosphorus, and PTH levels.

Levels of intact PTH 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).¹²⁻¹⁷ While the ability to discriminate between the histological types of osteodystrophy of CKD has been demonstrated with determination of blood levels of intact PTH, the optimal target level for PTH in CKD is not known due to limitations in the

BACKGROUND

A disorder of bone remodeling, the osteodystrophy of CKD, is a common complication. By the time patients require dialysis, nearly all are

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Table 2. Frequency of Measurement of PTH, Calcium, Phosphorus, Total CO₂, and Alkaline Phosphatase by Stage of CKD

Stage	GFR	Calcium, Phosphorus, Total CO ₂	PTH & Alkaline Phosphatase (mL/min/1.73 m ²)
2	60-89	at least yearly	at least yearly
3	30-59	at least every 6 months	at least every 6 months
4	15-29	at least every 3 months	at least every 3 months
5	<15 or dialysis	at least every month	at least every 3 months

Table 3. Target Range of Serum PTH by Stage of CKD

CKD Stage	GFR Range (mL/min/1.73 m ²)	Target Serum PTH
2	60-89	35-70 pg/mL (OPINION)
3	30-59	35-70 pg/mL (OPINION)
4	15-29	70-110 pg/mL (OPINION)
5	<15 or dialysis	200-300 pg/mL (EVIDENCE)

available data, and the emerging consensus is that those target levels may be lower than currently thought.¹⁸ Recent studies demonstrate that 1st PTH-IMA 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 1st PTH-IMA have been developed to overcome this problem by using an antibody that detects the first several amino acids in a two-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 PTH levels is increased by concomitant consideration of alkaline phosphatase levels,¹⁹ although insufficient data exist to determine the sensitivity and specificity of alkaline phosphatase in osteodystrophy of CKD, or its concomitant use with PTH levels. These studies were performed in the era of high prevalence of osteomalacia, and it remains to be determined whether alkaline phosphatase determinations are additive to the newer 2nd generation PTH-IMA. 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.¹⁹ No bone imaging methods exist for measuring bone disease that can be used diagnostically in place of bone biopsy for osteodystrophy of CKD.

RATIONALE

In adults, blood levels of intact PTH begin to rise when GFR falls below 60 mL/min/1.73 m², and evidence of bone disease due to this 2^o HPT may be present at Stage 3 of CKD (Figure 1). Based on data using a less sensitive assay for PTH, it appears that 2^o HPT can occur in children in Stage 2 CKD.²⁰ 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 dis-

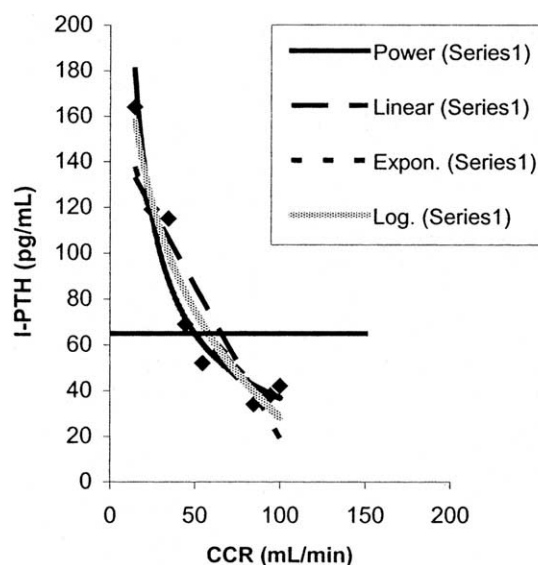


Fig 1. Relationship between Serum iPTH Levels and CCR. Values on the y-axis are serum iPTH levels (pg/mL). Values on the x-axis are CCR in mL/min. The lines fitted to the data set are based on 4 different mathematical functions (power, linear, exponential, and logarithmic), rather than on any assumptions about an underlying physiological mechanism. The horizontal line represents the upper limit of the normal range of serum iPTH levels. Reproduced with permission.²¹

ease. Therefore, measurements of serum levels of phosphorus, calcium, and PTH should be made when GFR falls below Stage 2 CKD levels, and these parameters should be monitored thereafter in patients with CKD (Table 2).

Most children with CKD or those on maintenance dialysis have some form of osteodystrophy. 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. In adults, 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 (Figure 2). Skeletal radiography is therefore an inadequate test to diagnose 2^o HPT. 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

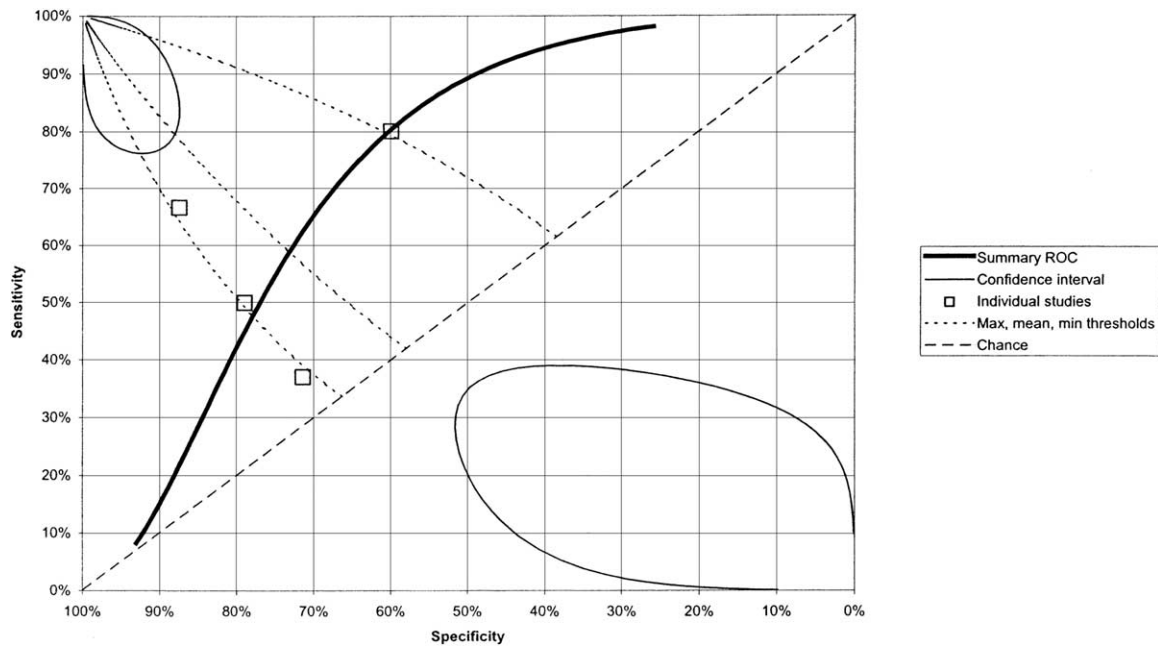


Fig 2. Summary ROC Analysis of Erosions on X-Ray as Diagnostic for Osteitis Fibrosa. Summary ROC derived from four individual studies assessing the diagnostic characteristics of erosions on X-ray for diagnosis of osteitis fibrosa. Values on the y-axis are the diagnostic sensitivity and values on the 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% confidence interval provide a summary estimate of the performance of the test based on the meta-analytically combined results from all four studies. The mean threshold point is our best single point estimate of the sensitivity and specificity of erosions on x-ray. In this case, the sensitivity for presence of erosions on x-ray as a tool for diagnosing osteitis fibrosa was 59.8% (95% CI: 44.9-73.2) and specificity was 79.9% (95% CI: 63.2-85.2).

detection of vascular calcification than it is for osteodystrophy.

In children and adults, multiple studies have been performed using 1st PTH-IMA to diagnose high-turnover bone disorders and distinguish them from low-turnover disorders. In children with CKD Stage 5, data suggest that PTH levels of approximately 200 pg/mL are useful for distinguishing patients with low-turnover lesions of renal osteodystrophy from those with 2^o HPT and high-turnover disease.^{22,23} A receiver operating characteristics (ROC) analysis (in essence, a diagnostic meta-analysis) of using 1st PTH-IMA to diagnose high-turnover disorders revealed an estimate of the sensitivity at 93% (95% CI, 87%-97%) and a specificity of 77% (95% CI, 62%-87%), using threshold PTH levels between 150-200 pg/mL. In children, the combination of a serum PTH level >200 pg/mL and a serum calcium value <10 mg/dL was 85% sensitive and 100% specific for identifying patients with high-turnover bone lesions. Serum PTH values

<200 pg/mL were 100% sensitive but only 79% specific for patients with adynamic bone.²² Thus, 1st PTH-IMA is a useful test in detecting high-turnover bone disorders (Figure 3).

In adults, studies performed using 1st PTH-IMA 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, 1st PTH-IMA is also useful in diagnosing low bone turnover (Figure 4). Newer assays specific for 1-84 PTH have recently become available and will likely refine and update this information. In the diagnosis and management of osteodystrophy of CKD, the usefulness of these newer assays for PTH is being examined. The normal range for the new assay for 1-84 PTH is 7-36 pg/mL (0.77-3.96 pmol/L), compared to 16-65 pg/mL (1.76-7.15 pmol/L) for 1st PTH-IMA. Thus, the relationship between the two assays is about 1:2 (1-84 PTH to 1st PTH-IMA). The differences in the levels be-

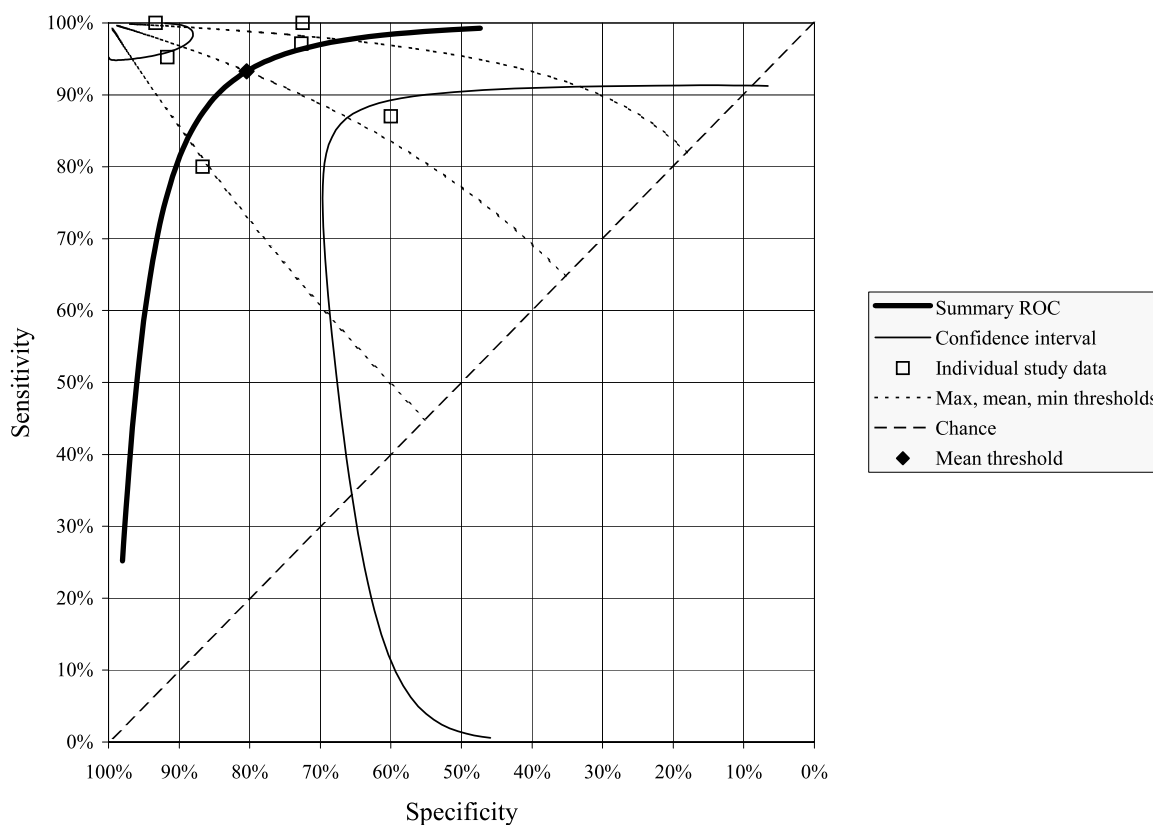


Fig 3. Summary ROC Analysis of Intact PTH for Diagnosis of High-Turnover Bone Disease. Summary ROC derived from six individual studies assessing the diagnostic characteristics of iPTH levels for the diagnosis of high-turnover bone disease. Values on the y-axis are the diagnostic sensitivity and values 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 95% CI provide a summary estimate of the performance of the test based on the meta-analytically combined results from all five 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.

tween the two types of assays are a reflection of the levels of circulating PTH fragments that are detected by the 1st PTH-IMA 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 compounds in the diagnosis of high- versus low-turnover bone disease.

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 in adults and one in children that provided GFR data showed an inverse relationship between serum PTH levels and GFR (Figure 3). The two studies that presented creatinine clearance data in adults showed that serum PTH levels increase as creatinine clearance decreases (Figure 1). A similar finding was seen in children with CKD. It was not possible to find a function that best described the relationship between GFR and PTH levels, or the relationship between serum creatinine or creatinine clearance and PTH levels. 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

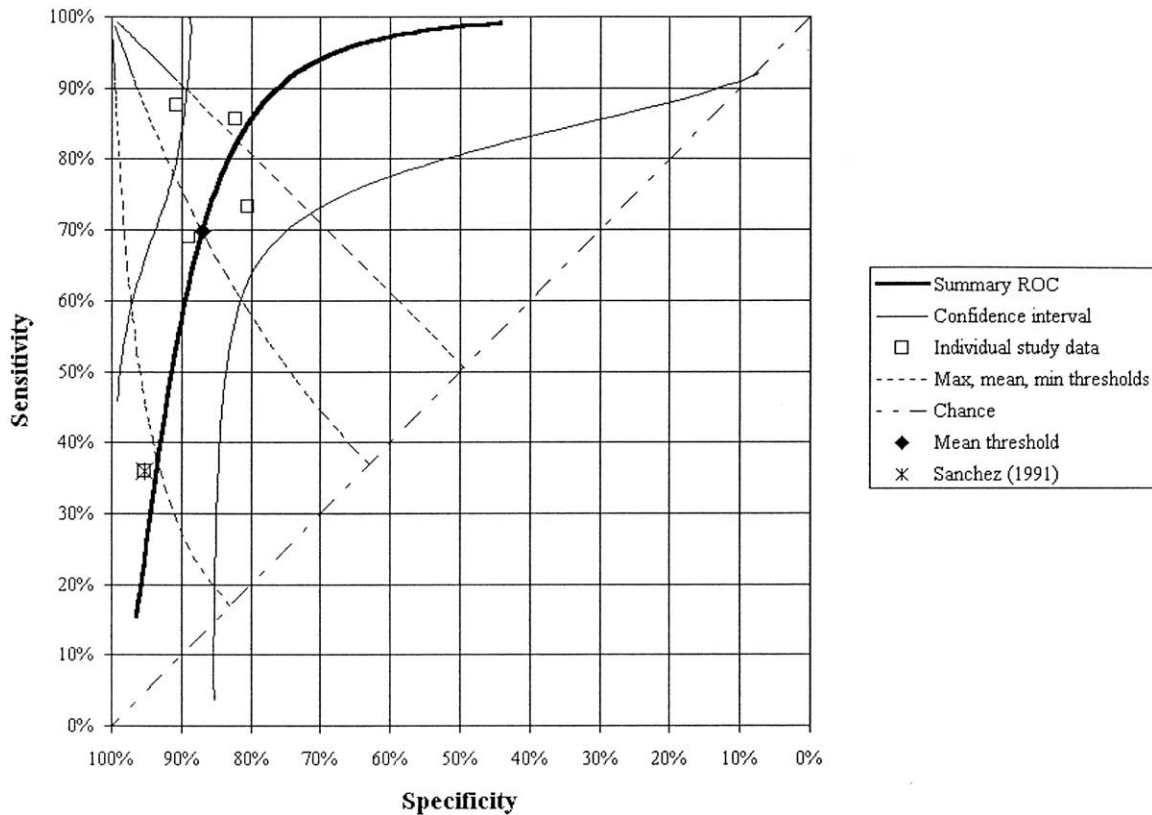


Fig 4. Summary ROC Analysis of Intact PTH for Diagnosis of Low-Turnover Bone Disease. Summary ROC derived from five individual studies assessing the diagnostic characteristics of iPTH levels for the diagnosis of low-turnover bone disease. Values on the y-axis are the diagnostic sensitivity and values 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 provide a summary estimate of the performance of the test based on the meta-analytically combined results from all five 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.

serum PTH levels in CKD patients should be initiated when CKD Stage 2 is reached.

The most robust available data were related to the use of PTH levels as a marker of osteodystrophy of CKD. In this instance, there were seven studies in adults that met the defined criteria selected for meta-analysis and derivation of an ROC curve.^{14,17,24-26} These data demonstrated the usefulness of PTH levels for predicting both high- and low-turnover bone disease (Figure 3 and Figure 4, respectively). Data in children with CKD Stage 5 allow PTH levels also to serve as a predictor of bone turnover based on bone biopsy.²² 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 demon-

strated in standard X-rays as a diagnosis of osteitis fibrosa, or in the demonstration of rickets in growing children. A meta-analysis of five studies met the criteria to perform an ROC curve.^{14,27-30} 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 considered an adequate diagnostic tool. There were no adequate studies evaluating the usefulness of quantitative computed tomography (QCT), dual photon absorptiometry, or DXA in the diagnosis of osteodystrophy in CKD patients.

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 1^{st} PTH-IMA, 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. Data on PTH and bone disease in CKD Stages 2-4 are missing in children.

CLINICAL APPLICATIONS

These Guidelines promote the use of 1^{st} PTH-IMA in the diagnosis and management of os-

teodystrophy in patients with CKD. They indicate the limited usefulness of other biochemical markers related—in large part—to lack of information. Inadequate data exist for the utilization of imaging techniques.

RESEARCH RECOMMENDATIONS

Much work is needed to relate biochemical markers of bone turnover to growth and osteodystrophy in CKD. The role of new PTH assays must be further defined. 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:
 - 2.2.a Fractures with minimal or no trauma (pathological fractures); (OPINION)
 - 2.2.b Suspected aluminum bone disease, based upon clinical symptoms or history of aluminum exposure; (OPINION) (See Guideline 12)
 - 2.2.c Persistent hypercalcemia with PTH levels between 400-600 pg/mL.
- 2.3 Bone radiographs are indicated in patients with clinical manifestations suggestive of avascular necrosis (AVN), symptomatic proximal femoral slipped epiphyses (SCFE), rickets, or for the assessment of skeletal maturation. (EVIDENCE)
- 2.4 Dual-energy X-ray absorptiometry (DXA) should not be used to monitor bone mineral density (BMD) in children with CKD. (OPINION)

BACKGROUND

The renal bone diseases represent a spectrum of skeletal disorders that range from high-turnover lesions to low-turnover osteodystrophy. Patients may change from one histological subtype to another over time, according to the degree of renal insufficiency and the type of specific treatment of renal osteodystrophy. The use of bone biopsy has contributed substantially to our current understanding of the different subtypes of renal bone diseases. Indeed, quantitative histomorphometry of bone provides information about the status of skeletal mineralization, the structural characteristics of cancellous and cortical bone, the levels of osteoclastic and osteoblastic activities, and the presence of marrow fibrosis.

Bone Biopsy

Determinations of bone formation are estimated by the use of the technique of double tetracycline labeling. Patients are given either demeclocycline or tetracycline HCl; the doses should not exceed 10 mg/kg/day in a tid dosage. Phosphate-binding agents should not be given while patients are receiving the antibiotic. The antibiotics are given on 2 consecutive days, followed by a 10- to 20-day interval when no antibiotic is given and then a second, 2-day course of antibiotics is given; the bone biopsy should be performed within 3-7 days after finishing the second course of antibiotics. In addition to the bone histomorphometry, special staining can be used for identification of aluminum or iron in bone. Iliac crest bone biopsy can be done safely with minimal morbidity.

Patients with histological features of high-turnover renal osteodystrophy may have a bone lesion defined as osteitis fibrosa or the mild lesion of 2° HPT. Osteitis fibrosa is the most common high-turnover lesion of renal osteodystrophy in pediatric patients treated with maintenance dialysis. The disorder is characterized by histological evidence of active bone formation with increase in the number and size of osteoclasts and in the number of resorption bays, or Howship's lacunae within cancellous bone (Table 4). Fibrous tissue is found immediately adjacent to bony trabeculae, or it may accumulate more extensively within the marrow space. Osteoblastic activity is increased and the combined increase in osteoblastic and osteoclastic activity accounts for the high rates of bone remodeling and turnover.

The other bone disorder of high-turnover, the mild lesion of 2° HPT, is characterized by only moderate increases in osteoclastic activity and bone formation and without evidence of peritrabecular fibrosis (Table 4). This disorder is a less severe manifestation of hyperparathyroid bone disease. Serum PTH levels are elevated but to a lower degree than in those with osteitis fibrosa, although in some instances it is difficult to assess the degree of fibrosis without a bone biopsy. Tetracycline-based measurements of bone formation are useful for distinguishing this subgroup from those with either normal or reduced rates of

Table 4. Histological Features of High-Turnover Renal Osteodystrophy

Feature	Mild Lesion of 2° HPT	Osteitis Fibrosa
Bone Formation		
Trabecular bone volume	Normal	Normal-high
Osteoid volume	Normal-high	Normal-high
Osteoid seam thickness	Normal	Normal-high
Number of osteoblasts	High	Very high
Bone formation rate	High	Very high
Mineralization lag time	Normal	Normal
Bone Resorption		
Eroded bone perimeter	High	Very high
Number of osteoclasts	High	Very high
Marrow fibrosis	Absent	Present

bone formation. In order to carefully characterize the different subtypes of renal osteodystrophy according to bone formation rates (BFRs), it is imperative to have tetracycline-based determinations of bone formation in children with normal renal function to be used as controls.

Patients with low-turnover bone renal osteodystrophy may have a bone histological manifestation of osteomalacia or adynamic/aplastic osteodystrophy. The lesion of osteomalacia is characterized by excess osteoid, which accumulates in bone because of a primary defect in mineralization. Osteoid seams are wide and they have multiple lamellae; the extent of trabecular bone surfaces covered with osteoid also is increased. Osteoblastic activity is markedly re-

duced and bone formation often cannot be measured because of the lack of tetracycline uptake into bone (Table 5). In contrast, bone biopsies from patients with adynamic/aplastic osteodystrophy have normal or reduced amounts of osteoid, no tissue fibrosis, diminished numbers of osteoblasts and osteoclasts, and low or immeasurable rates of bone formation (see Table 1 in Introduction). Patients with aluminum-related osteomalacia or adynamic bone have elevated the bone aluminum content. Currently, the adynamic lesion of renal osteodystrophy that is not related to aluminum, is the most common lesion of renal osteodystrophy in adult patients treated with dialysis. In contrast, 2° HPT remains the predominant lesion in children with CKD. However, a

Table 5. Histological Features of Low-Turnover Renal Osteodystrophy

Feature	Adynamic	Osteomalacia
Bone Formation		
Trabecular bone volume	Normal, low	Variable Low, normal or high
Osteoid volume	Normal, low	High-very high
Osteoid seam thickness	Normal, low	High-very high
Number of osteoblasts	Low	Low
Bone formation rate	Low-very low	Low-very low
Mineralization lag time	Normal	Prolonged
Bone Resorption		
Eroded bone perimeter	Normal, low	Variable Often low; may be high
Number of osteoclasts	Low	Low; may be normal or high
Marrow fibrosis	Absent	Absent

substantial proportion of children developed adynamic bone after intermittent calcitriol therapy. In adults, currently the most common factors involved in the pathogenesis of adynamic bone are:

- Diabetes
- Older age
- Corticosteroid therapy
- Parathyroidectomy
- Excess doses of active vitamin D sterols
- Calcium supplementation
 - Oral calcium salts
 - Dialysate
- Treatment with peritoneal dialysis.

As measured by conventional histomorphometry, the mineralization lag time reflects the average value for all osteoid seams, and it is often prolonged in adynamic renal osteodystrophy. In contrast, the osteoid maturation time represents the average only for osteoid seams that are undergoing active mineralization, and it is usually normal in the adynamic lesion. The disparity in these values between adynamic bone and osteomalacia is due to differences in the proportion of osteoid seams undergoing active mineralization at any given point in time.

Some patients demonstrate histological features of both osteitis fibrosa and osteomalacia and this combination is defined as the mixed lesion of renal osteodystrophy. Patients may have biochemical evidence of 2° HPT, but other factors such as hypocalcemia and/or hypophosphatemia may account for the defective mineralization. However, most of the described cases have been associated with aluminum toxicity.

Dual-Energy X-ray Absorptiometry (DXA)

The DXA technique is widely accepted as a quantitative measurement for assessing skeletal status in adults. The World Health Organization criteria for the diagnosis of osteoporosis in adults is based on the comparison of a measured BMD result with the average BMD of young adults at the time of peak bone mass (PBM), defined as a *T-score*.³¹ A *T-score* ≤ 2.5 SD below the mean PBM is used for the diagnosis of osteoporosis. While the *T-score* is a standard component of DXA BMD results, it is clearly inappropriate to assess skeletal health in children through comparison with peak adult bone mass. At present, there

are no evidence-based guidelines for classification of bone health in children.

Dual-energy X-ray absorptiometry is a projectional technique in which three-dimensional objects are analyzed as two-dimensional, and bone is presented as the total bone mineral content (BMC) within the projected bone area. It provides an estimate of BMC expressed as grams per anatomical region (e.g., individual vertebrae, whole body, or hip). Dividing the BMC (g) by the projected area of the bone (cm²) then derives “areal BMD” (g/cm²). This BMD is not a measure of true volumetric density (g/cm³) because it provides no information about the depth of bone. Furthermore, because the bone is presented as the combined sum of cortical and trabecular BMC within the projected bone area, it is not possible to assess the distinct structural characteristics of these discrete bone components.

The DXA technique has several limitations that are pronounced in the assessment of children. These can be broadly classified as (a) difficulties in scan acquisition due to limitations in the bone edge detection software in children with low bone mass³²; (b) inadequacy of pediatric reference data across varied maturational stages, ethnic groups, and gender groups in healthy children³³; and (c) difficulties in the interpretation of DXA results in children with impaired growth, altered body composition, or delayed maturation due to childhood illness. Although varied techniques have been proposed to address these pitfalls, the third limitation remains the greatest challenge in the assessment of childhood osteopenia.³⁴

A significant limitation of DXA is the reliance on measurement of areal rather than volumetric BMD. Bones of larger width and height also tend to be thicker. Since bone thickness is not factored into DXA estimates of BMD, reliance on areal BMD inherently underestimates the bone density of short people. Therefore, a child with smaller bones will appear to have a mineralization disorder (decreased areal BMD). Recent pediatric studies have recognized the importance of short stature in the assessment of DXA-based measures of BMD in chronic childhood disease, including renal disease,³⁵ and have adjusted the DXA BMD result for height and/or weight.^{34,35} Unfortunately, this too is a misleading approach

since healthy children of the same height or weight as a chronically ill child will be younger than the ill child. Skeletal maturity and Tanner stage are key determinants of bone mass, and comparison with less mature controls is a flawed solution to the influence of bone size.

Limitations of DXA in Renal Osteodystrophy

Dual-energy X-ray absorptiometry has been used extensively to evaluate renal osteodystrophy. Clearly, since trabecular and cortical bone behave differently in response to increased parathyroid activity (increase and decrease, respectively), and DXA does not allow distinction of the effects of renal osteodystrophy on the two types of bone, the technique is inherently less useful than three-dimensional techniques such as peripheral QCT. The conflicting data on DXA-derived measures of BMD in patients with renal osteodystrophy are consistent with these limitations. Predictably, DXA results have been quite variable with mean BMD values that are higher than, the same as, or lower than control subjects.³⁵⁻⁴¹ These studies have contributed very little to management of individual patients.

Quantitative computed tomography findings in the vertebrae seem to confirm available histomorphometric data in that trabecular BMD was found to be increased in high-turnover disease (+1.6 SD) and decreased in low-turnover disease (-1.2 SD), relative to age-matched controls.⁴² On the other hand, vertebral BMD was unable to predict the occurrence of fractures nor was there an association between BMD and the time on dialysis. This is not unanticipated, given that increased BMD in high-turnover disease does not equate with improved structural integrity.

In summary, it is clear that integrated measures of BMD—which do not allow distinction between cortical and trabecular bone and provide no information on bone architecture—are limited in their usefulness to differentiate the spectrum of skeletal disorders in renal osteodystrophy.

Utility of Skeletal Radiography

Bony deformities, most commonly involving rapidly growing bones of the extremities, may occur in children with CKD and chronic metabolic acidosis, osteomalacia associated with vita-

min D deficiency, or aluminum-associated adynamic bone disease, and in children with severe 2° HPT. However, any bone may be affected, including the skull, the chest, the spine, or the hip. Atraumatic, pathological fractures are seen more commonly in patients with adynamic bone disease, while fractures may occur in children with CKD with deformed bones subjected to the trauma of normal childhood activities.

The radiographic manifestations of the bone disease associated with CKD in children are quite varied, ranging from the many manifestations of severe 2° HPT to those of frank rickets. Radiographic findings from plain film radiography are technique-dependent, with X-ray voltage, film grain quality, and processing methods influencing the ability to diagnose abnormalities. Magnification techniques can increase the sensitivity of finding abnormalities. Cortical bone is over-represented by plain film radiography when compared to cancellous bone. Bone scintigraphy is a sensitive method for finding bone abnormalities in patients with CKD. However, it may be poorly discriminating, as most patients on maintenance dialysis have diffuse bony uptake of the radionuclide tracer. Accumulation at a single site or two may yield information about pathological fractures in advance of their appearance on plain film radiography. Overall, the technique is employed sparingly. Pathological visceral calcifications may be seen by routine radiography; recently, the use of EBCT in a population of adolescents and young adults with CKD detected pathological coronary calcium deposition.

Standards have been developed in children with normal kidney function to correlate chronological age and pubertal status with radiographic appearances of bones of the hand and wrist, giving rise to a “bone age.” Standard deviations of bone age versus chronological age have been calculated for children with normal kidney function from birth through the end of growth (epiphyseal closure). Bone age is often retarded in children with CKD. It remains unclear if the calculated bone age, if reduced substantially below chronological age, is truly as low as that seen radiographically, since the disease process itself alters the radiographic image in addition to producing a true reduction in bony maturation. Standard deviations of bone age versus chronological age in children with CKD have not been developed to date. However, the presence of

normal or advanced bone age is likely correct, and may guide the clinician as to the utility of using GH to treat the failure in linear growth often seen in children with CKD (see Guideline 11).

RATIONALE

Despite considerable advances in our understanding of 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 yet developed. Quantitative bone histomorphometry with double tetracycline labeling has become the “gold standard” for the diagnosis of metabolic bone disease in CKD patients.

Given the extensive limitations of DXA in children, and in the setting of renal osteodystrophy, there is no current rationale for performing DXA.

An initial determination of bone age, and the presence or absence of the many radiographic abnormalities in the bones of children presenting with CKD, is useful to the clinician in planning the therapeutic approach for the patient. Rickets may not be appreciated clinically, and the extent of severe hyperparathyroid bone disease can be assessed only in the presence of the lesions, since an absence of bony changes by plain-film radiography does not preclude its presence by the more sensitive technique of dynamic bone histomorphometry. Bone age is an important component of determining the utility of growth hormone therapy.

STRENGTH OF EVIDENCE

The importance of bone biopsy has been established by many studies, and it is now accepted as

the gold standard for the diagnosis of the various types of osteodystrophy in CKD if performed and interpreted using standard techniques. Normal bone histomorphometry should be performed and the results should be reported in accordance with the standard nomenclature suggested by the American Society of Bone and Mineral Research.⁴³

There are no data that support the utility of DXA in children with CKD.

Definitive diagnosis of AVN, SCFE, or rickets requires skeletal radiography. Assessment of skeletal maturation can only be accomplished by determination of a bone age using skeletal radiography.

LIMITATIONS

There are no recent data utilizing bone biopsy to characterize osteodystrophy in the early stages of CKD in children. Skeletal radiography is an insensitive test when used to classify osteodystrophy in CKD.

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 pediatric patients with CKD.

Future studies are needed to determine if non-invasive imaging techniques, such as quantitative computed tomography and magnetic resonance imaging, in combination or not with biochemical determinations, are useful in the assessment of trabecular and cortical manifestations of renal osteodystrophy in children.

GUIDELINE 3. SURGICAL MANAGEMENT OF OSTEODYSTROPHY

- 3.1 Lower extremity angular deformity should be surgically corrected if the deformity is progressive or severe as defined by interference with gait, or by the presence of a mechanical axis deviation of more than 10° between the femur and tibia. Control of secondary HPT is recommended prior to surgical correction. (OPINION)**
- 3.2 Symptomatic proximal femoral slipped epiphyses (SCFE) should be surgically stabilized if K/DOQI target values for PTH are not achieved within 3 months of the diagnosis of SCFE. (OPINION)**

BACKGROUND

Renal osteodystrophy refers to the effects of chronic renal failure (CRF) on the skeletal system. Although the underlying defect is metabolic in nature, this section is primarily concerned with the consequences of CKD most likely to be encountered by the orthopedic surgeon. These issues are largely the result of mechanical failure superimposed on the underlying metabolic and histological changes. They occur either acutely as seen in pathological fractures, or on a chronic basis as exemplified by severe and progressive knock-knees and bow-legs. From an orthopedic perspective, skeletal abnormalities are primarily the result of 2° HPT. Along with optimal metabolic treatment of these patients is a need for concurrent orthopedic management.

RATIONALE

General

Prompt treatment of musculoskeletal deformity prevents further deformity, restores patient function and mobility, and improves patient self-esteem. Patients with renal osteodystrophy exhibit delayed acquisition of motor milestones. Skeletal age is also delayed, and short stature is to be expected with children often falling below the 5th percentile in height.⁴⁴ The role of the orthopedist is to recognize these associated conditions, refer for management of metabolic issues (including possible GH treatment), and treat bony deformity. One of the frequently overlooked associations is a severe myopathy. Resistance training in adults can result in significant increases in both muscle mass and strength, and

physical therapy is an essential part of treatment for these patients.⁴⁵

The treatment of musculoskeletal complications must be tailored to the individual. Medical stabilization of 2° HPT is an important component of the care of angular deformity and slipped epiphyses. When surgery is necessary, medical management to achieve metabolic stability is of great importance. This improves surgical fixation and healing by improving the biomechanical strength of bone while limiting the incidence of postoperative recurrence. Elevated serum alkaline phosphatase levels (above 500 U/L) are associated with poor healing and continued bony deformity despite surgery.^{46,47}

Angular Deformities

Angular deformity of the weight-bearing bones is the most common musculoskeletal abnormality in children with renal osteodystrophy. Of these, the most common is genu valgum, although genu varum, ankle valgum or varum, and coxa vara may also be seen.^{48,49} The cause of angular deformity is likely multifactorial. Metabolic abnormalities suppress physeal maturation, and asymmetric forces placed across the physis may compound the situation according to the Heuter-Volkman principle (excessive compressive forces inhibit physeal growth).⁵⁰ Finally, slipping of the epiphyses (discussed below) with subsequent healing may also result in residual angulation.

Although no one parameter predicts which patients go on to angular deformity, there is general consensus that it is related to metabolic instability, and that prompt correction of this instability can lead to improvement of skeletal deformity.^{46,51-55} The age at onset of renal failure impacts which deformity is more common. Patients with physiological knee varus at the onset of renal failure tend to develop genu varum, while older patients with physiological valgus at disease onset tend to develop genu valgum.⁴⁸

Evaluation of patients with angular deformity⁵⁶ can be quantified with clinical photographs.⁵⁶ For deformity out of the range of normal, standing lower extremity radiographs from hips to ankles on a 36" cassette are war-

ranted. Deformity may be primarily at the distal femur, or proximal tibia, or variably divided between them. Angular deformity can improve with medical therapy alone.⁵¹ Patients without much growth remaining or with severe deformity are unlikely to satisfactorily improve, and they are usually treated with corrective osteotomy.^{47,49} Patients with open physes and moderate valgus deformity may be treated with medial hemiepiphyseal stapling.⁴⁷

Surgery is indicated when correction of the metabolic bone disease does not lead to resolution. The goal of surgery is to restore a normal anatomic axis such that a straight line passes simultaneously through the femoral head, center of the knee, and center of the ankle (talar surface), with the patient in a standing position. In addition, the ankle and knee joints should be parallel to the floor. Depending on the relative contribution of the distal femur versus the proximal tibia, the condition may require osteotomies above, below, or simultaneously above and below the knee joint in order to achieve these goals. Occasionally a varus deformity in the distal tibia may require a separate correction at that level.

Slipped Epiphyses

In contrast to adolescent idiopathic slipped epiphyses, slipped epiphyses in the renal osteodystrophy patient commonly occur through the metaphyseal—and not the physeal—regions of long bones. Although the most typical location is the proximal femur, slips have been reported in the distal radius and ulna, distal femur, proximal humerus, and distal tibia and fibula.^{48,57-60} They likely occur due to 2° HPT, which leads to osteopenia and fibrosis of the metaphysis, thereby weakening it. Application of shear forces through weight bearing or unequal muscle pull at the ends of long bones are presumably the forces leading to gradual deformity through the area.

With lower extremity slips, patients usually present with an abnormal waddling gait. Upper extremity slips usually result in obvious skeletal deformity, though subtle deformity can be overlooked because these patients have widening of the metaphyses of long bones, giving them a pre-existing abnormal appearance at any rate. Radiographs of the affected areas are diagnostic.

The vast majority of slips stabilize with medical treatment of the bone disease.^{57,58,61} Biomechanically, slip progression with further varus deformity is likely and can be prevented by medical and surgical stabilization of the slip. Therefore, if medical stabilization is not achieved promptly, pinning is undertaken.⁵⁷ Many children are less than 10 years when the hips first slip, and many children do not close their physes for another 10 years since maturation is delayed. Thus, terminally smooth pins are usually placed with threads engaging bone only at the lateral cortex of the femur. This allows continued growth of the physis along the axis of the smooth portion of the pin.⁶² For non-hip-slipped epiphyses, observation and medical therapy alone are indicated, as long as there is skeletal growth remaining and the deformity is improving. An unacceptable deformity in a patient with little or no skeletal growth remaining is treated with surgical stabilization.

Avascular Necrosis

Avascular necrosis of bone occurs in the setting of CRF. The femoral head is a common site, and symptoms are often mild when compared to the radiographic appearance.⁶³ While GH treatment may play a role in the development of AVN in these patients,⁶⁴ the majority of reports associate the incidence of AVN with chronic immunosuppression after renal transplantation.^{48,65-67} The incidence of this complication appears to be dose-related, though no specific dose-time guidelines exist.^{65,68,69} While the femoral head is the most common site, reports delineate the talus, humeral head, femoral condyles, and metatarsals as other involved sites. The diagnosis can be somewhat confusing in these patients because approximately 20% develop osteosclerosis, the cause of which is poorly understood. The increased bone density seen radiographically with avascular necrosis before collapse can have a similar appearance to osteosclerosis. The advent of magnetic resonance imaging (MRI) has aided in making a more secure diagnosis.

STRENGTH OF EVIDENCE

Case-based series of children with either SCFE or lower-extremity angular deformities support

the idea that prompt optimal metabolic control is an integral component of the orthopedic care. There are only retrospective studies regarding the surgical treatment of angular deformity and SCFE.^{46,47,57,62}

LIMITATIONS

Because few centers treat large numbers of patients with renal osteodystrophy, no prospective studies exist regarding optimal treatment of the orthopedic manifestations of the disease. Treatment recommendations are therefore largely based on the opinions of those who treat the largest number of these patients.

RESEARCH RECOMMENDATIONS

Although it is accepted that metabolic disease control is important if surgery is planned, future studies should examine the importance of control duration in the perioperative period and how this relates to surgical outcome. Also, the musculoskeletal manifestations of disease can improve with metabolic disease control, and a prospective study examining deformity improvements without surgery might lead to a better understanding of surgical indications. Studies comparing different surgical techniques for treatment of angular deformity are needed, as are studies exploring the optimal surgical fixation for SCFE stabilization.

GUIDELINE 4. TARGET SERUM PHOSPHORUS LEVELS

- 4.1 In CKD patients (Stages 1-4), the serum level of phosphorus should be maintained at or above the age-appropriate lower limits (EVIDENCE) and no higher than the age-appropriate upper limits. (OPINION)**
- 4.2 For children with kidney failure (CKD Stage 5), including those treated with hemodialysis or peritoneal dialysis, the serum levels of phosphorus should be maintained between 3.5-5.5 mg/dL (1.13-1.78 mmol/L) during adolescence and between 4-6 mg/dL for children between the ages of 1-12 years. (EVIDENCE)**
- 4.3 In children with renal tubular phosphate wasting, or other causes of hypophosphatemia, hypophosphatemia should be corrected via dietary modification, enteral supplementation, or reduction in the use of phosphate binders. (EVIDENCE)**

BACKGROUND

There are substantial effects of age on the fasting serum concentration of phosphorus. Serum phosphorus levels in infants range from 4.8-7.4 mg/dL (mean 6.2 mg/dL) in the first 3 months of life, and decrease to 4.5-5.8 mg/dL (mean 5.0 mg/dL) at age 1-2 years.⁷⁰ The higher serum phosphorus concentration in infants is attributed to an increased fractional phosphate reabsorption, possibly further augmented by a low GFR.⁷⁰ In mid-childhood, values range from 3.5-5.5 mg/dL (mean 4.4 mg/dL) and decrease to adult values by late adolescence.⁷¹⁻⁷³ Representative target ranges for serum phosphorus concentration in children with CKD are depicted in Table 6. The normal range for serum phosphorus concentration can vary somewhat between laboratories.

In healthy children and in children with GFR ranging from 25-50 mL/min/1.73 m² (approximately Stage 3 CKD), the serum phosphorus concentration decreased after breakfast to a nadir in late morning, and increased during the early afternoon,⁷⁴ exhibiting a circadian pattern similar to that observed in healthy adult subjects ingesting typical diets.⁷⁵ The amplitude of the circadian variation in serum phosphorus concentration in healthy adolescents (3.0 mg/dL) is greater than that in healthy adults (1.2 mg/dL).⁷⁶ Restriction of dietary phosphorus induces substantial decreases in serum phosphorus levels during late morning, afternoon, and evening, but little or no change in morning fasting phosphorus levels.⁷⁵ Thus, values obtained in the afternoon are more likely to be affected by diet and may be more useful in monitoring the effect of phosphorus restriction or administration of phosphate-binding agents on serum phosphorus concentrations.

Hyperphosphatemia leads to 2° HPT and elevated blood levels of PTH by: (a) lowering the levels of ionized calcium; (b) inhibiting the production of 1,25(OH)₂D₃; and (c) directly stimulating PTH secretion.^{77,78}

These processes lead to high-turnover bone disease and other adverse consequences of excess PTH, in part due to an increase in calcium-phosphate product (CaXP)⁷⁹⁻⁸² and in adults, is associated with increased morbidity^{83,84} and mortality.⁸⁵⁻⁸⁸ With respect to vascular calcification, hyperphosphatemia exerts a direct calcifying effect on vascular smooth muscle cells.⁸⁹ Calcification of coronary arteries, cardiac valves, and pulmonary tissues results in cardiac disease, the leading cause of death in patients with CKD.^{83,90-92} In young adults who developed CKD in childhood years, there is high incidence

Table 6. Representative Normal Values for Serum Phosphorus, Total Calcium, Blood Ionized Calcium, and Alkaline Phosphatase Concentrations

Age (yrs.)	Serum Phosphorus (mg/dL)	Serum Total Calcium (mg/dL)	Blood Ionized Calcium (mM)	Alkaline Phosphatase (IU)
0-0.25	4.8-7.4	8.8-11.3	1.22-1.40	
1-5	4.5-6.5	9.4-10.8	1.22-1.32	100-350
6-12	3.6-5.8	9.4-10.3	1.15-1.32	60-450
13-20	2.3-4.5	8.8-10.2	1.12-1.30	40-180

of coronary artery calcification, associated with an elevated CaXP.^{80,93} It is therefore imperative to prevent hyperphosphatemia and maintain serum phosphorus levels within the normal range.

Children with CKD may have renal tubular wasting of phosphorus. Fanconi syndrome due to cystinosis is the most common etiology in childhood. A variety of other genetic disorders and drug or toxin exposure may also cause Fanconi syndrome. In addition, some children develop CKD and hypophosphatemia due to Dent's disease. Hypophosphatemia may also be secondary to excessive use of phosphate binders, vitamin D deficiency, inadequate dietary intake of phosphorus intake, or other tubular disorders. Chronic hypophosphatemia in children results in rickets and poor growth.

RATIONALE

Among the factors that contribute to 2° HPT in CKD patients are phosphate retention and/or elevated levels of serum phosphorus. In adult CKD patients, hyperphosphatemia is associated with increased morbidity and mortality.⁷⁹⁻⁸⁶ Conversely, in adults, hypophosphatemia is associated with increased mortality. In children with CKD, hypophosphatemia leads to rickets and growth retardation. Therefore, the maintenance of normal serum levels of phosphorus in CKD patients is critical for the prevention of abnormalities in PTH metabolism, and for the reduction of morbidity and mortality.

STRENGTH OF EVIDENCE

While available experimental data support a direct role of phosphorus in the regulation of PTH secretion,^{77,78} 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).⁸³ On the other hand, other studies have failed to demonstrate consistent changes in PTH levels across a range of serum phosphorus levels,⁹⁴ and no direct correlation between the level of serum phosphorus and PTH has been established.⁷⁸ Many studies measuring serum PTH levels are confounded by the use of phosphate binders and vitamin D, thus precluding 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, for adults and for children with CKD, elevated phosphorus levels in CKD and dialysis patients contribute to the development of 2° HPT.

In order to eliminate the potentially confounding influence of aluminum-containing phosphate binders on outcomes, only studies of adult 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.^{83,85-87} These studies correlate serum phosphorus levels with multiple end-points in patients treated with hemodialysis.

The four cross-sectional studies^{83,85-87} that met the inclusion criteria evaluated the association of serum phosphorus levels with extraskelletal outcomes. Two studies evaluated the relative risk of mortality associated with serum phosphorus levels in patients treated with hemodialysis. In one study, a reference serum phosphorus range of 4.6-5.5 mg/dL (1.49-1.78 mmol/L) was used⁸⁵; 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 5-7 mg/dL (1.61-2.26 mmol/L) was used⁸⁶; 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.⁹⁴

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.⁸³ One study failed to find an association between serum phosphorus levels and quality of life.⁹⁴

In patients with tubulopathy and hypophosphatemia, phosphate therapy is a critical component of the treatment of the bone disease, as is provision of alkali and vitamin D.

The available evidence supports an association between serum phosphorus levels both above and below the normal range with poor outcomes, including mortality.

LIMITATIONS

In adults with CKD, 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^{85,86} 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.

In children with CKD, there are no prospective studies or retrospective analysis to establish the effect of normalization of serum phosphorus on clinical outcome outside of rachitic bone disease.⁹⁵ Even the successful treatment of rickets generally requires additional pharmacological therapy, making the independent impact of normalization of serum phosphorus uncertain.

CLINICAL APPLICATIONS

This Guideline supports intensive control of serum phosphorus in patients with CKD. Most data indicate that <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 status.

RESEARCH RECOMMENDATIONS

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

GUIDELINE 5. MANAGEMENT OF DIETARY PHOSPHORUS INTAKE IN CHILDREN WITH CKD

- 5.1 Dietary phosphorus should be decreased to the Dietary Reference Intake (DRI) for age (Table 7) when the serum PTH concentration is above the target range for the stage of CKD and serum phosphorus is within the target range for age (Table 6, Guideline 4). (OPINION)**
- 5.2 Dietary phosphorus should be decreased to 80% of the DRI for age (Table 7) when the serum PTH concentration is above the target range for the stage of CKD and serum phosphorus is above the target range for age (Table 6, Guideline 4). (OPINION)**
- 5.3 After initiation of phosphorus restriction, serum phosphorus concentrations should be monitored at least every 3 months in patients with CKD Stages 3-4, and monthly in patients with CKD Stage 5. Serum phosphorus values below the target range for age should be avoided.**

BACKGROUND

In children^{20,74,96} and adult patients⁹⁷⁻¹⁰³ with CKD, serum concentrations of PTH are increased early, i.e., when the GFR is only mildly to moderately reduced, and the values of PTH vary inversely with those of GFR.¹⁰³ When the GFR decreases into CKD Stage 3 and below (<60 mL/min/1.73m²), serum concentrations of PTH are above the normal range in most children and adult patients, and histological evidence of bone disease is observed.^{20,104,105} At this level of GFR, however, serum concentrations of phosphorus are within the normal range or even mildly decreased,^{74,96,98,106,107} and values become clearly increased only when CKD Stage 4-5 is reached. Thus, in CKD Stages 2 and 3, hyperphosphatemia

is rarely present and 2° HPT can be attributed, at least in part, to the reduction in serum concentrations of 1,25(OH)₂D.^{74,96,101-103,108-117}

RATIONALE

Although serum phosphorus levels are not increased in the early stages of progressive CKD, dietary phosphorus is nevertheless an important determinant of the severity of hyperparathyroidism in mild and moderate, as well as severe, renal insufficiency. In both children and adult patients with mild and moderate CKD (Stages 2 and 3) in whom serum concentrations of PTH were increased and those of serum phosphorus normal, dietary phosphorus restriction induced a decrease in serum levels of PTH and an increase in levels of 1,25(OH)₂D, the latter to normal or supernormal values.^{74,100,118} Conversely, in children with Stage 3 CKD, supplementation of dietary phosphorus to intakes approximately twice the DRI for age induced a worsening of hyperparathyroidism and further decrease in serum levels of 1,25(OH)₂D.⁷⁴ Such changes in serum PTH could be attributed, at least in part, to diet-induced changes in serum levels of 1,25(OH)₂D. Phosphorus manipulation in patients with CKD Stage 2 and 3 induced little or no change in morning fasting serum phosphorus concentrations.^{74,100,118}

Thus, in CKD Stages 2 and 3, the severity of hyperparathyroidism can be amplified or reduced by increases or decreases, respectively, in dietary phosphorus intake. Since dietary phosphorus intakes above the DRI can contribute to the severity of hyperparathyroidism, it is the opinion of the Work Group that phosphorus intakes be decreased to the DRI even when serum phosphorus levels are within the target range. In CKD

Table 7. Dietary Reference Intakes of Phosphorus in Children

Age (Years)	Phosphorus DRI (mg/day)
0-0.5	100
0.5-1.0	275
1-3	460
4-8	500
9-18	1,250

Stages 4 and 5, serum phosphorus levels are typically above the target range, and phosphorus restriction to approximately 80% of the DRI is recommended.

The higher serum concentrations of calcium and phosphorus in healthy infants and young children, and their physiological decrease with age, presumably reflect the increased requirements of these minerals by the growing skeleton. This is particularly important in the newborn infant, as infancy is the period of most rapid accretion of bone mineral. Hence, when dietary phosphorus is restricted to control hyperphosphatemia and 2° HPT in children with CKD, serum phosphorus values below the target range should be avoided. Rickets due to phosphorus deficiency occurs in preterm infants fed insufficient amounts of phosphorus, and in infants and children with hypophosphatemia due to inherited disorders of renal phosphate transport.¹¹⁹ Severe restriction of dietary phosphorus in children with moderate and severe renal insufficiency was associated with a decrease in fasting levels of serum phosphorus and histological findings of worsening osteomalacia.¹¹⁸

STRENGTH OF EVIDENCE

Studies in children with CKD Stages 2-3 that examine the relationship between serum phosphorus concentration and 2° HPT suggest that dietary phosphorus restriction can improve 2° HPT and maintain normal serum phosphorus levels. Data in adult patients with CKD support an association between the increase in serum phosphorus concentration and decrease in GFR, and reveal that hyperphosphatemia is observed when the creatinine clearance decreases to CKD Stages 4-5.¹²⁰

The effectiveness of dietary phosphate restriction in controlling the hyperphosphatemia of CKD in children and adults was analyzed in 19 studies examining 2,476 patients. Fifteen randomized controlled trials¹²¹⁻¹³⁵ and four nonrandomized controlled trials¹³⁶⁻¹³⁹ met the inclusion criteria. 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^{94,140-147} and vitamin D supplements were used,^{80,83,85,86,94,140-148} 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 endpoints were utilized:

Quality of life. One study reported that low protein diet did not adversely affect employment,¹³⁸ 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.¹⁴⁹

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.^{121,124,125,129-131,133,136,139} 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,^{123,125,134,137} PTH levels,^{125,134,136,138} serum calcium levels,^{123,125,134,136,137} serum phosphorus levels,^{123,132,134,136,137,150} and urinary phosphate excretion.^{127,129,132} In contrast, in a careful and well-controlled study of four 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)₂D₃ and intestinal absorption of calcium.¹⁰⁰ 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.¹⁰⁰

In children, the initiation of moderate dietary phosphate restriction needs to be accompanied by close monitoring of linear bone growth. In four studies in children, there was no evidence for adverse effects as a result of dietary phosphate restriction.^{124,128,151,152} In addition, studies in adults did not support any adverse effect on

nutritional status as a result of dietary phosphate restriction.^{123-125,127,129,131,133,134,137,139,153,154}

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%-91% with low-protein diets.^{124,132,149,155} One study reported 41% and 77% compliance at years 1 and 3, respectively.¹⁵⁶ 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 pediatric (and adult) Work Group that modification of dietary phosphate intake be initiated in patients with CKD when PTH levels are elevated.

LIMITATIONS

Despite the relatively large number of prospective randomized trials evaluating dietary phosphorus restriction, most of these studies specifically utilized protein-restricted diets and therefore restricted phosphate intake indirectly. While protein and phosphorus are closely related in foods, it is possible to restrict protein without fully restricting phosphorus. Much of the data are 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 sta-

tus 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 renal 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 CKD, compliance with dietary phosphate restriction is difficult and requires intensive dietitian support. In CKD patients treated with dialysis (Stage 5), care must be taken to reduce phosphate intake while maintaining adequate protein intake as recommended by the K/DOQI Guidelines on Nutrition.¹⁵⁷ 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 by 10-12 mg phosphate per gram of protein, a reasonable phosphate level can be estimated. The average amount of phosphorus per gram of protein ranges from 12-16 mg. In order to limit phosphorus significantly, those protein sources with the least amount of phosphorus must be prescribed (see Table 12, Guideline 7).

RECOMMENDATIONS FOR RESEARCH

There is a need for large, multicenter 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.

GUIDELINE 6. USE OF PHOSPHATE BINDERS IN CKD

In Patients with CKD Stages 2-4:

- 6.1 If serum phosphorus levels cannot be controlled within the target range (see Guideline 4), despite dietary phosphorus restriction (see Guideline 5), phosphate binders should be prescribed. (OPINION)
- 6.2 Calcium-based phosphate binders are effective in lowering serum phosphorus levels (EVIDENCE) and should be used as the initial binder therapy. (OPINION)

In Patients with CKD Stage 5 (Dialysis):

- 6.3 Both calcium-based phosphate binders and the non-calcium, non-metal-containing phosphate binders, such as sevelamer HCL, are effective in lowering serum phosphorus levels. (EVIDENCE) As of this writing, calcium-based phosphate binders should be used as primary therapy in infants and young children. In older children and adolescents, either drug may be used. (OPINION)
- 6.4 In dialysis patients who remain hyperphosphatemic (above the upper target value) despite the use of either calcium-based phosphate binders or other noncalcium, non-metal-containing phosphate binders, the dialysis prescription should be modified to control hyperphosphatemia. (OPINION)
- 6.5 The total dose of elemental calcium provided by the calcium-based phosphate binders and dietary calcium should not exceed up to 2X DRI for calcium, based on age (OPINION), and the total intake of elemental calcium (including dietary calcium) should not exceed 2,500 mg/day. (OPINION)
- 6.6 The dosage of calcium-based phosphate binders should be lowered in dialysis patients with corrected serum calcium of >10.2 mg/dL (2.54 mmol/L), or with serum PTH levels <150 pg/mL (150 ng/L) on two consecutive measurements. (EVIDENCE)
- 6.7 In adolescent 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 (up to 4-6 weeks), and for one course only, to be

replaced thereafter by other phosphate binders. (EVIDENCE)

- 6.8 In children receiving aluminum-based phosphate binders, concurrent use of citrate-based products should be avoided, due to the risk of increasing aluminum absorption and potential toxicity. (EVIDENCE)

BACKGROUND

When dietary phosphate restriction is inadequate to control serum levels of phosphorus and/or PTH, phosphate binders should be administered. Different phosphate binder compounds have been utilized to control serum phosphorus levels, but the search still continues for the best possible binder. 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 levels. Table 8 describes the steps to calculate the initial prescription of phosphate binders, and Table 9 describes the characteristics of various phosphate-binding agents.

In children, calcium-based phosphate binders have been shown to be safe and effective.¹⁵⁸⁻¹⁶² Recently, pediatric experience with sevelamer HCl is accumulating, and it appears to be safe and effective as well.^{163a} Long-term use of aluminum-containing phosphate binders has been associated with severe complications of bone disease and encephalopathy.¹⁶⁴⁻¹⁶⁶ Thus, only a short-term course (4-6 weeks) of aluminum can be recommended for control of hyperphosphatemia. Data demonstrate that concurrent administration of citrate containing compounds dramatically increases enteral absorption of aluminum and must be avoided if aluminum-containing phosphate binders are used.^{167,168}

RATIONALE

The goal of phosphate-binder therapy is to maintain serum phosphorus levels within the range as outlined in Guideline 4 without adversely affecting nutritional status or causing serious side-effects. It is recommended to initiate phosphate binder therapy when: (a) serum phosphorus levels remain elevated, despite restriction

Table 8. 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) ¹⁶⁹	Dietary P intake multiplied by average 50%-60% absorbed	600 per day or 4,200/week
Average HD/PD clearance HD = 800 per treatment PD = 300-315 per treatment	Amount abs – dialysis clearance = remaining P to be bound by phosphate binder	HD: 4,200 – 2,400 = 1,800 mg P/wk or 257 mg/d PD: 4,200 – 2,205 = 1,995 mg P/wk or 285 mg/d
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 ₃ ¹⁷⁰ 257/45 (approx. P bound by 1 g calcium acetate) = 5.7 gm ¹⁷¹ 257/15-30 (approx. P bound by one Al(OH) ₃ tablet) = 12-17 tabs ¹⁷² 257/64 (approx. binding power of 800 mg sevelamer HCl) = 4 caplets 257/32 (approx. binding power per 400 mg sevelamer HCl) = 8 caplets

Note: 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.

Table 9. 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, Calci Chew, Caltrate, Calci-Mix, Titalac, Chooz Gum	Approximately 20%-30% is absorbed ¹⁷³	Approximately 1 mg P bound per 8 mg Ca abs (Adapted from ¹⁷³)	Approximately 39 mg P bound per 1 g Calcium Carbonate	Inexpensive, wide variety of products/availability	Hypercalcemia, extraskelatal calcification, GI side-effects, constipation	Serum parameters within target ranges to minimize risk for extraskelatal calcification
Calcium Acetate	PhosLo	With meals: 21 ±1% Between meals: 40 ±4% ¹⁷⁰	Approximately 1.04 mg P bound per mg Ca abs ¹⁷⁴ 1 mg P bound per 2.9 mg Ca abs (Adapted from ¹⁷³)	Approximately 45 mg P bound per 1 g Calcium Acetate	Less calcium absorption than CaCO ₃ ; P binding similar to Al(OH) ₃ ¹⁷⁴	Hypercalcemia, extraskelatal calcification, GI side-effects	Same as above
Calcium Citrate	Citracal	22% ¹⁷⁴	NA	NA	NA	Increases aluminum absorption	Not recommended
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
Magnesium Carbonate/ CaCO ₃	MagneBind 200/300	Has 450/300 mg calcium acetate	Approximately 1 mg P bound per 2.3 mg Ca absorbed	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 ¹⁷²	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 ¹⁷⁵	Noncalcium, nonaluminum	GI side-effects, cost	Eliminates binder-related calcium load; especially appropriate for patients with hypercalcemia or extraskelatal calcification

of dietary phosphate restriction; or (b) the restriction of phosphate intake hinders the intake of other critical nutrients.

The majority of research in the recent decade has focused on calcium-based binders, which have been shown to be safe and effective in children with CKD. Recently, other non-calcium, non-metal containing, binder forms are available, but are incompletely studied in children. With recent concern that soft-tissue calcification may be worsened by calcium-based phosphate binders and vitamin D analogs, noncalcium, nonaluminum binders are being used more frequently in adults with CKD. As further data on efficacy and safety in children accumulate, it is expected that the frequency of use will increase for children with CKD.

An increase in the frequency of dialysis can enhance phosphorus clearance in hemodialysis patients.¹⁷⁶ Among patients treated with thrice-weekly nocturnal hemodialysis, serum levels of phosphorus were reduced despite increased dietary intake and reduced use of binders.¹⁷⁷ Some patients treated with nocturnal dialysis six times per week have required phosphate supplements in the dialysate to correct hypophosphatemia.¹⁷⁸ Where the escalation of phosphate-binder dose is either incapable of controlling serum phosphorus levels or is not tolerated, modification of the dialysis prescription in both hemodialysis and peritoneal dialysis patients should be strongly considered to improve phosphate clearance. During the use of aluminum-based phosphate binders, patients should be monitored to avoid additional morbidity described with their prolonged use^{179,180} (see Guidelines 12 and 13).

STRENGTH OF EVIDENCE

Studies of the efficacy and safety of phosphate binders in children with CKD Stages 3-4 are limited to uncontrolled case series.^{160,161,181} Three studies reported effective control of phosphorus with calcium carbonate^{160,161,181}; the largest series reported treatment in 45 children with a follow-up period of 6-54 months.¹⁶⁰ All subjects were on a phosphate-restricted diet and 42 were also treated with vitamin D sterols; transient hypercalcemia occurred in 11 patients. The two smaller series^{161,181} also

reported transient hypercalcemia that responded to adjustments in vitamin D and binder doses. The required doses of calcium carbonate ranged widely, from 64-1,578 mg/kg/day in one study,¹⁶¹ to 21-228 mg/kg/day in another.¹⁶⁰ One study provided data on the absolute dose of elemental calcium required to control PTH: 240-6,000 mg elemental calcium per day.¹⁶¹

Additional case series have been published in children with CKD Stage 5.^{159,162} One of these suggested that episodes of hypercalcemia were more common in children with a history of prior aluminum therapy.¹⁵⁹ Another study reported a comparison of calcium acetate with calcium carbonate in nine hemodialysis patients.¹⁵⁸ Calcium carbonate was administered for 7 weeks, followed by withdrawal of therapy; then calcium acetate was administered for an additional 7 weeks. Both agents lowered the serum phosphorus concentration significantly. Although significantly less elementary calcium was ingested with calcium acetate (mean 750 [range 375-1,500] mg calcium/day) than with calcium carbonate (mean 1,200 [range 0-3,000] mg calcium/day), the number of episodes of hyperphosphatemia or hypercalcemia did not differ between treatments.

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 in association with hyperphosphatemia, it is the opinion of the Work Group that the use of phosphate binders may become necessary if the serum levels of PTH cannot be lowered to the target levels (see Table 3, Guideline 1) by dietary phosphate restriction and/or vitamin D therapy.

In CKD Stage 5, there were 16 prospective, controlled studies in adults 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. A meta-

analysis of these studies was performed to compare the efficacy of the phosphate binders on outcomes, including: serum levels of phosphorus, PTH, and calcium; bone biochemical markers; and extraskeletal calcification.^{173,182,183} No studies evaluated the effect of phosphate binders on patient quality of life, mortality rate, incidence of bone disease or fractures. Recently, the use of both calcium based binders and non-calcium, non-metal containing P binders, such as sevelamer HCL, have been shown to be effective phosphate binders in children on peritoneal dialysis and bone biopsy proven secondary hyperparathyroidism.^{163a} Furthermore, the skeletal lesions of high-turnover bone disease markedly improved with both binders and active vitamin D sterols. However, therapy with sevelamer HCL allows the use of higher doses of active vitamin D without increments in serum calcium levels.^{163a}

Effect on Phosphorus

In all studies, serum phosphorus was lowered by the phosphate binder studied. In assessing the relative efficacy of the various phosphate binders in controlling serum phosphorus levels, 15 studies were evaluated: nine studies examined calcium carbonate and six 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.^{182,184-188} It showed that calcium acetate

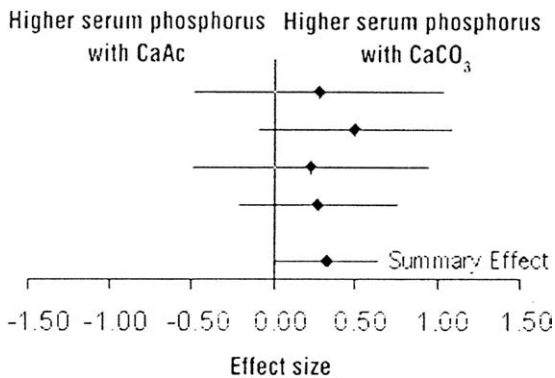


Fig 5. Meta-Analysis of Size of Effect on Serum Phosphorus Levels of Calcium Acetate versus Calcium Carbonate

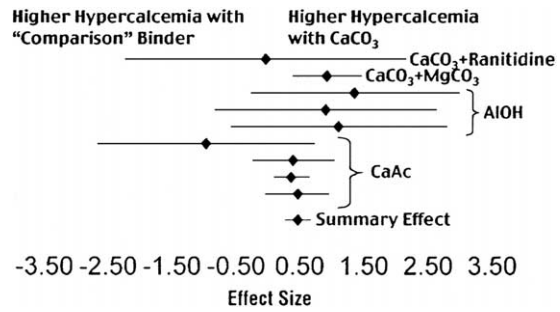


Fig 6. Meta-Analysis of Size of Hypercalcemic Effect of Calcium Carbonate versus Other Phosphate Binders

decreased serum phosphorus 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 four studies that directly compared calcium carbonate to calcium acetate¹⁸⁵⁻¹⁸⁸ found that post-treatment serum phosphorus levels were significantly higher following treatment with calcium carbonate compared to calcium acetate (Figure 5). 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 acetate¹⁷³ and sevelamer,¹⁸⁹ and both showed that efficacy of these binders was superior compared to placebo.

A single study evaluated magnesium as a phosphate binder: it was a crossover study that evaluated patients on calcium carbonate compared to a combination of calcium carbonate and magnesium carbonate.¹⁹⁰ 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 CaXP

Ten studies evaluated the effect of different phosphate binders on corrected serum calcium levels, ionized calcium, total calcium, or CaXP.^{173,185-189,191-194} Five of these studies compared different binders to calcium carbonate,^{173,186,187,190,193} 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 CaXP in the calcium acetate-treated group compared to placebo.¹⁷³ 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 (Figure 6).^{183,185-188,190,192-195} Six studies assessed calcium-phosphorus product, one placebo-controlled and the others comparing different phosphate binders. Differences were observed in only two of these studies. Calcium acetate led to a lower calcium-phosphorus product than placebo,¹⁷³ and calcium carbonate led to a greater product than calcium ketoglutarate.¹⁹⁴ This latter study found that ionized calcium levels were higher in patients treated with calcium carbonate compared to calcium ketoglutarate.¹⁹⁴ 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 patient's tolerance of the binder.

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.^{186,188,190,192,194,195}

Six studies evaluated the effect of phosphate binders on nutritional outcomes,^{182,184,189-191,194} but different outcome measures were utilized, precluding comparative analyses. Two studies found that sevelamer HCl led to lower serum cholesterol levels compared to placebo or cal-

cium acetate, primarily due to a decrease in LDL cholesterol levels.^{184,190} In addition, sevelamer HCl allows the use of higher doses of active vitamin D without inducing changes in serum calcium levels.^{163a}

Patient compliance with prescribed binder therapy was not reported consistently, but ranged from 30%-100%.^{149,156,196-202} 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 10-15 minutes before, or during, the meal.

In a study comparing calcium carbonate and aluminum hydroxide, bone mineral content was lower in aluminum hydroxide-treated patients. Minor, and inconsistent, differences were found. Because of the potential for neurotoxicity and osteomalacia associated with aluminum-containing phosphate binders,^{179,180,203} the use of these compounds should be reserved for patients with serum phosphorus >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 >6.5-7.0 mg/dL (2.10-2.26 mmol/L). Thus, the two 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 during treatment with aluminum-based compounds, since citrate increases the absorption of aluminum from the intestine²⁰³ and may precipitate acute aluminum toxicity.

In summary, the available evidence supports the hypothesis that all of the current phosphate binders are effective in controlling serum phosphorus levels. The majority of studies evaluated

calcium-containing phosphate binders. However, recent studies on the use of the non-metal-containing phosphate binder sevelamer HCl suggest that it was effective,^{184,189,204-206} and the Work Group felt that this agent has an important emerging role in the control of serum phosphorus in dialysis patients. Sevelamer HCl has been shown to be an effective binder in children on dialysis.^{163,163a}

In CKD Stage 5, the current evidence and the opinion of the pediatric Work Group support the recommendation that the choice of calcium-based 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 CaXP, and limiting the total calcium intake. Additionally, the pediatric Work Group also recommends reducing the dosage of calcium-based phosphate binder in dialysis patients with low PTH levels. 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,²⁰⁷ 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 such patients, one should consider the use of sevelamer HCl to control serum levels of phosphorus while avoiding excessive calcium intake.

LIMITATIONS

The available data do not quantify an exact amount of calcium that can be given safely as a calcium-based phosphate binder. This is an important issue as recent studies suggest that excessive calcium intake may worsen vascular and other extraskeletal calcification.^{80,84,208} Additional data that either did not fully meet the inclusion criteria, or that became available after the evidence report was completed, support the consensus of the Work Group about limitation of calcium intake from phosphate binders. 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 (EBCT) scan in children, adolescents, and young adults,

the CaXP, prescribed calcium intake from phosphate binders, and duration of CKD were much higher in the young adult 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 group with no calcification.⁸⁰ 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.⁸⁴ There was a progressive increase from 1.35 ± 1.10 g/day of elemental calcium in patients with no calcification by ultrasound, to 1.50 ± 0.81 g/day in those with a calcification score of 2, and 2.18 ± 0.93 in those with a calcification score of 4 ($P = 0.001$ by ANOVA).⁸⁴ 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, CaXP, cholesterol and LDL levels, and aortic and coronary artery calcification evaluated by EBCT. 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 ide-

ally should be equal to the recommended daily adequate intake (AI) for adults (1,000-1,500 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 500-1,000 mg elemental calcium from calcium-containing phosphate binders. However, the pediatric Work Group recognizes the overwhelming importance of controlling serum phosphorus levels, and recognizes the difficulty of doing so with calcium-containing phosphate binders while adhering to this limited daily calcium intake. Based on this and the above data, the pediatric Work Group recommends that the amount of calcium provided by calcium-based phosphate binders and diet should not exceed 2X the age-specific DRI (maximum to not exceed 2.5 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 whom the total elemental calcium intake, (including dietary sources)

exceeds the upper limit recommended, the pediatric Work Group recommends consideration of adding a non-calcium, non-metal-containing phosphate binder to decrease the total calcium intake.

CLINICAL APPLICATIONS

The best phosphate binders are those that the patient will take consistently and as prescribed while limiting total calcium intake. 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 are needed to evaluate phosphate binders and their efficacy, side-effects, and impact on morbidity and mortality. A recently completed study in adults demonstrated an advantage of sevelamer HCl compared to calcium-based phosphate binders in preventing progression of aortic and coronary arteries calcification. Further studies in both adults and children evaluating cardiovascular morbidity and mortality in dialysis patients are needed.

GUIDELINE 7. SERUM CALCIUM AND CALCIUM-PHOSPHORUS PRODUCT

In CKD Patients Stages 2-4:

- 7.1 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):

- 7.2 Serum levels of corrected total calcium should be maintained within the normal range for the laboratory used (8.8-9.7 mg/dL [2.20-2.37 mmol/L]), and preferably toward the lower end. (OPINION)
- 7.3 In the event that the corrected total serum calcium level exceeds 10.2 mg/dL (2.54 mmol/L), therapies that increase serum calcium should be adjusted as follows:
- 7.3.a In patients taking calcium-based phosphate binders, the therapy should be discontinued and the use of non-calcium, non-metal based phosphate binders should be considered. (OPINION) See Guideline 6.
- 7.3.b In patients taking active vitamin D sterols, the therapy should be discontinued until the serum levels of corrected total calcium return to the target range (8.8-9.5 mg/dL [2.20-2.37 mmol/L]). (OPINION) See Guideline 8B.
- 7.3.c If hypercalcemia (serum levels of corrected total calcium >10.2 mg/dL [2.54 mmol/L]) persists despite discontinuation of therapy with vitamin D and/or modification of calcium-based phosphate binders, dialysis using lower dialysate calcium may be used for 3-4 weeks. (OPINION) See Guideline 10.

In CKD Patients Stages 3-5:

- 7.4 The total dose of elemental calcium provided by the calcium-based phosphate binders should not exceed up to 2X DRI for calcium based on age, (OPINION) and the total intake of elemental calcium (including dietary calcium) should not exceed 2,500 mg/day. (OPINION)
- 7.5 The serum CaXP should be maintained at <55 mg²/dL² in adolescents >12 years,

and <65 mg²/dL² in younger children. (OPINION) This is best achieved by controlling serum levels of phosphorus within the target range. (OPINION) See Guidelines 4-6.

- 7.6 Patients whose serum levels of corrected total calcium are below the lower limit (<8.8 mg/dL [2.20 mmol/L]) should receive therapy to increase serum calcium levels:

7.6.a Therapy for hypocalcemia should include calcium salts such as calcium carbonate or calcium acetate orally, or calcium gluconate or calcium chloride parenterally (EVIDENCE), and/or oral vitamin D sterols. (EVIDENCE) See Guideline 9.

BACKGROUND

Maintenance of normal calcium balance and serum calcium levels depends on integrated regulation of calcium absorption and secretion by the intestinal tract, the excretion of calcium by the kidney, and calcium release from and deposition into bone. Parathyroid hormone increases serum calcium levels by stimulating bone resorption and kidney distal tubular calcium reabsorption in the kidney, and activating renal hydroxylation of 25(OH)D₃ to 1,25(OH)₂D₃. 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 the parathyroid gland within seconds. Subsequently, PTH biosynthesis by the parathyroid gland increases over 24-48 hours and, if hypocalcemia persists, 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.

During childhood and adolescence, total skeletal calcium increases from approximately 25 g at birth to 900 g and 1,200 g in adult females and males, respectively. Of the total body calcium, 99% is in the skeleton, 0.6% in soft tissues, and 0.1% in extracellular fluid.²⁰⁹ Normal values for serum total calcium concentration according to

age are summarized in Table 6, Guideline 4. In adults, variations in serum levels of calcium depending on age and gender have been observed.²¹⁰

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 4.65-5.28 mg/dL (1.16-1.32 mmol/L).^{211,212} Ionized calcium should be assessed if subtle changes are expected or total calcium measurements are not adequate. Generally, measurement of ionized calcium is more expensive than total calcium measurement. For this reason, and because ionized 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 ionized calcium if serum levels of protein are normal.

If serum 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 ionized calcium both in healthy subjects and patients with CKD, but all of them are encumbered with limitations. 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 the binding of calcium to albumin.²¹⁰

There are no biochemical measurements that reflect calcium nutritional status in subjects

with normal kidney function and in patients with kidney disease. The major indirect measures of calcium nutritional 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) Committee²¹³ 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%-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 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 10.

The total daily intake of elemental calcium in CKD patients should not exceed 2,500 mg per day, including both dietary sources and calcium from phosphate binders. Table 11 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

Table 10. Recommendations for Calcium Intake

Age Range (Years)	Adequate Intake (mg/day)	Tolerable Upper Level (g/day)
0 to 0.5	210	ND
0.5 to 1.0	270	ND
1 to 3	500	2.5
4 to 8	800	2.5
9 to 13	1,300	2.5
14 to 18	1,300	2.5
19 to 50	1,000	2.5
50 to >70	1,200	2.5

Abbreviation: ND, not determined
Reproduced with permission.²¹³

Table 11. Calcium Content of Common Calcium-Based Binders

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

Source: Manufacturers' Information, Internet.

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 positive throughout childhood and adolescence. Calcium accrual is maximal during adolescence (+200 mg to +300 mg/day).²¹³ Additionally, in CKD patients, the fraction of intestinal calcium absorption in the duodenum and jejunum is reduced¹⁴¹ because this process is vitamin D-dependent,²¹⁴ and CKD patients have reduced blood levels of 1,25(OH)₂D.²¹⁵ However, passive intestinal calcium absorption, which is gradient-dependent, can be augmented by increasing calcium intake.²¹⁴

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.^{216,217}

Hypercalcemia, together with hyperphosphatemia, or individually, can be responsible for

increased blood CaXP. Since serum phosphorus levels in patients with CKD are usually increased by a higher factor compared to calcium, the relative importance of serum phosphorus levels in generating higher CaXP (expressed in mg²/dL²) is greater than the serum calcium levels. Still, the serum calcium levels could be critical²¹⁸ if the serum phosphorus levels are very high, which is indeed the case in patients with Stage 5 CKD.

In the presence of high CaXP in blood, soft-tissue calcification is likely but not always associated with high CaXP, since many factors are involved in the genesis of soft-tissue calcification (see Table 6, Guideline 4).

Adequate dietary calcium intake during childhood is necessary for the development of optimal peak bone mass.²¹⁹ Infants on breast milk or standard formulas should meet the DRI with the consumption of adequate volumes of breast milk/formula. For younger children (2-8 years of age), reaching the recommended levels of adequate intake of calcium is more feasible than in the 9- to 18-year-old range due to their greater acceptance of high-calcium foods in the diet. The largest source of dietary calcium for most persons is milk and other dairy products.²²⁰ Mean intakes in the 9- to 18-year-old age group are between 700-1,000 mg/day, with values at the higher end of this range occurring in males.²¹⁹

An intake of 100% of the DRI for calcium is a reasonable starting point for children with CKD Stages 1-4. The challenge is to ensure that it is achieved. Infants with CKD may not get adequate amounts of calcium if breast milk is contraindicated, if low-electrolyte infant formulas are required, or if fluids are restricted. In these situations, calcium supplementation may be required. Since many high-phosphorus foods are also high in calcium, restricting dietary phosphorus will inadvertently restrict dietary calcium as well. Therefore, it is beneficial to avoid over-restriction of phosphorus or the premature initiation of a phosphorus-restricted diet in the early stages of CKD, in order to maximize dietary calcium intake.

If the patient's serum phosphorus and dietary phosphorus intake is elevated, the necessary dietary calcium intake can be accomplished with the incorporation of low-phosphorus, high-calcium foods²²⁰ (Table 12), calcium-fortified foods, and supplementation with oral calcium²²¹⁻²²³ (Table 13). However, one should note that the food items in Table 12 characteristically do not make up a substantial part of a child's diet and may, in fact, be contraindicated as kidney function worsens and dietary potassium restriction becomes necessary.

The bioavailability of calcium from vegetables is generally high. An exception is spinach, which is high in oxalate, making the accompanying calcium virtually unavailable. Some high-phytate foods, such as bran cereal, also may have poor bioavailability of calcium.²²⁴⁻²²⁶

Several products have been introduced that are fortified with calcium.²²⁰ These products range from juices to breakfast foods, and it is probable that additional products will soon become available. Limited studies of the bioavailability of calcium when added to these products suggest that it is at least comparable to that of milk.²²² Calcium-fortified products may be considered a practical approach to increasing the calcium intake in children/adolescents with CKD.

As noted above, supplementation should be considered if the dietary intake alone does not meet or exceed the DRI, which is often the case with progression of the kidney function through Stages 2-4. Calcium supplementation, whether a combination of calcium and gluconate (9% elemental calcium), lactate (13% elemental calcium), acetate (25% elemental calcium), or carbonate (40% elemental calcium), is well tolerated and is not toxic if used at dosages that do not exceed the DRI. Calcium carbonate—in particular—is inexpensive, tasteless, and relatively well tolerated by children of all ages with impaired kidney function.

In contrast, calcium chloride should be avoided as a supplement in uremic patients due to the possible development of metabolic acidosis. Calcium citrate should not be given to patients receiving aluminum salts since citrate augments aluminum absorption, increases the body burden of aluminum, and increases the risk of aluminum toxicity.²⁰³

When calcium salts are prescribed for the purpose of binding phosphorus in the intestine, they are more effective if given with meals. On

Table 12. Low-Phosphorus, High-Calcium Foods

Food	Portion	Calcium* (mg)	Phosphorus (mg)
Collards, frozen, cooked	½ cup	179	23
Dandelion greens, cooked	½ cup	74	22
Kale, frozen, boiled	½ cup	90	18
Molasses, blackstrap	1 Tablespoon	172	4
Mustard greens, cooked	½ cup	52	28
Rhubarb	½ cup	174	10
Spinach, boiled	½ cup	122	50
Turnip greens, boiled	½ cup	99	21
Vitamite 100 (nondairy beverage)	½ cup	150	75

* Calcium values listed are milligrams of elemental calcium.

Source: 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>

Table 13. Partial List of Calcium-Containing Supplements

Product	Dose	Elemental Calcium (mg)
Calcium Carbonate		
Caltrate	1 tab	600
Oscal 500	1 tab	500
Tums	1 chewable	200
Tums E-X	1 chewable	300
Tums Ultra	1 chewable	400
Titralac Tabs	1 tab	168
Titralac Extra Strength	1 tab	300
Children's Mylanta	5 cc	160
Children's Mylanta	1 tab	160
Ex. Str. Mylanta Calcium	1 tab	300
Ultra Mylanta Calcium	1 tab	400
Calcium Citrate		
Citrical	1 tab	200
Calcium Acetate		
Phos-Lo	1 tab/1 gelcap	169

Source: Physician's Desk Reference, Medical Economics Co, 112, 2002.

the other hand, to ensure the optimal absorption of calcium when it is used as a supplement, it should be taken between meals.^{107,141,223}

It is noteworthy that the dietary calcium intake of children and adolescents on dialysis who consume a phosphorus-restricted diet generally has a serious calcium deficit; typically, the estimated dietary calcium intake is <500 mg per day. Calcium-containing phosphate binders become the primary source of elemental calcium in the diet. At the same time, limiting the calcium intake from binders and dialysate solutions may be necessary in order to prevent soft-tissue calcifications as a potential consequence of long-term positive calcium balance. One must note, however, that it is impossible to accurately assess the actual absorption of calcium derived from binders, which is in large part dependent upon the kind and amount of food present in the stomach with the binder.

RATIONALE

It is important that patients with CKD have normal serum levels of corrected total calcium, since chronic lower levels of calcium cause 2° HPT, 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. 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 ionized calcium.²¹⁰ The Evidence Report of these Guidelines cites two major studies that evaluated various formulas for correction of total calcium for albumin in 82 hemodialysis and 34 continuous ambulatory peritoneal dialysis (CAPD) patients.^{227,228} One of these studies used preferable statistical methods and also employed strict control of blood drawing and handling.²²⁷ 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:

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

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 for adjusting total serum calcium concentration for changes in serum albumin concentration can be used by clinicians.²¹⁰ This formula yields similar results to that described above:

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

Patients with GFR <60 mL/min/1.73 m² (Stage 3 CKD) usually, but not invariably, show a detectable decrease in the blood levels of total and ionized calcium.^{229,230} The serum calcium levels decrease further as kidney function deteriorates. In advanced stages of CKD, the fraction of total calcium bound to complexes is increased²³¹; 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 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 of adults published in the early 1970s suggest that hypocalcemia may have detrimental consequences for patients with CKD.^{142,146,147,232-234} In one cohort study, 433 patients beginning dialysis therapy were followed prospectively for an average of 41 months.²³⁵ In 281 of the patients, the level of total calcium was <8.8 mg/dL. After adjusting for comorbid conditions, serum 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, mineralization surface, and osteoid surface.¹⁴⁷ A statistically significant relationship between the serum calcium level and the percentage of metacarpal cortical/total bone area was found by X-ray.¹⁴⁶ 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 subjects with normal kidney function.¹⁴² Serum levels of total alkaline phosphatase activity, used as a marker of the severity of 2° HPT in patients with CKD, did not correlate with the serum levels of calcium.^{142,146,147,232-234} Despite a moderate significant inverse correlation between serum calcium levels and serum PTH levels,^{232,233} it was not possible to calculate the relative risk for development of 2° HPT for particular levels of serum calcium. Some of the more recent studies²³⁶ 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 for this Guideline indicate that hypocalcemia is a risk factor for bone disease and for development of 2° HPT 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 one study, there was no evidence that isolated hypercalcemia is associated with increased morbidity in the hemodialysis population.⁸⁵ Hypercalcemia poses a risk for CKD patients as it increases the CaXP in blood. Severe hypercalcemia with clinical symptoms must be treated appropriately.

Net calcium absorption is reduced in CRF 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.^{107,141,237-239} Initiation of dialysis does not improve calcium absorption.^{107,238,239} It is common to observe

significant variability in intestinal calcium absorption within a group of patients with the same degree of kidney dysfunction,^{107,141,237-239} 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 300-700 mg/day^{107,240}; in those treated with hemodialysis, calcium intake averaged 549 mg/day²⁴¹; and it was 80% of the recommended daily allowance in children with GFR between 20-75 mL/min/1.73 m².²⁴² When dietary calcium intake was <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.²⁴³

There are no data on calcium retention as a function of increased long-term calcium intake in patients with CKD. In data calculated for healthy adolescents, young adults, and adult men, calcium retention reached a plateau despite an increase in calcium intake from 1,000-2,500 mg/day.²¹⁴ 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 2X age-specific DRI (maximum 2,500 mg/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 14). These data show that the requirement of daily calcium intake in Stage 3 CKD is 1.5X to 2X age-specific DRI (maximum 2,500 mg/day) and in Stages 4 and 5 CKD (patients not on dialysis), it is 1.5-1.8 g/day. The Work Group's recommendation of total daily calcium intake of 2X age-specific DRI (maximum 2,500 mg/day) is in agreement with these data.

Furthermore, in dialysis patients, calcium supplementation of 3.0 g/day in addition to the 400-500 mg in dietary calcium resulted in hypercalcemia in up to 36% of patients.²⁴⁴ Other studies show lower, but still significant, incidences of hypercalcemia during high calcium intake.^{171,245} This clearly suggests that there is a tolerable upper intake level for patients with CKD and, therefore, higher daily calcium intake (>2X age-specific DRI [maximum 2500 mg/day]) should be avoided.

The effectiveness of different calcium salts used for calcium supplementation was partially addressed by four studies.^{21,205,246,247} Only one of these studies²⁴⁷ directly compared the efficacy of two 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 three studies compared the use of calcium carbonate to placebo or no calcium supplement. Because of the different study conditions and

Table 14. Determining Calcium Requirements in Adults Aged 19-30 Years

Factor	Creatinine Clearance 20-40mL/min/1.73 m ²		Creatinine Clearance <20 mL/min/1.73 m ²	
	Female (mg/day)	Male (mg/day)	Female (mg/day)	Male (mg/day)
Peak calcium accretion	10	50 ^a	10	50 ^a
Urinary losses	89 ^b	89 ^b	59 ^b	59 ^b
Endogenous fecal calcium	132	156 ^a	132	156 ^a
Sweat losses	63	63 ^a	63	63 ^a
Total calcium	294	358	264	328
Absorption, percent	18 ^c	18 ^c	18 ^c	18 ^c
As adjusted for absorption	1,547	1,988	1,466	1,822

^a Institute of Medicine. Dietary references intakes: calcium, phosphorus, magnesium, vitamin D3, and fluoride. Washington, D. C.: National Academy Press.

^b Friis T, Hahnemann S, Weeke E. Serum calcium and serum phosphorus in uraemia during administration of sodium phytate and aluminium hydroxide. Acta Med Scand. 183:497-505, 1968.

^c Coburn JW, Koppel MH, Brickman AS, Massry SG. Study of intestinal absorption of calcium in patients with renal failure. Kidney Int. 3:264-72, 1973.

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 four 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 one 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.

In adults, an association was observed between CaXP and the risk of death in a random sample of the U.S. population of 2,669 patients treated for at least 1 year with hemodialysis from 1990-1993.⁸⁵ Patients with CaXP >72 (20% of all patients) had a 34% higher relative risk of death compared to patients with CaXP in the range of 42-52.⁸⁵ The increased risk was observed in proportion to the elevation of CaXP; indeed, for every increase of 10 in CaXP, there was an 11% increase in relative risk of death.

The Evidence Report cites four studies that address the issue of CaXP 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 CaXP (above 60) had increased aortic calcification index (ACI = 26.1) as compared to 20 patients of the same age with well-controlled CaXP <60 (ACI = 17.7).⁷⁹ Another prospective, controlled study using step-wise discrimination analysis showed significantly higher risk for mitral annular calcification in hemodialysis patients with CaXP of 63 ± 13 compared to those with CaXP of 56 ± 13 .²⁴⁸ An additional study showed that, in young adults on

hemodialysis who had CaXP of 65 ± 10.6 , coronary artery calcification was significantly higher than in those with CaXP of 56 ± 12.7 .⁸⁰ One retrospective, controlled study in CAPD patients showed no significant differences in CaXP in 17 patients with mitral annular calcification as compared to 118 patients without this abnormality.²⁴⁹ 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 CaXP can pose a risk of vascular calcification.

The level of CaXP 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, CaXP levels 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 CaXP increases; however, evidence on this relationship is scant and is presented below.

Studies in adults and children^{80,93,248-253} examined the calcium phosphorus product as a risk for extraskeletal calcification. None examined risk for future calcification. All were cross-sectional studies. Four were retrospective^{249,251-253} and four prospective.^{80,93,248,250} They used different methods (radiography, scintigraphy, CT, echocardiography) for detection of calcification and examined different organs for calcification (e.g., soft tissue, mitral and aortic valve, aorta, lung). Two studies^{249,252} provided enough information to calculate risk ratios for CaXP for inducing soft-tissue calcification. One study²⁴⁹ included 135 Stage 5 CKD predialysis patients and 76 patients on CAPD, and the other²⁵² reported on 47 patients for more than 2 years on CAPD. This limited information suggests that CaXP may be a useful indicator of calcification in patients with Stage 5 CKD, as no trend for risk was seen.²⁴⁹ Data on patients treated with CAPD for 2 years showed that the risk for mitral calcification increased as CaXP increased.²⁵² In contrast, in patients treated with CAPD for 1 year, there was no relationship between the risk for calcification and the levels of CaXP.²⁴⁹ The confidence intervals in this small study are very wide, and thus firm conclusions cannot be reached. Neither of

these studies examined whether CaXP can be used as a predictor of future calcification.

Two case-controlled studies indicated that there were significant differences in CaXP between patients with and without aortic valve calcification and mitral annular calcification,^{248,251} and normal and abnormal visceral uptake of ⁹⁹Tc-PP or ⁹⁹Tc-MDP.²⁵⁰

The incidence of visceral calcification in a selected dialysis population was high when mean CaXP exceeded 68 and low when mean CaXP was 51.²⁵⁰ Frequent incidence of visceral calcification²⁴⁸ and mitral valve calcification²⁵¹ was reported when CaXP exceeded 60 and calcification was unlikely when mean CaXP was around 50.^{250,251} It must be noted that a significant number of patients did not develop extraskeletal calcification despite a high CaXP.^{80,250,251}

Thus, the available evidence is limited, but convincing, that primary outcome (increased death rate) and secondary outcome (extraskeletal calcification) are related to CaXP. If this value exceeds 55, there is increased risk for development of calcification and possibly increased risk for lower patient survival. Thus, the goal level of CaXP should be below 55 in adolescents, and below 65 in infants and children, due to the

normal higher serum phosphorus level in the latter groups.

LIMITATIONS

There are no evidence-based studies in adults or children to define an upper limit of calcium intake to help prevent metastatic calcifications. There are no prospective studies that address imaging modalities to detect extraskeletal calcification in children. There are no prospective studies that address the risk factors for vascular calcifications in childhood years. There are no studies in children with vascular calcifications to understand how the lesions may be best treated to promote regression.

RECOMMENDATIONS FOR RESEARCH

Calcium needs of infants, children, and adolescents in Stages 1-5 of CKD should be determined by prospective, longitudinal studies. Factors that regulate the percentage of calcium absorption in the gastrointestinal tract with the use of calcium-containing binders in patients of different ages with CKD and receiving either peritoneal dialysis or hemodialysis should be determined.

Longitudinal studies of patient morbidity (e.g., growth, vascular calcifications) as a function of calcium intake should be determined.

GUIDELINE 8. PREVENTION AND TREATMENT OF VITAMIN D INSUFFICIENCY AND VITAMIN D DEFICIENCY IN CKD PATIENTS

In CKD Stages 2-4:

- 8.1 If serum PTH is above the target range for the stage of CKD (Table 3, Guideline 1) serum 25-hydroxyvitamin D should be measured. (EVIDENCE) Periodic assessment is warranted thereafter if dietary or lifestyle changes have occurred in the patient. (OPINION)
- 8.2 If the serum level of 25-hydroxyvitamin D is <30 ng/mL, supplementation with vitamin D₂ (ergocalciferol) should be initiated (see Table 15). (OPINION)
- 8.3 Following initiation of vitamin D supplementation:
 - 8.3.a The use of ergocalciferol therapy should be integrated with the serum calcium and phosphorus levels (Algorithm 1).
 - 8.3.b The serum levels of corrected total calcium and phosphorus should be measured after 1 month, and then at least every 3 months. (OPINION)
 - 8.3.c If the serum levels of corrected total calcium exceed 10.2 mg/dL (2.54 mmol/L), discontinue ergocalciferol therapy and all forms of vitamin D therapy. (OPINION)
 - 8.3.d If the serum phosphorus exceeds the upper limits for age, initiate dietary phosphate restriction (see Guidelines 4 and 5) or, if hyperphosphatemia persists but the 25(OH)D is <30 ng/mL, initiate oral phosphate binder therapy. If the

25(OH)D is normal, discontinue vitamin D therapy. (OPINION)

- 8.3.e 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(OH)D, as should the continued assessment of corrected total calcium and phosphorus per stage of CKD (see Table 15). (OPINION)

In CKD Stage 5:

- 8.4 Therapy with an active vitamin D sterol (calcitriol) should be provided if the serum levels of PTH are >300 pg/mL. (OPINION) See Guideline 9.

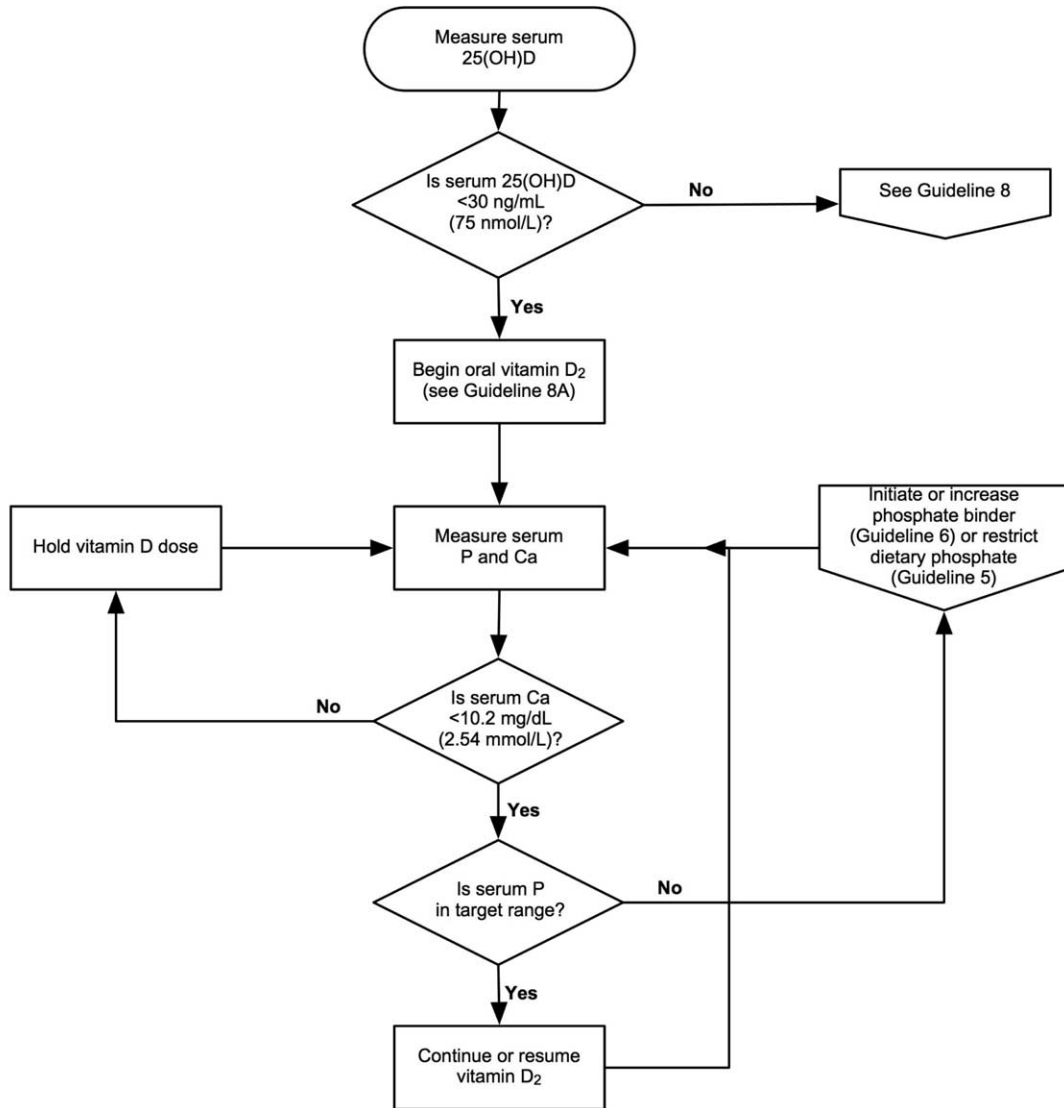
BACKGROUND

Serum levels of 25(OH)D (*not* the levels of 1,25-dihydroxyvitamin D) are the measure of body stores of vitamin D. Recent studies in adolescents with normal kidney function in Boston have associated levels of 25(OH)D <25 ng/mL with considerable elevations of PTH. Levels of 25(OH)D are lower in young children with fractures, compared to an age-matched population without fractures. In individuals with normal kidney function over age 60, levels of 25-hydroxyvitamin D below the “normal” limit of 15 ng/mL, and also low to

Table 15. Recommended Supplementation for Vitamin D Deficiency/Insufficiency in Patients with CKD Stages 3-4

Serum 25(OH)D (ng/mL)	Definition	Ergocalciferol Dose (Vitamin D ₂)	Duration (months)	Comment
<5	Severe vitamin D deficiency	8,000 IU/day orally x 4 weeks or, (50,000 IU per week X 4 weeks); then 4,000 IU/day or, (50,000 IU 2X per month for 2 months) X 2	3 months	Measure 25(OH)D levels after 3 months
5-15	Mild vitamin D deficiency	4,000 IU/day orally x 12 weeks or, (50,000 IU every other week, for 12 weeks)	3 months	Measure 25(OH)D levels after 3 months
16-30	Vitamin D insufficiency	2,000 IU daily or, (50,000 IU every 4 weeks)	3 months	Measure 25(OH)D levels after 3 months

In CKD patients with serum P < upper target value, serum Ca <9.5 mg/dL (2.37 mmol/L), and serum PTH above the target range for CKD stage (Stage 3: 35-70 pg/mL; Stage 4: 70-110 pg/mL)



Algorithm 1. Vitamin D Supplementation in CKD (Stages 2-4)

normal levels of 16-32 ng/mL, are both associated with increased PTH levels, reduced BMD, and increased rates of hip fracture. Such levels of reduced 25(OH)D are common in patients with CKD and GFR of 20-60 mL/min/1.73 m², and in CKD patients undergoing dialysis. The prevention and treatment of vitamin D insufficiency in patients with CKD Stages 2-4 reduces the frequency and severity of 2° HPT. 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)₂D₃ is markedly reduced or absent. The role of reduced or absent levels of 25(OH)D remains controversial in the patient on recovery maintenance dialysis.

RATIONALE

A reduction of serum 25(OH)D, the substrate for the kidney's generation of calcitriol [1,25(OH)₂D₃], produces 2° HPT in individuals with normal kidney function,²⁵⁴⁻²⁵⁶ and may aggravate 2° HPT in those with CKD and decreased kidney function.^{257,258} Severe manifestations of vitamin D deficiency, with osteomalacia and hypocalcemia, is rare unless 25(OH)D levels are <5 ng/mL (12 nmol/L); however, levels <30 ng/mL are indications of vitamin D "insufficiency"²⁵⁹ as manifested by significant elevations of serum levels of PTH.^{259,260} Individuals with normal kidney function and with low "normal" 25(OH)D levels of 16-32 ng/mL (40-80 nmol/L) have lower BMD²⁵⁶; also, patients with hip fractures have lower 25(OH)D levels than age-matched patients without hip fracture.²⁶¹ The only real disagreement in the literature is the upper range of 25(OH)D levels at which one does not encounter significant numbers of patients with 2° HPT,²⁵⁹ indicating that 25(OH)D should be maintained at higher levels.

Studies of 25(OH)D levels in patients with CKD and varying degrees of decreased kidney function from five reports were reviewed.^{117,236,262,263} Among 63 non-nephrotic adult CKD patients, the median values of 25(OH)D levels in those with GFR of 60-90, 40-60, and 20-40 mL/min/1.73 m² were 12, 19, and 18 ng/mL (30, 47, and 45 nmol/L), respectively.²³⁶ Obviously, a high fraction of these patients had levels <30 ng/mL (75 nmol/L) and many were <16 ng/mL (40 nmol/L). In a report of 76 CKD patients, 37 had CKD due to diabetes and 39 from other causes.¹¹⁷ 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 diabetic patients; in diabetics, serum albumin levels were lower and 76% had urinary protein concentrations >300 mg/dL, compared to 23% of nondiabetics.¹¹⁷ For the total group with GFR of 20-50 mL/min/1.73 m², 47% had 25(OH)D levels < 16 ng/mL (40 nmol/L) and 76% had 25(OH)D levels <26ng/mL (65 nmol/L). In these two studies,^{117,236} serum 1,25(OH)₂D levels correlated with 25(OH)D levels [*r* = 0.51²³⁶ and *r* = 0.47¹¹⁷], and *P* < 0.001. In the third study of the 19 CKD patients with GFR of 20-90 mL/min/1.73 m², 79% had 25(OH)D lev-

els <26 ng/mL (65 nmol/L) and 18% had 25(OH)D levels <16 pg/mL (0.4 nmol/L). In a U.S. study that included nine CKD patients with GFR of 12-60 mL/min/1.73 m², 25(OH)D levels averaged 20 ± 6 ng/mL (50 ± 15 nmol/L) indicating that values were <30 ng/mL (75 nmol/L) in the majority of patients. Over a wide range of GFR, from 11-111 mL/min/1.73 m², a large percentage were frankly vitamin D-deficient. Of those in CKD Stages 1-4, 86% had values <30 ng/mL. The findings that 1,25(OH)₂D levels correlated with 25(OH)D levels in the three largest series^{117,236} differ from observations in the population with normal kidney function, where 1,25(OH)₂D levels are not dependent on the 25(OH)D levels, even in patients with vitamin D deficiency.²⁶⁴ 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.^{265,266}

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: (a) many are inactive with reduced exposure to sunlight; (b) the ingestion of foods that are natural sources of vitamin D (fish, cream, milk, and butter) is likely to be lower than in the population with normal kidney function; and (c) serum 25(OH)D levels may be subnormal in CKD patients because the endogenous synthesis of vitamin D₃ in the skin following identical exposure to sunlight is reduced in those with reduced GFR,²⁶⁷ in individuals over age 60,²⁶⁸ and in individuals with increased melanin content of the skin.²⁶⁹

The ingestion of a diet low in calcium content leads to greater conversion of 25(OH)D to calcitriol and the need for more vitamin D intake and/or production,²⁷⁰ and dietary calcium intake is frequently low in CKD patients.¹⁰⁷ Furthermore, there is increased need for vitamin D in CKD patients with nephrotic-range proteinuria, because urinary losses of 25(OH)D and vitamin D-binding protein (DBP) are high.^{262,271} Kidney disease was found to be a major risk factor for low serum 25(OH)D levels in a population study of patients hospitalized in New England (with

patients on dialysis excluded from the analysis).²⁶⁰

In countries such as the U.S. where many foods are supplemented with vitamin D, and in 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.²⁵⁹ Nonetheless, 14%-42% of apparently healthy individuals over age 60 in the U.S. had serum levels of 25(OH)D <24-25 ng/mL (60 or 62 nmol/L).^{272,273}

In patients with Stage 5 CKD, there may be less need for vitamin D as a substrate for the renal 25-hydroxyvitamin D-1- α hydroxylase, 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 2° HPT even in CKD patients on dialysis.²⁷⁴ Nonetheless, the value of supplementation with ergocalciferol in these patients is less certain; although in dialysis-dependent patients, including anephric individuals, high doses of ergocalciferol or 25(OH)D can raise the serum levels of calcitriol.²⁷⁵⁻²⁷⁷

In patients with CKD and GFR of 20-60 mL/min/1.73 m², nutritional vitamin D deficiency and insufficiency can both be prevented by supplementation with vitamin D₂ (ergocalciferol) or vitamin D₃ (cholecalciferol). If there is evidence of true vitamin D deficiency, this should be treated; the best available treatment is vitamin D₂, although the doses needed are larger than those needed for vitamin D insufficiency. For the prevention of vitamin D deficiency, the RDA for vitamin D in children and adolescents remains at 400 IU, while in older individuals >60 years it is 800 IU. Little is known about the DRI of vitamin D for patients of any age with CKD.

There are problems with the dosage forms available. In the U.S., the only forms available are tablets of 400 IU (over the counter), and liquid forms (8,000 IU/mL) or capsules containing 50,000 IU, requiring a prescription. In individuals with normal kidney function, 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.^{278,279} This dose can be achieved by giving one capsule (50,000 IU) once a

month.^{280,281} 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.^{282,283} Ergocalciferol vitamin D sterol may be safer than cholecalciferol,^{284,285} 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 α -hydroxylated vitamin D sterol should not be used to treat vitamin D deficiency. In CKD Stages 1-4, when evidence of severe vitamin D deficiency is found, [25(OH)D levels <5 ng/mL (12 nmol/L)], rickets in the growing child, or osteomalacia, may be present. Treatment with ergocalciferol may be appropriate (see Table 15).²⁸¹

STRENGTH OF EVIDENCE

There is strong evidence that vitamin D insufficiency, defined as 25(OH)D levels <27-32 ng/mL (67-80 nmol/L), is common in individuals >60 years in the U.S.,^{272,273} and many locations in Europe.²⁸⁶ Such low levels have clinical significance based on the finding of: a) the elevated serum levels of intact PTH as evidence of 2° HPT; and b) reduced BMD²⁵⁶ and higher rates of hip fracture compared to age-matched controls.²⁸⁷ 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.^{286,288} 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 levels <15 ng/mL pose a major risk factor for the presence of severe 2° HPT (with radiographic abnormalities) in CKD patients on dialysis,²⁷⁴ 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 20-60 mL/min/1.73 m² 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^{282,283} indicates a rec-

ommended dose of 1,000-2,000 IU/day would be safe.

LIMITATIONS

In patients with GFR <20 mL/min/1.73 m² and those requiring dialysis, there is no evidence that modest supplementation with ergocalciferol to raise serum 25(OH)D levels to 30-60 pg/mL (8.25-16.5 pmol/L) will increase the serum levels of 1,25(OH)₂D (calcitriol) or lower the elevated serum levels of PTH. In CKD patients with higher GFR, 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.¹¹⁶

CLINICAL APPLICATIONS

The treatment of vitamin D insufficiency or deficiency when present in CKD patients is warranted, since such therapy may reduce or prevent 2° HPT in the early stages of CKD.

RECOMMENDATIONS FOR RESEARCH

Prospective, controlled clinical trials with the daily administration of ergocalciferol in a monthly amount equivalent to 1,000-2,000 IU/day are clearly warranted in patients with CKD and those undergoing dialysis, to assess the effects on serum PTH levels, serum 1,25(OH)₂D levels, bone histomorphometry, and fracture rates. With the higher fracture rates known to occur in adult patients with Stage 5 CKD,²⁸⁹ studies to evaluate measures to minimize early 2° HPT would be warranted in patients with CKD of all ages.

GUIDELINE 9. ACTIVE VITAMIN D THERAPY IN CKD PATIENTS

This Guideline encompasses two parts: Guideline 9A, which is specific for CKD Stages 2-4, and Guideline 9B, which refers to CKD Stage 5.

GUIDELINE 9A. ACTIVE VITAMIN D THERAPY IN PATIENTS WITH CKD STAGES 2-4

9A.1 In patients with CKD Stages 2-4, therapy with an active oral vitamin D sterol (calcitriol) should be initiated when serum levels of 25(OH)D are >30 ng/mL (75 nmol/L), and serum levels of PTH are above the target range for the CKD stage (see Table 3, Guideline 1). (EVIDENCE)

9A.1.a An active vitamin D sterol should be administered only in patients with serum levels of corrected total calcium <10 mg/dL (2.37 mmol/L) and serum levels of phosphorus less than age-appropriate upper limits (Table 16). (OPINION)

9A.2 After initiation of active vitamin D sterols, serum levels of calcium and phosphorus should be measured at least monthly for the first 3 months, and at least every 3 months thereafter. Serum PTH levels should be measured at least every 3 months. (OPINION)

9A.3 The dosage of active vitamin D sterols should be adjusted as follows:

9A.3.a If serum levels of PTH decrease to values below the target range for the CKD stage (Table 3, Guideline 1), active vitamin D sterol therapy should be held until serum levels of PTH in-

crease to above the target range; treatment should then be resumed at half the previous dose of active vitamin D sterols. If the dosage is below a 0.25 µg capsule or 0.05 µg dose as liquid, alternate-day dosing should be used. (OPINION)

9A.3.b If serum levels of corrected total calcium exceed 10.2 mg/dL (2.37 mmol/L), active vitamin D sterol therapy should be held until serum calcium decreases to <9.8 mg/dL (2.37 mmol/L); treatment should then be resumed at half the previous dose. If the lowest daily dose of the active vitamin D sterol is being given, alternate-day dosing should be used. If the dosage is below a 0.25 µg capsule or 0.05 µg dose as liquid, alternate-day dosing should be used. (OPINION) See algorithm 2.

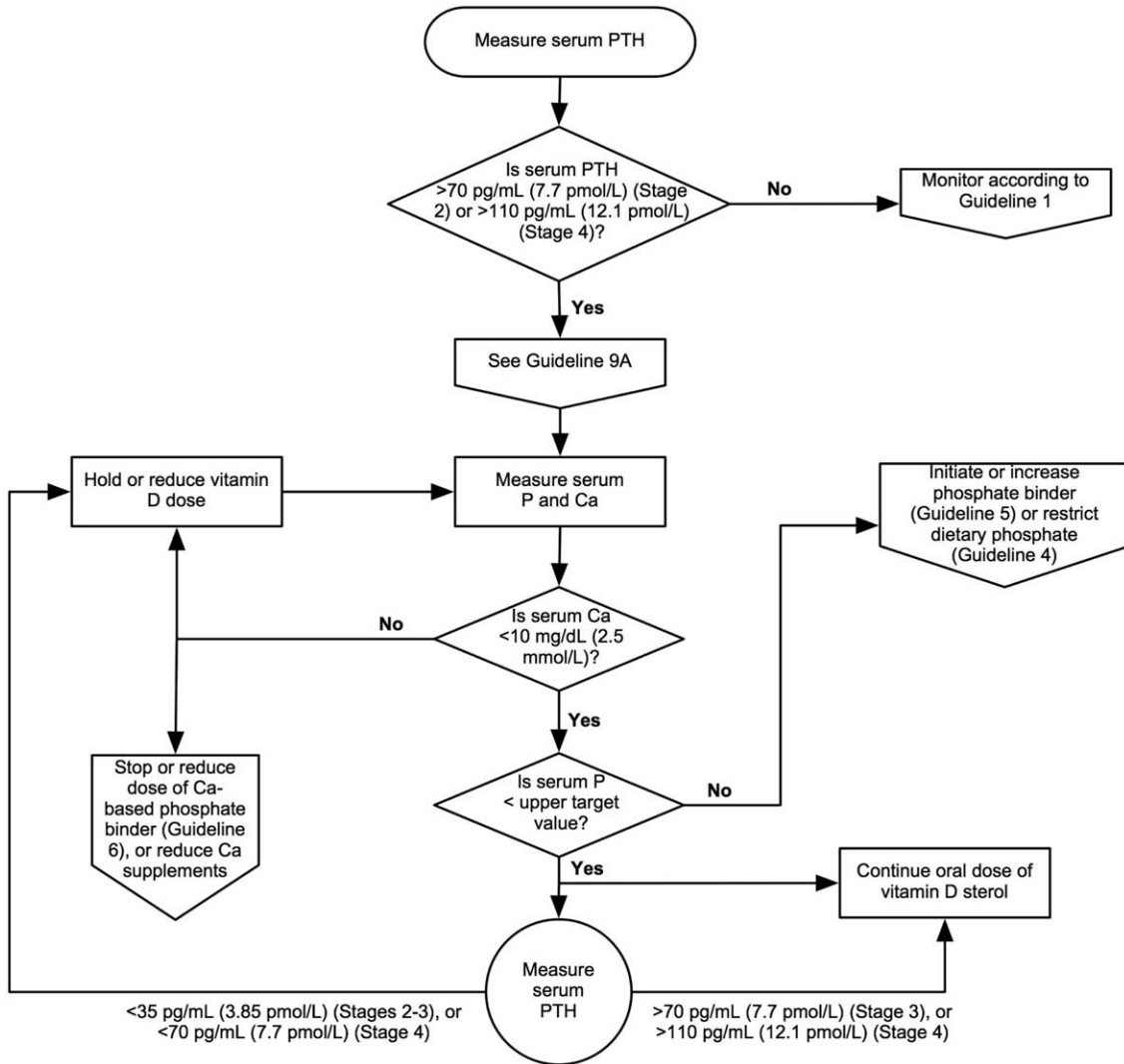
9A.3.c The dosage of active vitamin D sterols should be adjusted downward as follows: If serum levels of phosphorus increase to greater than age-appropriate upper limits, active vitamin D therapy should be held; the dose of phosphate binders should be increased or initiated until the levels of serum phosphorus decrease to age-appropriate levels; then, treatment at half the prior dose of active vitamin D sterol should be resumed. (OPINION)

9A.4 The dosage of active vitamin D sterols should be adjusted upward as follows:

Table 16. Serum Levels of PTH, Calcium, and Phosphate Required for Initiation of Oral Vitamin D Sterol Therapy, and Recommended Initial Doses in Patients with CKD Stages 2-4

Serum PTH (pg/mL or ng/L)	Serum Ca (mg/dL) [mmol/L]	Serum P (mg/dL)	Dose Oral Calcitriol
>70 (CKD Stage 2,3)			
>110 (CKD Stage 4)	<10 [2.37]	≤ age-appropriate levels	<10 kg: 0.05 µg every other day 10-20 kg: 0.1-0.15 µg/day >20 kg: 0.25 µg/day

In CKD patients, Stages 2-4, with stable renal function, compliant with visits and medications with serum phosphorus levels < upper target value, calcium <10 mg/dL (2.5 mmol/L), and 25(OH)D \geq 30 ng/mL (75 nmol/L)



Algorithm 2. Management of CKD Patients (Stages 2-4) with Active Vitamin D Sterols

If serum levels of PTH fail to decrease by at least 30% after the initial 3 months of therapy, and the serum levels of calcium and phosphorus are within the target ranges based on CKD stage, the dose of active vitamin D sterols should be increased by 50%. Serum levels of PTH, calcium, and phosphorus must be measured monthly for 3 months thereafter.

BACKGROUND

In patients with CKD, 2° HPT occurs when the GFR declines to <75 mL/min/1.73 m² (Stages 2-3). The administration of small doses of the active vitamin D sterol, calcitriol, can reduce the serum levels of PTH and may improve linear growth. With the use of low dosages of calcitriol, hyperparathyroidism can be suppressed without evidence of worsening of kidney function; how-

ever, careful monitoring of serum levels of calcium, phosphorus, and PTH is essential.

RATIONALE

In adult CKD patients with GFR <60 mL/min/1.73 m² (Stage 3), serum levels of PTH are increased.^{103,116,290,291} In such patients, bone biopsies show histomorphometric features of hyperparathyroid bone disease despite only modest elevations of PTH.^{10,292-294} Serum levels of 1,25(OH)₂D₃ are either normal or in the lower range of normal,^{103,116,290,291} despite the elevated PTH levels and serum levels of phosphorus that are often in the low range of normal.^{74,100,230} Normal 1,25(OH)₂D₃ levels in the face of high levels of PTH are inappropriate and thus contribute to defective feedback suppression by 1,25(OH)₂D₃ of prePTH synthesis in the parathyroid glands, with a resultant increased secretion of PTH.²⁹⁵

In controlled trials in adult patients with Stage 3 CKD, the administration of oral calcitriol, 0.25 µg/day and occasionally up to 0.5 µg/daily,^{292,296} or of alfacalcidol, 0.25-0.5 µg daily¹⁰ were associated with lowering of PTH levels,^{294,296} improvement of histological features of hyperparathyroid bone disease,^{292-294,297} or an increase of BMD.²⁹⁶ Preliminary evidence also suggests that patients who had calcitriol therapy initiated when the creatinine clearance exceeded 30 mL/min/1.73 m² (0.50 nmol/L/min/1.73 m²) had normal bone histology when they 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.²⁹⁸ Calcitriol deficiency may also contribute to growth retardation and bone disease in children with CKD. Indeed, treatment with daily doses of calcitriol (1,25-dihydroxyvitamin D₃), has been reported to improve linear growth in small numbers of children with CKD Stages 2-4.²⁹⁹ Such findings provide the rationale for the routine administration of calcitriol to nearly all children with CKD. However, in other studies, enhanced growth velocity was not demonstrated on long-term follow-up and further studies have not shown that calcitriol consistently improves linear growth in children with CKD Stages 2-4.³⁰⁰ A more recent study demon-

strated a direct relationship between changes in growth velocity and PTH levels in children with CKD Stages 2-3 treated with either daily or intermittent calcitriol therapy,³⁰¹ similar to the findings reported in children with CKD Stage 5 and treated with peritoneal dialysis.³⁰² Furthermore, more severe growth retardation was observed in those patients that developed adynamic bone after treatment with calcitriol was given intermittently, either orally or intraperitoneally.³⁰² These results suggest that large doses of intermittent calcitriol therapy in conjunction with calcium-containing binders adversely affect epiphyseal growth plate chondrocytes activity, and thereby contribute to reduction in linear growth. On the other hand, others have described catch-up growth associated with PTH levels within the normal range in children with CKD Stages 2-3 treated with calcium supplements and low doses of 1-α-calcidol.³⁰³ Although the optimal PTH levels that are required to maximize growth remain to be defined, it may be prudent to maintain serum PTH according to the stage of CKD.

There has been concern about the safety of the use of vitamin D metabolites with regard to a possible adverse effect on kidney function. With the use of calcitriol in doses ≤0.25 µg/day 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.^{10,292,294,297,304} 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, reductions of creatinine clearance were observed,^{305,306} although it is not certain that true GFR (inulin clearance) was affected.^{306,307} In CKD patients with serum levels of phosphorus greater than upper limits suggested by Guideline 4, 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 adult CKD patients with GFR of 20-60 mL/min/1.73 m²,^{10,292,297} and two studies without a placebo-

control group^{293,294} have shown evidence of hyperparathyroid bone disease in a high fraction of baseline “control” bone biopsies. 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 PTH totally unknown.^{10,292,296,297} In each of the placebo-controlled trials, there was either no improvement or worsening^{10,292,297} 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.^{10,292,293,297} Meta-analysis could not be done for these studies because one reported their data as mean \pm SD,²⁹³ one reported medians and ranges,¹⁰ and another reported the fractions of patients who showed improvement or worsening of various histological features on bone biopsy.¹⁰ Another study was excluded because the number of subjects was too small ($n < 10$).²⁹⁷

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 entered into these trials and using relatively low doses.^{10,292,293,296,297} Should hypercalcemia develop during vitamin D treatment, particularly with higher doses, transient or even long-lasting deterioration of kidney function has been observed.³⁰⁸⁻³¹⁰ 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.¹⁰

LIMITATIONS

The available evidence in adults 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 noted to be less hypercalcemic. Data in children with CKD Stages 2-4 are not available or very limited with respect to PTH and bone

histology, or the effects of vitamin D sterol therapies.

CLINICAL APPLICATION

It appears that the active vitamin D sterols are useful in the treatment of 2° HPT and high-turnover bone disease in early stages of CKD in adults. This provides a good therapeutic tool for the prevention and management of these two abnormalities in CKD patients, before these derangements advance and their treatment becomes more difficult. Attention should be paid to the beneficial effect on linear growth in reducing hyperparathyroid bone disease in CKD Stages 2-4 as well.

RECOMMENDATIONS FOR RESEARCH

In children with CKD Stages 2-4, randomized, placebo-controlled trials of the extent and therapy of hyperparathyroid bone disease are warranted. In adults, further trials with longer-term treatment (≥ 24 months) 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 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. 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 PTH that should be achieved are not established, and biopsy evaluations in such trials with correlations between PTH or iPTH levels and skeletal findings would be ideal. Also, in the trials that have been published,^{10,294} it would be useful if the data were reanalyzed to evaluate the relationship between serum levels of PTH and the degree of parathyroid bone disease found on biopsy in relation to the degree of impairment of kidney function.

GUIDELINE 9B. ACTIVE VITAMIN D THERAPY IN PATIENTS ON DIALYSIS (CKD STAGE 5)

- 9B.1** In patients with CKD Stage 5 and serum PTH levels >300 pg/mL, an active vitamin D sterol (calcitriol; see Table 17) should be administered to reduce the serum levels of PTH to a target range of 200-300 pg/mL. (EVIDENCE)
- 9B.2** The intermittent administration of calcitriol by intravenous or oral routes is more effective than daily oral calcitriol in lowering serum PTH levels. (EVIDENCE)
- 9B.3** When therapy with vitamin D sterols is initiated or the dose is increased, serum levels of calcium and phosphorus should be measured at least every 2 weeks for 1 month and then monthly thereafter. The serum PTH level should be measured monthly for at least 3 months and then at least every 3 months once target levels of PTH are achieved. (OPINION)
- 9B.4** For patients treated with peritoneal dialysis, initial oral doses of calcitriol (0.5-1.0 µg) can be given three times weekly. Alternatively, an equivalent lower dose of calcitriol (0.25 µg) can be administered daily. (OPINION)
- 9B.5** The dosage of active vitamin D sterols should be adjusted upward as follows: If

serum levels of PTH fail to decrease by at least 30% after the initial 3 months of therapy, and the serum levels of calcium and phosphorus are within the target ranges based on CKD stage, increase the dose of active vitamin D sterols by 50%. Serum levels of PTH, calcium, and phosphorus must be measured monthly for 3 months thereafter.

- 9B.6** Treatment with active vitamin D sterols should be integrated with the changes in serum calcium, phosphorus, and PTH. A separate algorithm is shown for each of these three variables with suggested interventions based on the values obtained. (OPINION)

BACKGROUND

Patients with CKD who undergo dialysis have reduced serum levels of 1,25(OH)₂D₃. This leads to reduced intestinal absorption of calcium (thereby contributing to hypocalcemia) and impaired suppression of the parathyroid gene that initiates the synthesis of PTH. The result is 2° HPT 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.

Table 17. Initial Calcitriol Dosing Recommendations for Children on Maintenance Dialysis

Serum PTH (pg/mL)	Serum Ca (mg/dL) [mmol/L]	Serum P (mg/dL) [mmol/L]	CaXP*	Calcitriol Dose per HD Session	Calcitriol Dose for Patients Receiving PD (TIW) ^{311, 312}
300-500	<10 [2.37]	<5.5 [1.78] for adolescents <6.5 [2.10] for infants and children	<55 for adolescents <65 for infants and children	0.0075 ?g/kg (maximum = .25 ?g) qd	0.0075 ?g/kg (maximum = 0.25 ?g) qd
>500-1000	<10 [2.37]	<5.5 [1.78] for adolescents <6.5 [2.10] for infants and children	<55 for adolescents <65 for infants and children	0.015 ?g/kg (maximum = 0.5 ?g) qd	0.015 ?g/kg (maximum = 0.5 ?g) qd
>1000	<10.5 [2.50]	<5.5 [1.78] for adolescents <6.5 [2.10] for infants and children	<55 for adolescents <65 for infants and children	0.025 ?g/kg (maximum = 1 ?g) qd	0.025 ?g/kg (maximum = 1 ?g) qd

HD Hemodialysis, thrice weekly (TIW)

PD Peritoneal dialysis, thrice weekly (TIW)

* <65 in children below 12 years of age

A major side-effect of vitamin D treatment is increased intestinal absorption of calcium and phosphorus; this can produce hypercalcemia and aggravate hyperphosphatemia. Treatment with active vitamin D sterols can also markedly lower serum levels of 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, phosphorus, and PTH must be monitored during vitamin D therapy, and vitamin D therapy adjusted accordingly (Algorithm 3, Algorithm 4, and Algorithm 5).

RATIONALE

Treatment of 2° HPT in patients with CKD Stage 5 by oral or intravenous calcitriol, intravenous paricalcitol, oral or intravenous doxercalciferol, or oral or intravenous alfacalcidol can reduce the elevated levels of PTH,³¹³⁻³²³ and may be useful to treat various clinical features of symptomatic 2° HPT.^{313,315,318} With such treatment, improved features of hyperparathyroid bone disease have been reported.^{314,315,324,325} Reductions of both serum 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.^{314-316,318,321,324,326}

STRENGTH OF EVIDENCE

Although daily calcitriol therapy has been recommended for more than two decades to children with chronic renal disease, 2° HPT remains the predominant bone lesion in children treated with dialysis.^{22,23} Indeed, when patients with bone biopsy-proven high-turnover bone disease were followed for 1 year with calcitriol therapy given daily, bone lesions of hyperparathyroid bone disease persisted or progressed in the vast majority of the patients.³¹¹ Dosage regimens have generally ranged from 0.25-1.0 µg/day in such patients undergoing peritoneal dialysis.³¹¹

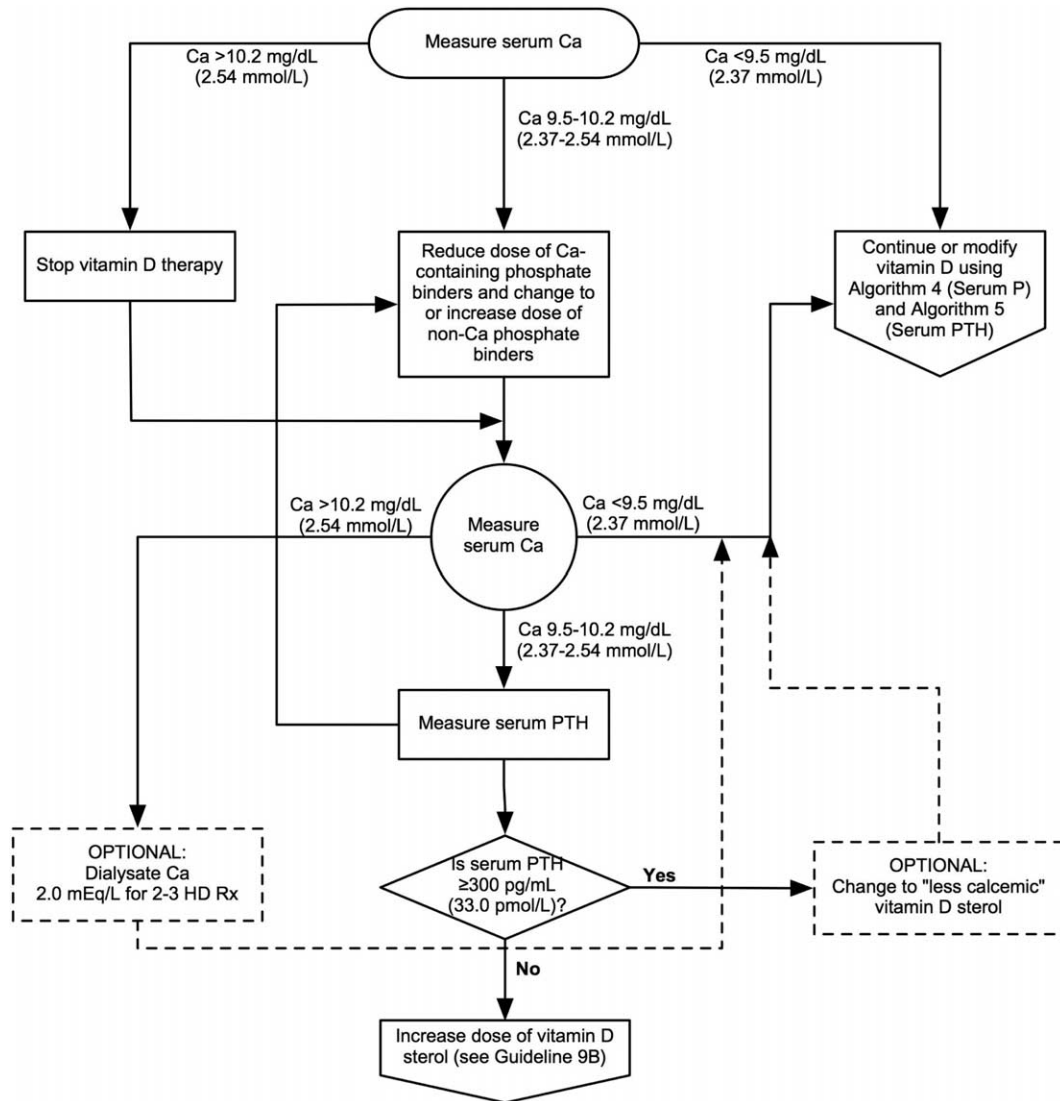
Over the last decade, the 1st PTH-IMA proved to be a reasonably reliable predictor of the different subtypes of renal osteodystrophy and it performed well in assessing the therapeutic response to active vitamin D sterols in patients with renal failure.^{22,23,327} In dialyzed children who are either untreated or are receiving small

daily oral doses of calcitriol, PTH levels (measured by 1st PTH-IMA) of approximately three times the upper limit of normal generally correspond to normal BFRs. Levels >250-300 pg/mL are associated with bone biopsy evidence of 2° HPT, while values <150 pg/mL indicate an adynamic bone lesion.²²

Similar values may not be applicable in dialyzed children receiving intermittent calcitriol therapy, since suppression of bone formation may develop despite persistently elevated PTH levels (measured by 1st PTH-IMA) in these patients.³¹² In patients treated with peritoneal dialysis, high-dose intermittent calcitriol therapy (both oral and intraperitoneal) results in marked decline in BFRs and development of the adynamic lesion in a substantial proportion of patients.^{312,328} Corresponding reductions in serum PTH levels were observed only in patients who received intraperitoneal doses of calcitriol, while serum PTH levels remained persistently elevated in those given intermittent oral doses of calcitriol, despite significant reductions in BFRs on repeat biopsy.³¹² Thus, the relationship between PTH and bone formation is disrupted during intermittent calcitriol therapy in children undergoing peritoneal dialysis.

The disparity between the histological and biochemical findings highlights the potential limitation of single PTH determinations to predict the skeletal manifestations of renal osteodystrophy, direct effects of calcitriol on osteoblastic activity and/or limitations of the current 1st PTH-IMA among the main potential factors.

In dialysis patients who have not received vitamin D, or those who have received daily oral calcitriol in doses lower than 0.5 µg/day, serum levels of PTH correlate with the degree of 2° HPT^{25,26,329}; moreover, patients with PTH levels <400 pg/mL (44.0 pmol/L) and normal (or low) serum levels of calcium usually have only mild hyperparathyroidism.^{26,329} 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 PTH exceed 500-600 pg/mL (55.0 to 66.0 pmol/L), moderate or even severe hyperparathyroid bone disease is usual. When PTH levels exceed 1,000 pg/mL (110.0 pmol/L), larger doses of the vitamin D sterols are generally required.^{322,330-333} During

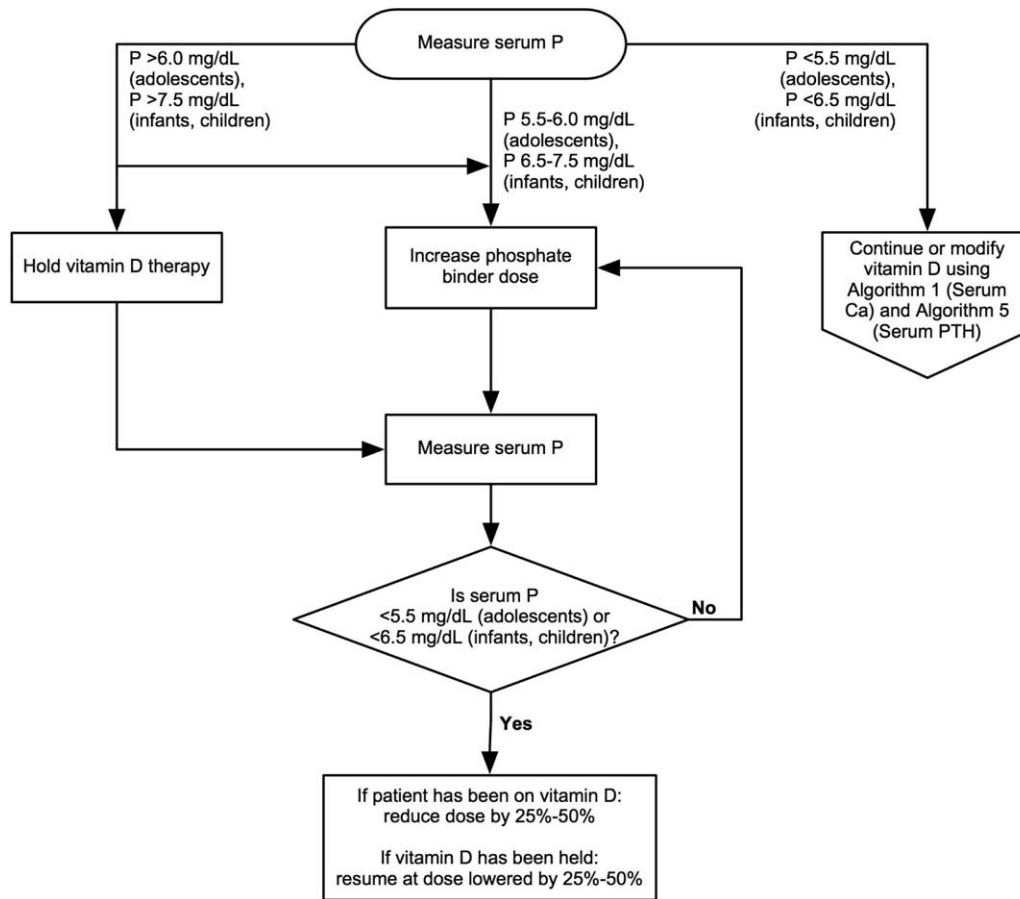


Algorithm 3. Managing Vitamin D Sterols Based on Serum Calcium Levels

treatment with intravenous calcitriol³³⁰ or oral doxercalciferol³²² in prospective trials, there was evidence that larger doses are required for the treatment of patients with severe 2° HPT compared to patients with less severe hyperparathyroidism. Moreover, the suppression of serum levels of PTH in patients with severe hyperparathyroidism may require treatment for longer periods of time, e.g., more than 12-24 weeks.^{322,330-332} 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 para-

thyroid glands in CKD Stage 5 patients with more severe 2° HPT.³³⁴

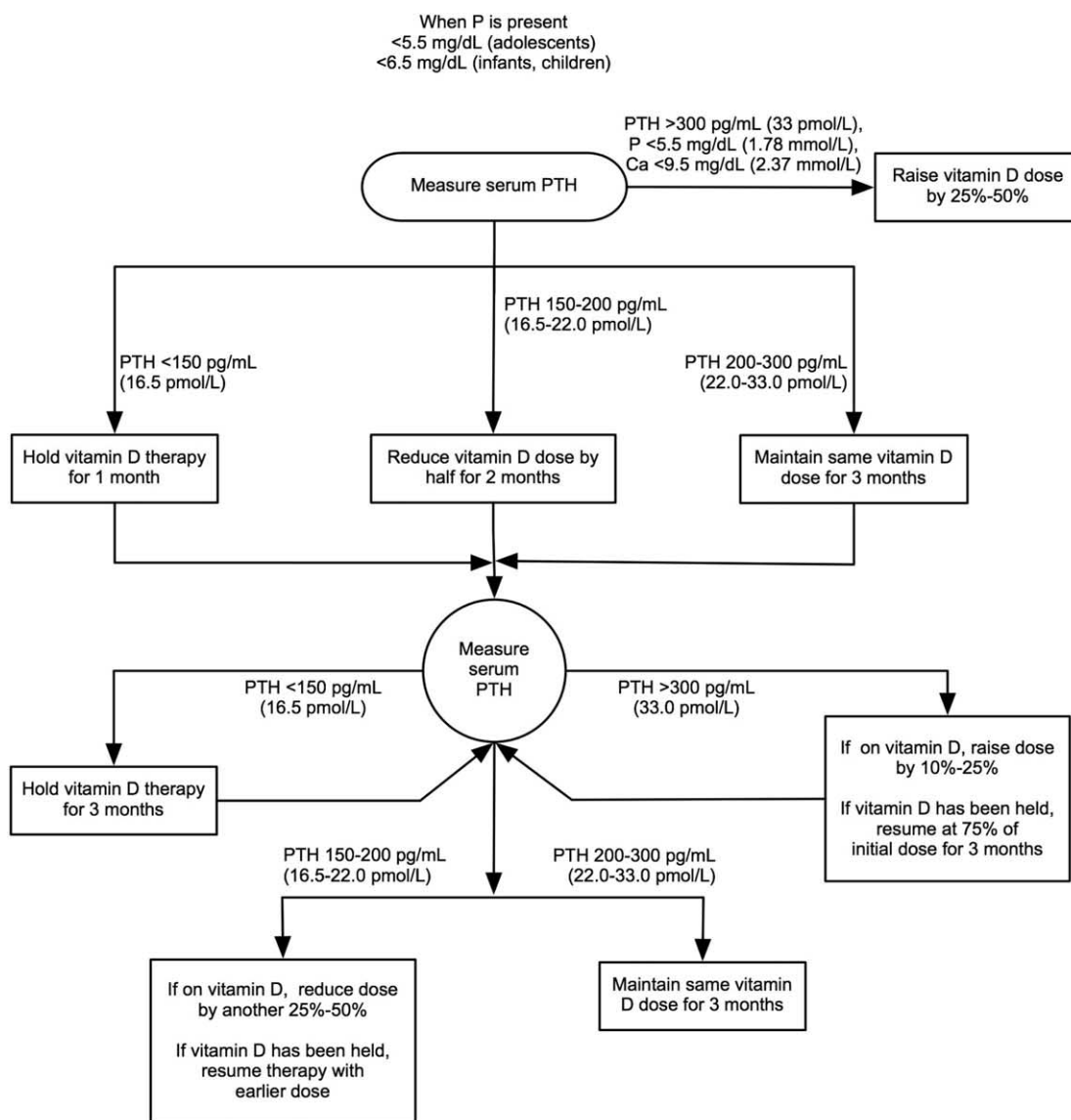
It is recommended that the dosage of a vitamin D sterol be adjusted in accordance with the severity of 2° HPT. The evidence that PTH levels correlate with the severity of bone disease in patients who have not received pulse-dose intravenous or oral calcitriol is quite good.^{25,26} However, the optimal doses of vitamin D sterols and the optimal serum levels of PTH that should be the target in patients who have received such therapy for longer than 6-12 months is less certain.



Algorithm 4. Managing Vitamin D Sterols Based on Serum Phosphorus Levels

Several trials that were not placebo-controlled have shown the effectiveness of intermittent intravenous and intermittent oral calcitriol to suppress serum levels of PTH in patients undergoing hemodialysis,^{335,336} including some patients with severe hyperparathyroidism³³⁶⁻³³⁹; moreover, these results appeared more favorable than earlier experiences with daily oral dosing when reductions of dosage were commonly needed.^{340,341} However, the meta-analysis of four trials that compared intermittent intravenous calcitriol with oral calcitriol in randomized, controlled studies^{342,343} or crossover trials^{344,345} indicated that intravenous therapy was more effective than oral treatment (either daily or “pulse” treatment) for the suppression of PTH levels (Figure 7). There are certain qualifications about the trials combined for this meta-analysis: Two trials

compared daily oral treatment with thrice weekly intravenous treatment^{343,345}; in the trial that studied patients with the highest pretreatment PTH levels, the oral “group” was a combination of one group randomly assigned to intermittent treatment and a second group assigned to daily therapy.³⁴⁶ The degree of hyperparathyroidism was very mild in two trials, as the entry PTH levels averaged <400 pg/mL (44.0 pmol/L).^{343,344} In two trials that prospectively compared intermittent oral and intravenous calcitriol in patients with more severe hyperparathyroidism,^{347,348} 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



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/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 PTH Levels in Children Not Receiving Growth Hormones

below 0.75-1.0 μg per treatment were often less effective in lowering PTH levels.^{330,349} Moreover, the earlier placebo-controlled trials with daily oral calcitriol found that patients

could rarely tolerate daily doses of 0.5 μg per day without developing hypercalcemia.^{340,341} The results of oral trials with calcitriol that were not placebo-controlled lead to the conclu-

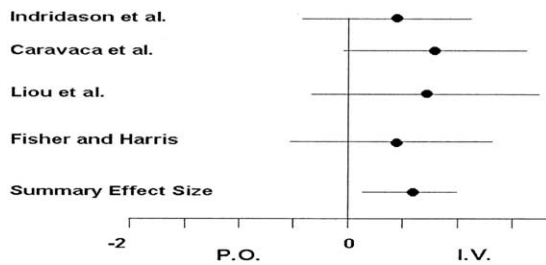


Fig 7. Meta-Analysis of Oral versus Intravenous Calcitriol on PTH Suppression

sion that pulse or intermittent therapy yielded better results than were reported with daily therapy; meta-analysis of the results of three randomized, controlled trials that compared daily oral with intermittent oral calcitriol failed to show any superiority of intermittent therapy over daily therapy.^{317,346,350} Two of these studies^{317,350} had patients with only mild hyperparathyroidism, and few patients entered into treatment with PTH levels above 600 pg/mL (66.0 pmol/L). Despite randomization of treatment in one study,³⁵⁰ each of the five patients having pretreatment PTH levels >600 pg/mL (66.0 pmol/L) were assigned to intermittent therapy. In another study,³⁴⁶ the trial with the highest pretreatment 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.^{351,352} 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.^{321,323,353,354} Extensive data in animals with normal kidney function 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.³⁵⁵⁻³⁵⁷ Studies in vitamin D-deficient animals with dox-

ercalciferol 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.^{358,359} Additional studies have shown that doxercalciferol is associated with less calciuria than alfacalcidol.^{360,361} 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,^{321,322,362-365} 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.^{328,366} In CKD Stage 5 patients who had not received pulse doses of calcitriol and had PTH levels <150 pg/mL (16.5 pmol/L), there was a high incidence of subnormal bone formation on bone biopsy, with adynamic or aplastic bone.²⁶ When PTH levels are <65 pg/mL (7.15 pmol/L), the occurrence of adynamic bone is nearly universal.^{17,26} Mild hyperparathyroid bone disease may be preferable to adynamic bone because of the loss of the capacity of bone buffering for the added extracellular calcium²⁰⁷; this likely accounts for the increased risk of hypercalcemia in patients with adynamic bone.^{327,366} Also, there may be increased risk of vascular calcification in patients with biochemical features that are consistent with adynamic bone.⁸⁴ In adolescents and young adults with CKD Stage 5, adynamic bone³²⁸ and even reduced linear growth occurred in association with intermittent calcitriol therapy when the PTH levels were reduced below 400-450 pg/mL (44.0-49.5 pmol/L).³⁰² Reported observations of the development of adynamic bone in adult CKD Stage 5 patients in association with pulse therapy with calcitriol are limited to a small number³⁶⁷; 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 PTH levels <600 pg/mL (66.0 pmol/L) without initiating vitamin D therapy, serial 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,^{313-316,318,324,325,368-370} and the assays for PTH were variable and some involved PTH fragments^{313-316,318} that are cleared by the kidney; thus, comparison with the current trials that utilize so-called “1st PTH-IMA” 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 2° HPT. With studies of the “newer” vitamin D sterols, such as falecalcitriol, paricalcitol, and doxercalciferol, there were often parallel controls.^{320-322,354} However, the severity of 2° HPT was mild to moderate, based on pretreatment serum levels of PTH, in most patients entered into trials with falecalcitriol^{320,354} or paricalcitol.³²¹ For these reasons, comparison of data with the different vitamin D sterols must be regarded as tentative, particularly for patients with severe 2° HPT, defined as serum levels of 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 than pulse oral treatment must also be regarded as tentative; similarly, the conclusions that daily oral therapy is as effective as pulse oral therapy given two or three times a week may

only apply to patients with mild 2° HPT 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 little or no hypercalcemic effects.

RECOMMENDATIONS FOR RESEARCH

Trials that compare different vitamin D sterols in CKD Stage 5 patients 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 PTH and bone turnover using double tetracycline labeling, to assess a possibly important side-effect of vitamin D treatment. Moreover, little is known about the ideal target for serum levels of 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 PTH levels. Studies are needed to examine the value of bone markers and to assess the relationship between the so-called “whole PTH molecule,” “1st PTH-IMA,” 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 CKD Stage 5 patients.

GUIDELINE 10. DIALYSATE CALCIUM CONCENTRATIONS

10.1 In patients receiving calcium-based phosphate binders, the dialysate calcium concentration should be targeted to 2.5 mEq/L (1.25 mM). (OPINION)

10.2 In patients not receiving calcium-containing phosphate binders, the dialysate calcium should be targeted to 2.5-3.0 mEq/L (1.25-3 mM) based on serum calcium levels and the need for therapy with active vitamin D sterols. (OPINION)

BACKGROUND

In patients receiving dialysis, the normal homeostatic mechanisms for regulating calcium balance are impaired. Calcium absorption cannot be adjusted, due to the kidney's inability to produce 1,25(OH)₂D. Further, the level of the peripheral tissue VDR may be reduced. Calcium excretion, usually regulated through urinary losses, is severely impaired or absent. Dialysate calcium, activated vitamin D sterols, and dietary calcium intake—itsself highly influenced by the use of oral, calcium-containing phosphate binders—are the physician-prescribed determinants of calcium balance in patients receiving dialysis.

Because bone mass increases dramatically during childhood and adolescence, there is significant net body accretion of calcium, where, on balance, absorption must exceed losses. Inadequate calcium absorption is an important cause of 2° HPT and osteodystrophy in the setting of CKD. Historically, dialysate calcium levels were set at a physiological level of 2.5 mEq/L, approximately equivalent to the serum ionized calcium concentration. However, it became clear that many patients were in a negative calcium balance in the era when oral aluminum-containing salts were the principal phosphate binder. Consequently, in both hemodialysis and peritoneal dialysis, a supraphysiological dialysate calcium concentration (3.0-3.5 mEq/L) became standard, permitting transfer of calcium to the patient during dialysis. This was effective in reducing PTH levels.³⁷¹ With the current widespread use of activated vitamin D sterols and oral, calcium-containing phosphate binders, calcium balance is shifted upward dramatically, so that a return to the use of 2.5 mEq/L calcium dialysate is safe. However, the use of calcium- and other metal-containing phosphate binders may require a higher dialysate calcium.

RATIONALE

There are three major clinical concerns related to excess calcium balance: bone, growth, and development of vascular calcifications. Patients may develop frank hypercalcemia, which most commonly occurs in patients receiving both oral calcium-containing phosphate binders, and activated vitamin D sterols. This may limit the use of calcium-containing phosphate binders to control hyperphosphatemia and 2° HPT. Excess calcium balance, resulting in hypercalcemia and thereby suppressing the parathyroid gland secretion of PTH, may contribute to the development of adynamic bone disease, which has become an increasing problem in both adults and children on maintenance dialysis.^{24,327,328,372} Patients with adynamic bone disease have an increased risk of hypercalcemia due to the limited capacity of their bone to incorporate calcium.²⁰⁷ There is concern that excessive calcium balance may contribute to systemic calcification, as reflected by EBCT evidence of enhanced coronary calcium scores, present in young adults who started dialysis as children.^{80,84} In addition, adynamic bone disease was associated with a greater degree of arterial calcification in patients on maintenance dialysis.³⁷³

The dialysate calcium concentration and the volume of ultrafiltrate determine calcium balance during dialysis. A higher dialysate calcium concentration increases diffusion of calcium into the patient. In contrast, the calcium present in the ultrafiltrate is a potentially important source of calcium loss from the patient. The calcium balance during peritoneal dialysis is usually negative with use of 2.5 mEq/L calcium dialysate and positive with 3.0-3.5 mEq/L calcium dialysate, although high volumes of dialysate ultrafiltrate can produce a negative calcium balance even with 3.5 mEq/L calcium dialysate.³⁷⁴⁻³⁷⁸ Calcium balance during hemodialysis may be neutral or negative with the use of a 2.5 mEq/L calcium dialysate.^{379,380} (See Guideline 14).

The use of dialysate with a calcium concentration of 2.5 mEq/L is an effective strategy for reducing calcium intake, and thereby reducing balance, if patients are treated with calcium-based phosphate binders. Studies in adults using this preparation have shown fewer episodes of hypercalcemia and patient tolerance of increased doses of

calcium-containing phosphate binders without the development of hypercalcemia.³⁸¹⁻³⁸⁴ Hyperparathyroidism may worsen after decreasing the dialysate calcium, but this often responds to increased use of calcium-containing phosphate binders and/or active vitamin D sterols.^{385,386} Patients with an elevated PTH prior to switching to a low-calcium dialysate are at greater risk for worsening hyperparathyroidism and may not tolerate the change.³⁸⁷ There are, however, biochemical data in patients suggesting that a 2.5 mEq/L calcium dialysate may have a positive effect on adynamic bone disease.³⁸⁸

Along with the reduction of dialysate calcium concentration, other strategies designed to decrease the intake of calcium have focused on active vitamin D sterols and calcium-containing phosphate binders. While reduction of the active vitamin D sterol dose is an alternative therapeutic option, the trade-off is decreased parathyroid gland suppression and possible worsening or production of 2° HPT. This has led to approaches such as intermittent active vitamin D sterol therapy, and the development of active vitamin D sterols that produce equivalent suppression of PTH but with less effective intestinal calcium absorption. Strategies to minimize calcium intake from calcium-containing phosphate binders include decreasing their use through improved control of dietary phosphorous intake, an increase in the dialysis prescription to improve phosphate clearance, and the use of calcium-containing phosphate binders that produce equivalent phosphate binding but less calcium absorption than calcium carbonate, such as calcium acetate.

Another approach to the excess dietary calcium intake is the substitution of a calcium-free phosphate binder.^{184,389-391} However, when only a resin is used, concern over appropriate calcium intake should be taken into consideration. Foodstuffs in younger children that provide calcium are often limited, since they represent sources of phosphorus too, and are therefore restricted. Such patients may benefit from a higher dialysate calcium concentration and/or calcium supplementation with a calcium-containing phosphate binder.²⁰⁴ No calcium and metal-free phosphate binder is currently approved by the FDA for use in children.

Finally, there is evidence in adult hemodialysis patients that a 2.5 mEq/L calcium dialysate

may predispose patients to arrhythmias^{392,393} although a higher dialysate calcium during hemodialysis may impair cardiac relaxation and arterial compliance.^{394,395} Similar experiences have not been reported in children, but cardiovascular disease is the leading cause of death in children.

STRENGTH OF EVIDENCE

There are no longitudinal studies evaluating different dialysate calcium concentrations in pediatric dialysis patients. There are few prospective adult studies addressing this issue. In these few adult-based studies, comparison of the data is difficult due to major differences in outcome measures, study design, and concurrent use of calcium-containing phosphate binders and active vitamin D sterols. In addition, the adult studies are characteristically in patients receiving either peritoneal dialysis or hemodialysis and these groups may not be comparable. Moreover, adult studies only include patients receiving CAPD or, less commonly, a mixture of patients receiving CAPD or CCPD, the latter being the most widely utilized form of dialysis in pediatric patients. The relevance of findings derived from CAPD patients to patients receiving CCPD is unknown.

A variety of outcome measures have been used in the adult studies. One study analyzed patient mortality, comparing a 3.5 mEq/L and 2.0 mEq/L calcium dialysate in patients receiving CAPD.³⁹⁶ There was no statistically significant difference, although both groups had a high attrition rate, making a meaningful analysis difficult. In the same study, the group that received 2.0 mEq/L calcium dialysate had fewer episodes of hypercalcemia and were able to receive more calcium carbonate.³⁹⁶ In contrast, another study of patients receiving either CCPD or CAPD found no statistically significant difference in the incidence of hypercalcemia when comparing 3.5 mEq/L and 2.0 mEq/L calcium dialysate, although the sample size was small.³⁹⁷

A number of studies have analyzed the risk of infection in patients receiving peritoneal dialysis with either a high or low dialysate calcium concentration, but none has shown an effect of the dialysate calcium concentration on the frequency of either peritonitis or exit-site infections.^{396,398,399}

Three studies have compared BMD in adult patients randomized to high- or low-calcium

dialysate. None of these studies demonstrated any effect of dialysate calcium on BMD, although all of these studies also had a small sample size.^{396,400,401}

Four studies have analyzed the effect of dialysate calcium on biochemical bone markers. Among the three studies that evaluated serum alkaline phosphatase levels, one showed a greater increase in alkaline phosphatase among the patients on 2.0 mEq/L dialysate calcium versus those on 3.5 mEq/L dialysate calcium.³⁹⁶ The other two studies showed no significant difference, but both had small numbers of patients.^{400,402} Two studies evaluated the effect of dialysate calcium concentration on bone gla protein (BGP, or osteocalcin). Both studies reporting BGP data found significantly higher levels of BGP in patients on low-calcium dialysate after about 6 months of treatment; however, at 12 months, the effect was not statistically significant in the smaller study⁴⁰³ in contrast to the larger study^{396,400} in which the effect was statistically significant at 24 months.

Three studies reported PTH levels as an outcome measure after 6 months follow-up when comparing 3.5 mEq/L calcium dialysate to 2.5 mEq/L calcium dialysate. In a study of CAPD patients, significantly higher PTH levels were noted at 6 months in patients who received the 2.5 mEq/L calcium dialysate.⁴⁰³ The remaining two studies showed no statistically significant effect of dialysate calcium on PTH, but these studies had small sample sizes with a clear trend towards higher PTH values in the low-calcium groups.^{397,400} Another study followed PTH levels in 10 dialysis patients with biopsy-proven adynamic bone disease after lowering the dialysate calcium from 3.25 mEq/L to 2.0 mEq/L.³⁶⁶ During the initial 9 months of follow-up, the mean PTH level increased from 37 to 106 pg/mL; there was no increase in the PTH level over the last 3 months of the study. In addition, hypercalcemia resolved.

Finally, there are studies that have evaluated the risk of hyperparathyroidism and the importance of calcium supplementation in patients treated with low-calcium dialysate but without use of calcium-containing phosphate binders. In adults receiving CAPD, it was shown that the use of 2.5 mEq/L calcium dialysate and aluminum

hydroxide as a phosphate binder resulted in a significant increase in the PTH level (from 259 to 405 pg/mL; $P = 0.0001$). The limitation of this study was that no patient received an active vitamin D sterol.⁴⁰⁴

CLINICAL APPLICATIONS

The use of 2.5 mEq/L calcium dialysate may help to prevent hypercalcemia, adynamic bone disease, and systemic calcification. This is recommended for children who are receiving calcium-containing phosphate binders. Alternate dialysate calcium concentrations may be required if calcium- and other metal-free phosphate binders are used. When the dialysate calcium concentration is decreased, careful monitoring of PTH is necessary to avoid the development of worsening 2° HPT and high-turnover bone disease. The risk is further increased if the PTH level is already elevated when the dialysate calcium is lowered. Patients on a 2.5 mEq/L calcium dialysate may require adjustment in activated vitamin D sterol dosing, or even a return to a higher dialysate calcium concentration. In the child with an inappropriately low PTH level (<150 pg/mL), even further reduction of the dialysate calcium concentration may be necessary in select circumstances. A reduction in the dialysate calcium concentration is also indicated in the child with symptomatic hypercalcemia, or hypercalcemia that does not respond to adjustments in the intake of oral calcium and/or active vitamin D sterol dosing.

Patients with hypocalcemia may require a 3.0 or 3.5 mEq/L calcium dialysate. This may also be necessary transiently in the setting of hungry bone syndrome following parathyroidectomy (see Guideline 15). A 3.0 mEq/L calcium dialysate may be necessary if persistent hypocalcemia (<8.5 mg/dL, corrected for serum albumin) persists despite adequate treatment with an active vitamin D sterol and there is refractory 2° HPT.

Children who are not receiving a calcium-containing phosphate binder probably do not have a positive calcium balance when they are on maintenance dialysis. They usually require a dialysate calcium concentration that allows for net absorption of calcium (≥ 3.0 mEq/L) and/or the use of a dietary calcium supplement, unless hypercalcemia is present. Such children must be monitored for adequate calcium intake and the

development of 2° HPT. It may be that the use of non-calcium, non-metal containing phosphate binder, combined with a low dialysate calcium concentration, may allow the use of higher doses of active vitamin D sterols.

LIMITATIONS

There are no pediatric studies that have addressed the topic of dialysate calcium concentration with specific attention to the correlation between calcium balance and growth. Adult studies have focused on hypercalcemia, 2° HPT, and control of serum phosphorus as outcome measures. Another limitation is the fact that there is less information available for hemodialysis patients than peritoneal dialysis patients, and no studies address the dialysate calcium concentration in patients receiving CCPD. Finally, studies are difficult to compare because of wide variations in the use of active vitamin D sterols and calcium-containing phosphate binders, and there

are limited data on the effect of the dialysate calcium concentration on long-term issues such as adynamic bone disease and systemic calcifications.

RECOMMENDATIONS FOR RESEARCH

Calcium balance studies are necessary in children receiving hemodialysis or peritoneal dialysis to determine the effect of different dialysate calcium concentrations. Research needs to determine the relative roles of dialysate calcium, active vitamin D sterols, and calcium-containing phosphate binders in the development of hypercalcemia, systemic calcifications, and adynamic bone disease. Calcium- and aluminum-free phosphate binders should be evaluated for use in children. Studies in patients not receiving calcium-containing phosphate binders should include an evaluation of higher dialysate calcium concentrations and/or oral calcium supplementation.

GUIDELINE 11. RECOMMENDATIONS FOR THE USE OF GROWTH HORMONE FOR CHILDREN WITH CKD

- 11.1** Children should have hip X-rays and a wrist bone age performed prior to initiation of GH therapy. Children with active rickets or a slipped capital femoral epiphysis should not begin GH therapy until these problems have been resolved. (EVIDENCE)
- 11.2** Growth hormone therapy should not be initiated until the PTH level is no greater than 2X the target upper limit for CKD Stages 2-4 or 1.5X (450 pg/mL) the target upper limit in CKD Stage 5 (dialysis) (see Guideline 1). (OPINION)
- 11.3** Growth hormone therapy should not be initiated until the phosphorus is no greater than 1.5X the upper limit for age (see Guideline 4). (OPINION)
- 11.4** Children receiving GH therapy in Stages 2-4 CKD should have calcium, phosphorus, PTH, and alkaline phosphatase monitored at least every 3 months during the first year of therapy. Children receiving GH therapy in CKD Stage 5 should have calcium, phosphorus, PTH, and alkaline phosphatase monitored at least every month during the first 6 months of therapy. Thereafter, interval measurements should be made according to stage of CKD (see Guideline 1). (OPINION)
- 11.5** Children receiving GH therapy should have a wrist bone age performed yearly. Hip X-rays should be performed when clinically indicated.
- 11.6** Growth hormone therapy should be stopped temporarily:
- 11.6.a** CKD Stages 2-4: If the patient has a PTH level >400 pg/mL; GH should not be restarted until the PTH level is \leq 200 pg/mL (EVIDENCE AND OPINION)
- 11.6.b** CKD Stage 5: If the patient has a PTH level >900 pg/mL; GH should not be restarted until the PTH level is \leq 450 pg/mL (EVIDENCE AND OPINION)
- 11.6.c** In all stages of CKD, if the patient develops a slipped capital femoral epiphysis or symptomatic high-

turnover renal osteodystrophy (EVIDENCE)

- 11.7** Growth hormone therapy should be stopped permanently when the epiphyses are closed.

BACKGROUND

Growth retardation is common in children with CKD, and frequently leads to decreased adult height. Metabolic acidosis, inadequate nutritional intake, and osteodystrophy may all contribute to this complication. In healthy children, GH acts by stimulating the production of insulin-like growth factor I (IGF-I), which is the primary stimulus for linear growth. In contrast, children with CKD have an inadequate response despite normal or elevated levels of GH, reflecting a state of apparent GH resistance. Possible mechanisms include: reduced GH-receptor expression especially in the liver, which decreases production of IGF-I; increased IGF-I-binding protein levels, which reduces the levels of free IGF-I; and decreased IGF-I receptor signaling.

Pharmacological doses of rhGH improve linear growth in children with CKD, although the efficacy appears to be less in children who are receiving dialysis.^{405,406} The recommended dose of rhGH, which is given as a daily subcutaneous injection, is 0.05 mg/kg/day or 30 IU/m²/week. While the response to rhGH therapy tends to decrease after the first year of treatment, there does appear to be a positive effect of the therapy on final adult height.⁴⁰⁵⁻⁴⁰⁷

For some children with CKD, an improvement in growth will occur with optimization of nutritional management and correction of metabolic acidosis.⁴⁰⁸ Malnutrition and metabolic acidosis should be corrected prior to initiating rhGH. Inadequate nutrition and metabolic acidosis diminish the effectiveness of rhGH therapy.¹⁵⁷

RATIONALE

There are complex interactions between growth, growth hormone, and bone metabolism. The use of rhGH is regularly associated with enhanced height velocity in children with CKD and poor growth, but may lead to complications, especially without careful attention to bone metabolism.

The skeletal complications of CKD in children include rickets, avascular necrosis of the femoral head,^{54,63} and slipped capital femoral epiphysis.^{49,58,409} Recombinant growth hormone therapy in children without CKD may cause slipped capital femoral epiphysis, perhaps due to an acceleration of growth.⁴¹⁰ In children with CKD, the inherent predisposition to these skeletal complications makes it necessary to screen for complications such as slipped capital femoral epiphysis,⁴⁰⁵ avascular necrosis of the femoral head,^{63,411,412} and active rickets, prior to the initiation of rhGH therapy.

Recombinant human GH may have beneficial effects on the BMD of children with CKD, although the long-term clinical consequences are not known.⁴¹³⁻⁴¹⁵ However, clinical reports suggest that rhGH therapy can have deleterious effects on bone metabolism through the worsening of 2° HPT.⁴¹⁶⁻⁴¹⁸ Hence, 2° HPT should be controlled prior to the initiation of rhGH therapy, and monitoring for this complication is necessary throughout the course of therapy. The risk of this complication is likely greatest during the first 6-12 months of rhGH therapy, and more vigilant monitoring is indicated during this period of time. Control of 2° HPT after the initiation of rhGH may require increased use of an active vitamin D sterol⁴¹⁷ in addition to the prevention of hyperphosphatemia. Therapy may need to be stopped until 2° HPT resolves. An increased alkaline phosphatase level secondary to new bone formation is expected with rhGH therapy, although a continued increase may be indicative of worsening 2° HPT.

STRENGTH OF EVIDENCE

The effectiveness of rhGH in improving linear growth in children with CKD and impaired height

velocity has been demonstrated in a placebo-controlled study.⁴⁰⁵ The clinical evidence for an interaction between rhGH therapy and bone metabolism has not been extensively studied in a prospective manner in CKD patients.

LIMITATIONS

In children with CKD, there is insufficient clinical research on rhGH therapy and bone disease. Guidelines for monitoring PTH, calcium, phosphorus, alkaline phosphatase, and X-rays are based on expert opinion, not firm clinical evidence. There is also an absence of firm clinical data supporting the levels of PTH upon which cessation and reinitiation of GH are based.

CLINICAL APPLICATIONS

These guidelines recommend close monitoring of mineral metabolism during rhGH therapy in children with CKD. A patient who has poorly controlled 2° HPT, active rickets, or a slipped capital femoral epiphysis may be at increased risk for more severe bone disease if rhGH therapy is continued. Given this potential, it is prudent not to use rhGH in children with poorly controlled osteodystrophy.

Along with appropriate monitoring of bone disease, optimal response to rhGH requires correction of malnutrition and metabolic acidosis.

RECOMMENDATIONS FOR RESEARCH

The mechanism for the variable response to GH in some children with CKD is unknown. There is little information on optimal dosing of GH in children with CKD, especially during puberty or while receiving dialysis. More information is needed on the relationship between GH and clinical outcomes beyond linear growth.

GUIDELINE 12. ALUMINUM OVERLOAD AND TOXICITY IN CKD

- 12.1** To prevent aluminum toxicity, the regular administration of aluminum should be avoided and the dialysate concentration of aluminum should be maintained at $<10 \mu\text{g/L}$. (EVIDENCE)
- 12.1.a** CKD patients ingesting aluminum should not receive citrate salts simultaneously. (EVIDENCE)
- 12.2** In CKD Stage 5, 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)
- 12.2.a** In children with CKD prior to Stage 5, serum levels of aluminum should be measured yearly if children have been exposed to aluminum for 3 months or more in the prior year. (OPINION)
- 12.2.b** Baseline levels of serum aluminum should be $<20 \mu\text{g/L}$. (OPINION)
- 12.2.c** If levels of serum aluminum are between $20\text{-}60 \mu\text{g/L}$, a search for and elimination of all sources of aluminum should be performed. (OPINION)
- 12.3** A deferoxamine (DFO) test should be performed if there are elevated serum aluminum levels ($60\text{-}200 \mu\text{g/L}$) or clinical signs and symptoms of aluminum toxicity (Table 18), or prior to parathyroidectomy if the patient has had aluminum exposure for at least 4 months or more. (OPINION) (See Algorithm 6 and Algorithm 7.)
- 12.3.a** The test is performed by infusing 5 mg/kg of DFO during the last hour of the dialysis session with a serum aluminum measured both before DFO infusion and 2 days later, before the next dialysis session. (OPINION)
- 12.3.b** The test is considered positive if the increment of serum aluminum is $\geq 50 \mu\text{g/L}$. (OPINION)
- 12.3.c** A DFO test should not be performed if the serum levels of

aluminum are $>200 \mu\text{g/L}$ to avoid DFO-induced neurotoxicity. (OPINION)

- 12.4** The presence of aluminum bone disease can be predicted by a rise in serum aluminum of $\geq 50 \mu\text{g/L}$ following DFO challenge combined with serum PTH levels of $<150 \text{ pg/mL}$ (150 ng/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 ($>15\%\text{-}25\%$) using an aluminum-specific stain, and often the presence of adynamic bone or osteomalacia. (EVIDENCE)
- 12.5** Asymptomatic patients receiving maintenance hemodialysis, with elevated levels of serum aluminum between $60\text{-}200 \mu\text{g/L}$, should be treated with removal of aluminum based gels and intensive dialysis. Treatment with DFO is optional unless desired serum aluminum levels are not achieved. (OPINION)

BACKGROUND

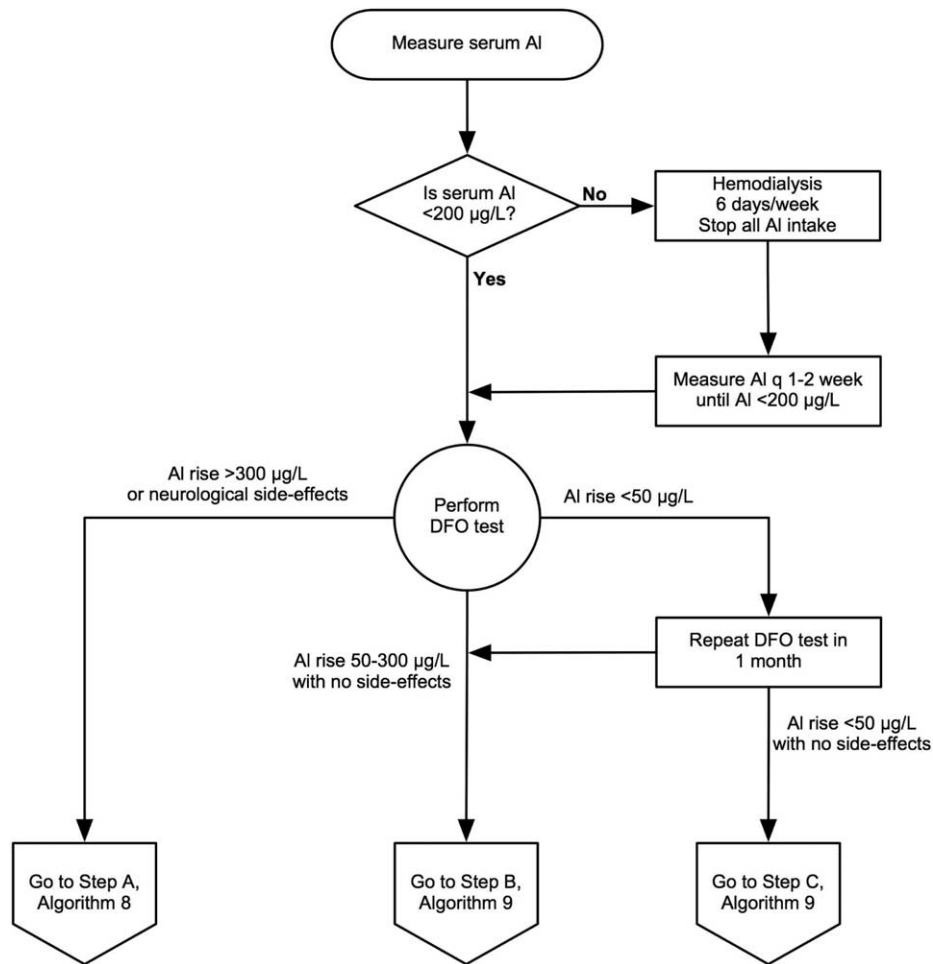
Aluminum is widely present in nature, but most aluminum salts are quite insoluble. Moreover, only a tiny fraction of ingested aluminum is absorbed; this small amount is normally excreted by the kidney so that the body burden of aluminum does not increase. When there is a markedly reduced or absent kidney 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 CKD Stage 4 patients and CKD Stage 5 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 recognized in addition to the specific biochemical methods used for their recognition. These problems have become substantially less common with the reduced use of aluminum gels as phosphate bind-

Table 18. Aluminum-Related Disorders: Features, Causes, and Considerations for Therapy

Condition	Features (Clinical Diagnosis)	Causes	Management	Special Treatment
Acute Aluminum Neurotoxicity	Acute neurological syndrome with: Altered consciousness Seizures Coma Usually progresses to death	1. Dialysate AI >200 ? g/L 2. HD patients with marked AI-loading (PAI >200 ? g/L) treated with DFO, 20-40 mg/kg 3. Stage 4 & 5 CKD patients who ingest both AI-drugs plus a salt containing citrate ^a	Measure serum AI Stop all AI intake Dialysate AI <5 ? g/L Daily dialysis High-flux dialyzer Follow algorithms for DFO testing & therapy	Standard management plus: Cause 2: Stop DFO until P _{AI} <200 ? g/L Cause 3: Withdraw all citrate ^a
Dialysis Encephalopathy	Subacute syndrome with: Speech abnormalities Defective spatial orientation Altered consciousness Seizures Often intermittent and worsens transiently after dialysis Usually slowly progressive	1. Dialysate AI >30-40 ? g/L (with dialysate AI levels of 100-200 ? g/L, symptoms appear sooner and progress more rapidly) 2. Rarely arises from AI ingestion alone, but ingestion of AI-containing agents can hasten its appearance	Measure serum AI Stop all AI intake Dialysate AI <5 ? g/L High flux dialyzer Follow algorithms regarding need for daily dialysis, DFO testing & therapy	Know level of serum AI before doing DFO test Specific electroencephalographic features can aid in the diagnosis (see text)
Aluminum Bone Disease	Insidious appearance of: Bone pain Fractures Proximal muscle weakness (Diagnosis by bone biopsy; prediction from DFO test result and intact PTH level)	1. Dialysate AI >30-40 ? g/L (with higher AI levels, symptoms appear sooner) 2. Ingestion of AI-containing agents may hasten its development	Measure serum AI Stop all AI intake Dialysate AI <5 ? g/L High flux dialyzer Follow algorithms regarding need for daily dialysis, DFO testing & therapy	Know level of serum AI before DFO test is done May coexist with dialysis encephalopathy, particularly when dialysate AI >30-40 ? g/L
Hypercalcemia	Search may reveal other features of AI toxicity when hypercalcemia appears in the absence of either: High intact PTH levels (e.g., when intact PTH >500 pg/mL), or Vitamin D therapy	1. Dialysate AI >30-40 ? g/L 2. Ingestion of AI-containing drugs Serum Ca can rise rapidly with use of Ca-based phosphate binders—probable manifestation of low bone turnover	Measure serum AI Stop all AI intake Dialysate AI <5 ? g/L 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: No evidence of iron deficiency No response to iron therapy	1. Dialysate AI >30-40 ? g/L 2. Ingestion of AI-containing drugs (uncommonly the only source of AI loading)	Measure serum AI Stop all AI intake Dialysate AI <5 ? g/L 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) (Defined by analysis of bone AI content or by a specific but arbitrary rise of P _{AI} after a DFO test)	1. Dialysate AI >20-40 ? g/L 2. Ingestion of AI-containing drugs	Measure serum AI Stop all AI intake Dialysate AI <5 ? g/L Follow algorithms regarding need for high-flux dialyzer use, DFO testing & therapy	May be subtle abnormalities on CNS testing May respond to withdrawal of all exposure to AI DFO treatment rarely needed

^a Citrate source may be Bicta™, Shohl's solution, AlkaSeltzer™, calcium citrate, or excess intake of citrate-containing juices.

Abbreviations: AI, aluminum; P_{AI}, serum aluminum; DFO, desferrioxamine; CNS, central nervous system; HD, hemodialysis



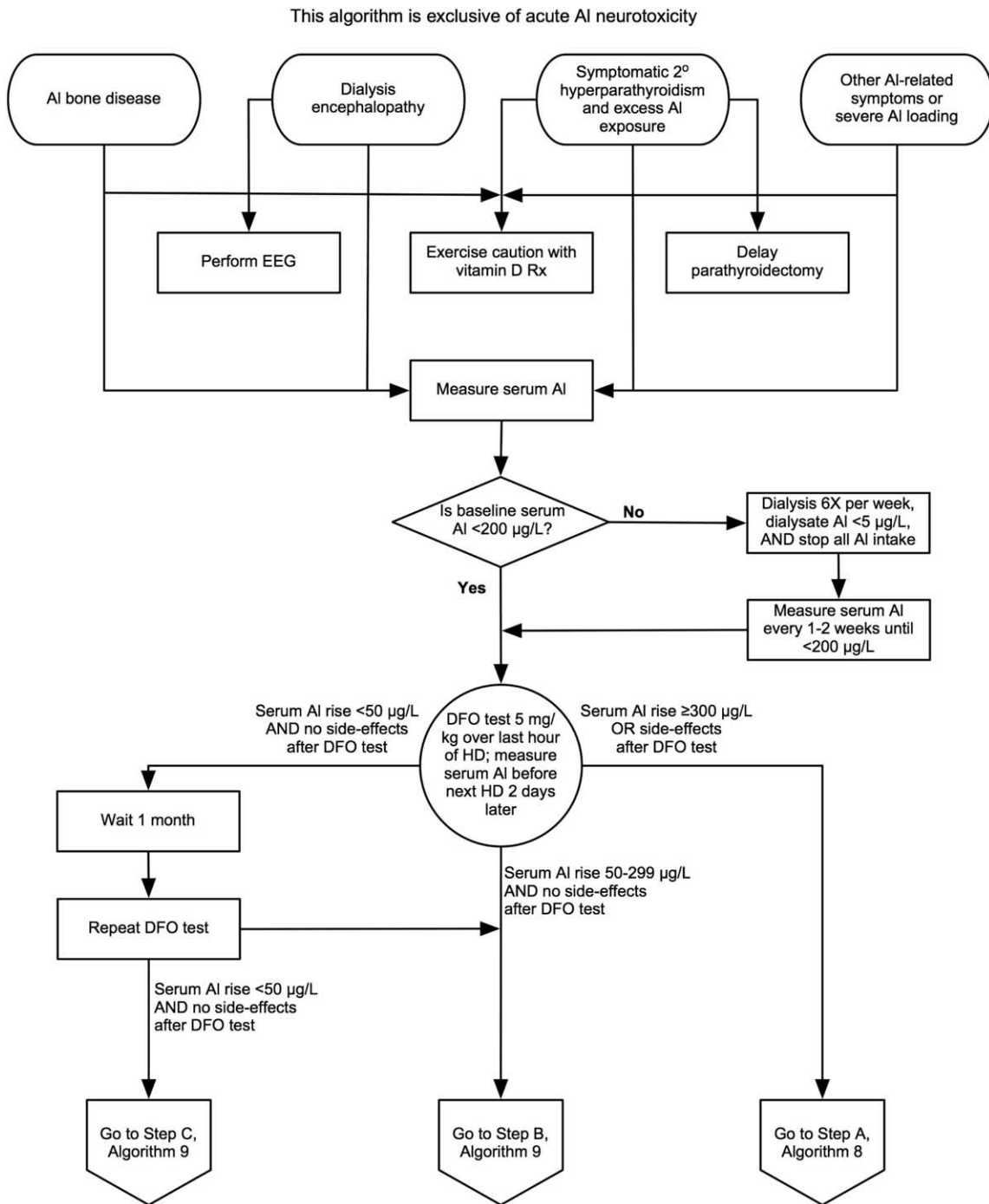
Algorithm 6. Evaluation of Aluminum Neurotoxicity

ers 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 $\text{GFR} < 30 \text{ mL/min/1.73 m}^2$ (CKD Stages 4 and 5) because aluminum that is absorbed from the gut or that enters the body from dialysate or another parenteral route⁴¹⁹ is not excreted, or is inadequately excreted by the diseased kidneys.^{420,421} When aluminum accumulates in dialysis patients, it is only slowly removed by dialysis because 90% of aluminum is

bound to serum proteins (primarily transferrin^{422,423}). The aluminum entering the body accumulates in various tissues, including bone, brain, parathyroid glands, and other organs.^{424,425} 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).^{426,427} Aluminum was then recognized as the cause of both “fracturing dialysis osteomalacia” (aluminum-related bone disease)⁴²⁷⁻⁴²⁹ and a microcytic anemia developing without iron deficiency.⁴³⁰⁻⁴³² A fulminant variant of dialysis encephalopathy, termed “acute aluminum neurotoxicity,” occurs with the sudden, marked elevation of serum aluminum levels and is commonly fatal.^{433,434}



Algorithm 7. Evaluation of Aluminum-Related Disorders: Considerations for DFO Test and Subsequent DFO Treatment

These disorders are briefly described below. The development and availability of a method to measure trace quantities of aluminum accurately in biological fluids and tissues⁴³⁵ permits detec-

tion of these disorders, and this methodology provides a means to identify patients with increased body burden of aluminum (see [Algorithm 7](#)).

Acute aluminum neurotoxicity is diagnosed based on clinical features and the elevation of serum aluminum levels to 400-1,000 $\mu\text{g/L}$. It arises from aluminum contamination of dialysate, often to levels of 150-1,000 $\mu\text{g/L}$. 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.^{433,434} The syndrome can also develop in patients with CKD Stages 3-4 (GFR <30 mL/min/1.73 m²) when they are given aluminum gels (to control hyperphosphatemia) plus sodium citrate (BicitraTM or Shohl's solution) for the correction of metabolic acidosis.^{436,437} Various citrate salts, including citric acid, sodium citrate, or calcium citrate, markedly enhance intestinal absorption of aluminum.^{203,438,439} Acute aluminum neurotoxicity can also appear in patients with large aluminum body load soon after the start of treatment with DFO in doses of 20-40 mg/kg.^{440,441} When acute aluminum neurotoxicity developed due to: a) very high dialysate aluminum levels; or b) the ingestion of both aluminum gels and citrate salts, most symptomatic patients had died.^{433,434,436,437} 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.^{440,441}

Dialysis encephalopathy is an insidious disorder with symptoms generally appearing after patients have undergone dialysis for 12-24 months or even longer.^{426,427} Initial symptoms include subtle personality changes and a progressive speech disorder, characterized by stuttering, stammering, and hesitant speech, or even total inability to talk.⁴⁴² 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 6-12 months after the onset of symptoms.⁴²⁶ The only distinctive laboratory findings were substantial elevations of serum aluminum, usually 150-350 $\mu\text{g/L}$. Findings from an electroencephalogram (EEG) differ from the general-

ized slowing noted with other causes of metabolic encephalopathy. The diagnosis of these neurological disorders rests on clinical suspicion, the finding of elevated serum aluminum levels, and the EEG features. New cases of this syndrome disappeared after the initiation of water purification using reverse osmosis.

Aluminum-related bone disease was first described in certain specific geographic areas of the U.K. and the U.S.^{428,443}; there was a suspicion of aluminum toxicity because many patients developed clinical features of dialysis encephalopathy.^{428,443} Epidemiological studies showed that this disorder—which presented with bone pain, a characteristic “waddling” gait, proximal muscle weakness, and fractures⁴³⁰—was associated with dialysate aluminum levels >100 $\mu\text{g/L}$.⁴²⁹ 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,^{444,445} and it was shown that small quantities of aluminum are absorbed from ingested aluminum gels.⁴⁴⁶ Such sporadic cases of aluminum bone disease have become less common since the use of aluminum gels was stopped or their dosage reduced substantially.^{327,447}

Patients with aluminum-related bone disease often exhibit hypercalcemia,^{448,449} and PTH levels which are variably elevated, particularly with older C-terminal or mid-region 1st PTH-IMA assays.^{449,450} 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.⁴⁵⁰ Other observations have documented the appearance or worsening of skeletal symptoms when patients with aluminum-related bone disease or aluminum loading had their PTH levels reduced by either parathyroid surgery⁴⁵¹ or by treatment with an active vitamin D steroid.^{367,452}

Indirect methods to identify aluminum-related bone disease were sought. Serum aluminum levels were elevated in afflicted patients, with values usually >100 $\mu\text{g/L}$; however, similar levels were found in many patients lacking bone biopsy evidence of aluminum-related bone disease.^{327,453}

The DFO infusion test, using DFO in doses of 20-40 mg/kg, was introduced to identify those with aluminum bone disease.^{454,455} The results indicated that the rise in aluminum correlated better with the total bone aluminum content than with surface staining of aluminum.^{456,457} Further, the presence of bone surface staining for aluminum of >15%-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.⁴⁵⁸⁻⁴⁶⁰

Population studies suggested that the combination of the increment of serum aluminum after DFO combined with PTH levels <150 pg/mL (16.5 pmol/L) provided better sensitivity and specificity to predict aluminum bone disease than the DFO test alone.^{455,461} 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.⁴⁶¹ Most information indicates that serum aluminum levels only reflect recent aluminum intake.⁴⁶²

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.^{463,464} Furthermore, the use of DFO, 20-40 mg/kg, was associated with fulminant and fatal mucormycosis in an unacceptable number of dialysis patients.⁴⁶⁵ As a consequence, there has been reluctance to use a DFO test dose of 40 mg/kg, and smaller doses have been evaluated.⁴⁶⁶⁻⁴⁶⁸

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 serum 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, and such trials can never be done.

Serum Aluminum Levels and Frequency of Monitoring

Early studies of serum aluminum measurements in dialysis patients indicated that serum aluminum levels reflect relatively recent exposure to aluminum.^{424,469} 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 serum aluminum levels is: (a) to identify excessive aluminum intake or absorption in individual patients; or (b) 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^{434,470,471}; deaths often occurred before the source was identified or corrected. Under these circumstances, dialysate aluminum levels were markedly elevated (>200 $\mu\text{g/L}$). 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 serum aluminum would be capable of detecting the slow accumulation of aluminum from oral absorption or from "modest" dialysate contamination (dialysate aluminum levels of 20-40 $\mu\text{g/L}$). Indirect evidence can be derived from studies showing the increment of serum aluminum levels during the ingestion of aluminum gels or from studies of serum aluminum levels after the withdrawal of aluminum gels. These studies suggest that serum levels change very slightly over 2-3 weeks of ingesting aluminum gels (when there is no intake of citrate). A prospective, controlled study in children and young adults undergoing peritoneal dialysis¹⁶⁶ with measurements of aluminum levels every 2 months showed a slow increase of basal (or unstimulated) serum aluminum from $22.4 \pm 30 \mu\text{g/L}$ to $57.8 \pm 13 \mu\text{g/L}$ after 12 months with intake of aluminum hydroxide, 30 mg/kg BW, a dose considered "safe" in children with CKD¹⁶⁵; this contrasts to serum aluminum decreasing from 21.6 ± 2.3 to $13.2 \pm 1.3 \mu\text{g/L}$ in the group given only calcium carbonate.¹⁶⁶ In the aluminum-gel group, serum 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 serum PTH and alkaline phosphatase, and worsening of hyperparathyroid bone disease on repeat bone biopsy after 13 months. Such data suggest that measuring serum aluminum every 4 months 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, serum aluminum fell from $105 \pm 21 \mu\text{g/L}$ to $34 \pm 11 \mu\text{g/L}$, 8 months after aluminum gels were stopped; the fall was slow with the magnitude of reduction being $-67.3 \pm 5.1\%$ of “baseline” after 8 months.²⁴⁴ In another study of individual serum aluminum values measured every 6 months in 13 patients,⁴⁷² serum aluminum levels—ranging up to $66 \mu\text{g/L}$ while the patients received aluminum gels—fell below $20 \mu\text{g/L}$ at 6 months in all except one patient who “consumed large doses of $\text{Al}(\text{OH})_3$.”

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 10-15 years in association with increased use of nonaluminum phosphate-binding agents in combination with purification of water used for dialysate.^{327,447} 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 two AlucapTM capsules thrice daily for 1 year).⁴⁷³ 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.⁴⁷⁴ Another report of 92 dialysis patients undergoing bone biopsy also showed a close relationship between

bone aluminum content and total intake of $\text{Al}(\text{OH})_3$ ($r = 0.83$)⁴⁷⁵; moreover, bone aluminum levels were trivially elevated above normal in the dialysis patients who never ingested aluminum gels. In these reports,^{474,475} 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 $>60 \mu\text{g/L}$ had bone aluminum content $>60 \text{ mg/kg BW}$.⁴⁷⁶ A study in children and young adults on CAPD¹⁶⁶ 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 $58 \pm 65 \mu\text{g/L}$ to $206 \pm 153 \mu\text{g/L}$. 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.⁴³⁸ Such intake is difficult to monitor since several over-the-counter preparations contain citrate (e.g., Alka-SeltzerTM or CitracalTM); they can be consumed without any knowledge of those treating the patient.⁴⁷⁷

Monitoring Serum Aluminum and Recognition of Aluminum Toxicity

One study reported monitoring serum aluminum twice yearly over a 4-year period, 1984-1987.⁴⁷² There were 1,193 Belgian dialysis patients in dialysis units with “negligible aluminum contamination of dialysate”; from 1986 onward, water aluminum concentrations were constantly $<3 \mu\text{g/L}$. 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 $60 \mu\text{g/L}$, there was a sensitivity and specificity for detecting aluminum bone disease of 82% and 86%, respectively. Among the total group of patients, six were diagnosed with dialy-

sis encephalopathy, based on clinical features and EEG abnormalities. The median serum aluminum was 121 $\mu\text{g/L}$ (range, 15-462 $\mu\text{g/L}$) in patients with dialysis encephalopathy compared to 42 $\mu\text{g/L}$ (range 4-140 $\mu\text{g/L}$) 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 20-40 mg/kg BW,^{463,464,478} such doses have been abandoned in favor of lower ones.⁴⁶⁶⁻⁴⁶⁸ In a study of patients from European countries, North Africa, and South America, DFO tests, both 10 mg/kg BW and 5 mg/kg BW, were given to 77 hemodialysis patients with bone biopsies. Both doses were given to 71 patients, with alternate order of giving the two doses. The indications for bone biopsy included a serum aluminum level above 60 $\mu\text{g/L}$ or in those with serum aluminum below 60 $\mu\text{g/L}$, 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 $\mu\text{g/g}$ wet weight combined with positive aluminum staining (>0%), 57 patients were classified as having aluminum overload; 15 others were classified with aluminum bone disease based on aluminum staining >15 % of bone surface and BFR reduced below normal. Using the DFO dose of 5 mg/kg BW, the combination of iPTH <150 pg/mL (150 ng/L) and an increment of serum aluminum >50 $\mu\text{g/L}$ had a sensitivity of 87% and a specificity of 95% for detecting aluminum bone disease. 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 two 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.⁴⁷⁹ Other reports utilized still lower doses of DFO: doses of 0.5, 2.5, and 5.0 mg/kg were each given to five patients with serum aluminum levels above 40 $\mu\text{g/L}$ and the change

in total and ultrafilterable aluminum measured after 44 hours.⁴⁶⁷ 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.⁴⁶⁸

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 a year of therapy.¹⁶⁶ Also, the studies that showed the close correlation between the quantity of aluminum ingested and that present in bone at postmortem⁴⁷⁴ or on biopsy⁴⁷⁶ 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 serum 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.

RECOMMENDATIONS FOR RESEARCH

Longitudinal studies with the measurement of serum aluminum at every 6 months 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 $>40 \mu\text{g/L}$, 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 “mini-doses” of DFO treatment⁴⁶⁸ would be useful to consider for a prospective trial, particularly with the growing concern about potential risks of calcium-based phosphate binders.

GUIDELINE 13. TREATMENT OF ALUMINUM TOXICITY

- 13.1** In all patients with baseline serum aluminum levels between 20-60 $\mu\text{g/L}$, a positive DFO test, or clinical symptoms consistent with aluminum toxicity (Guideline 12, Table 18) the source of aluminum should be identified and eliminated. (OPINION)
- 13.2** In symptomatic patients with serum aluminum levels $>60 \mu\text{g/L}$ but $<200 \mu\text{g/L}$ or increase in aluminum after DFO $>50 \mu\text{g/L}$, DFO should be given to treat the aluminum overload. (See Algorithm 8 and Algorithm 9.) (OPINION)
- 13.3** To avoid DFO-induced neurotoxicity in patients with serum aluminum $>200 \mu\text{g/L}$, DFO should not be given until the predialysis serum aluminum level has been reduced to $<200 \mu\text{g/L}$, which can be achieved by intensive dialysis with high-flux dialysis membrane and a dialysate aluminum level of $<5 \mu\text{g/L}$. (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 encephalopathy were observed with DFO given in doses of 20-40 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.

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.^{460,480-483} This is associated with an increase of BFR,^{460,480-482} and symptoms of proximal muscle weakness and bone pain commonly improve.^{480,484,485} Isolated reports have shown improved neurological symptoms in patients with dialysis encephalopathy.⁴⁸⁶⁻⁴⁹⁰ In these reports, DFO doses have varied from 1-6 g^{460,484} or, expressed in relation to body weight, 30-40 mg/kg BW per treatment.^{481,482,491} The treatment was given once weekly in some trials,^{460,485} and with each dialysis (thrice weekly) in others.^{481,482,491} In one study,⁴⁶⁰ the reduction of stainable aluminum and improved BFRs 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.^{483,491,492}

Side-Effects of DFO Treatment

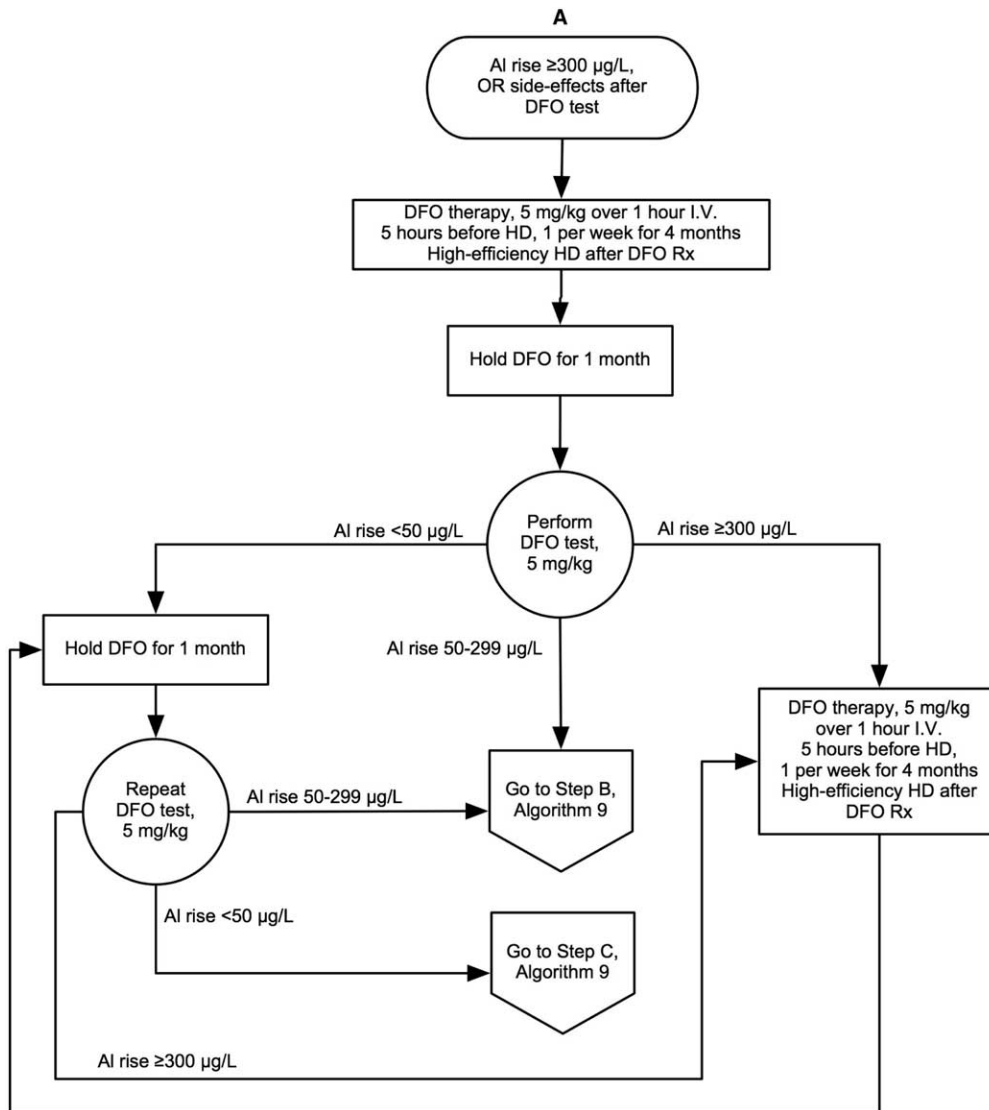
Two serious problems associated with DFO therapy are: (a) the precipitation of acute aluminum neurotoxicity; and (b) the development of mucormycosis, which is commonly fatal.

Precipitation of acute aluminum neurotoxicity

When DFO is given to patients with very high serum aluminum levels ($>200 \mu\text{g/L}$), acute and fatal aluminum neurotoxicity has been precipitated^{440,441}; 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.^{493,494} When DFO is given, it chelates iron to



Algorithm 8. DFO Treatment After P_{AI} Rise between 50-300 $\mu\text{g/L}$

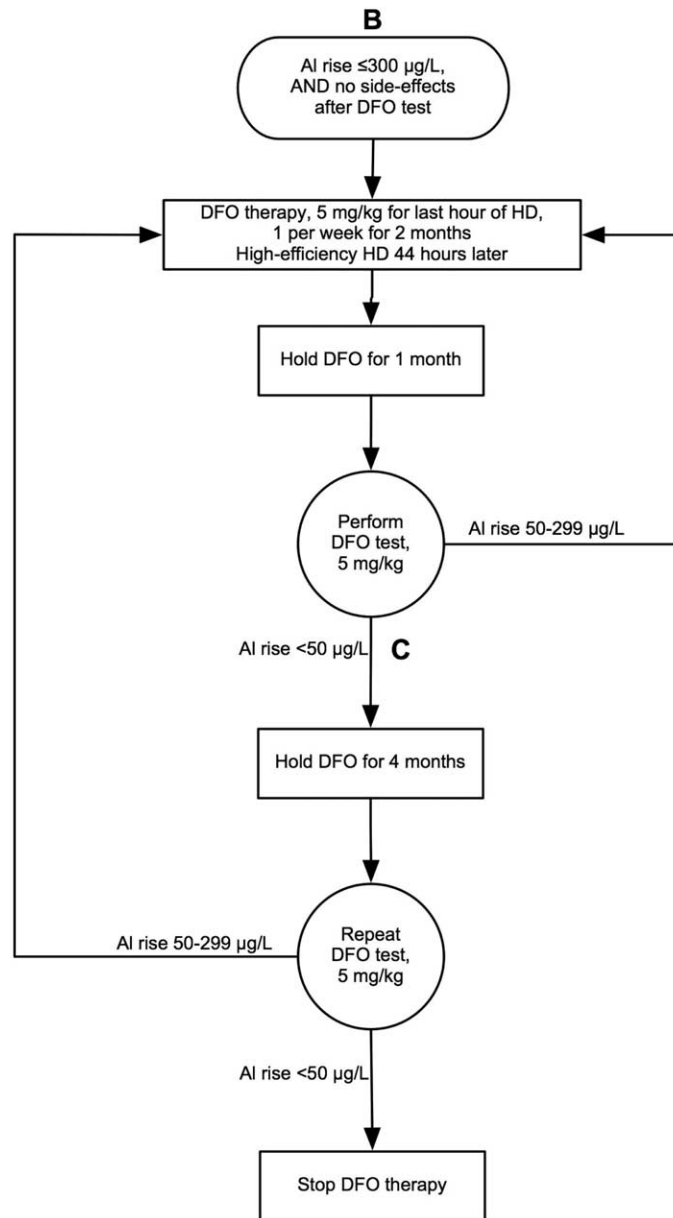
form feroxamine; the latter has a molecular weight of 714 Da and several dialysis treatments are needed to clear it from the circulation. Certain species of *Mucor*, with very low pathogenicity, exist widely in nature and are found on skin and mucous membranes; feroxamine enhances their growth and pathogenicity, thereby promoting the development of fatal disseminated or rhinocerebral mucormycosis in hemodialysis patients given DFO.^{465,495,496} Most afflicted patients had received DFO, 20-40 mg/kg BW, once or thrice weekly, with standard dialysis membranes (usually cuprophane) employed. The short-

est reported duration of treatment before infection appeared was 3 weeks.⁴⁶⁵

Methods to avoid serious side-effects

In patients exposed to high dialysate aluminum levels or with high serum aluminum levels ($>60 \mu\text{g/L}$), 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-



Algorithm 9. Subsequent DFO Treatment after P_{Al} Rise $\geq 300 \mu\text{g/L}$

containing drugs. With serum aluminum levels $>200 \mu\text{g/L}$, daily hemodialysis should be done using high-flux membranes and dialysate aluminum concentration $<5 \mu\text{g/L}$. The first “low dose” DFO test (5 mg/kg) should be done only after 4-6 weeks of such treatment, with increment of serum aluminum determining the timing of subsequent DFO treatments. If the increment of aluminum is high ($>300 \mu\text{g/L}$), 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 (aluminumoxamine).

If the increment of serum aluminum after the first DFO test is $<300 \mu\text{g/L}$ 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 3-4 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.^{465, 493}

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 DFO⁴⁹⁷; however, there are no data to support this recommendation. When CKD Stage 5 patients with aluminum overload and high serum aluminum levels have aluminum gels withdrawn and they undergo dialysis with aluminum-free dialysate (<5 µg/L), serum aluminum levels fall substantially and progressively.^{166,244,472} 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 BFR consistent with reversal of aluminum bone disease.^{498,499} The exception was two patients who had previously undergone parathyroidectomy; in these patients, there was a modest reduction of surface-stainable aluminum but BFR did not improve to normal.⁴⁹⁹ These data suggest that DFO therapy may not be needed for the treatment of such patients.

STRENGTH OF EVIDENCE

Beneficial Effects of DFO Therapy

Several trials with DFO therapy showed a reduction of surface aluminum staining,^{460,481-484} and an increase in BFR,^{460,481,482,484} after treatment periods of 8-12 months. Meta-analysis of four trials that provided data on aluminum staining and three trials with BFR are shown in [Figure 8](#) and [Figure 9](#), respectively. The doses used were variable, ranging from 20-40 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 numbers of patients who received such treatment.^{486-490,500-502}

Data on the most efficient means to clear DFO-bound aluminum from the circulation include dialysis using a high-flux membrane⁵⁰³ or hemoperfusion with a charcoal filter⁵⁰⁴; these methods remove aluminum more rapidly than standard dialysis using cuprophane membranes. A crossover study compared: a) the combination of charcoal perfusion combined with standard dialysis; b) dialysis using a high-flux membrane; and c) standard dialysis. The hemoperfusion/hemodialysis combination had a small advantage over the high-flux dialyzer,⁵⁰⁵ 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.^{506,507} The intramuscular administration of DFO, as it is sometimes given in hematological disorders, may provide a convenient method 4-5 hours before dialysis when an intravenous route is not available.⁵⁰⁷

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.⁵⁰⁸ 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 µg/L). The initial basal aluminum levels were 506 ± 253 µg/L [mean ± SD; range, 104-1,257 µg/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 clear-

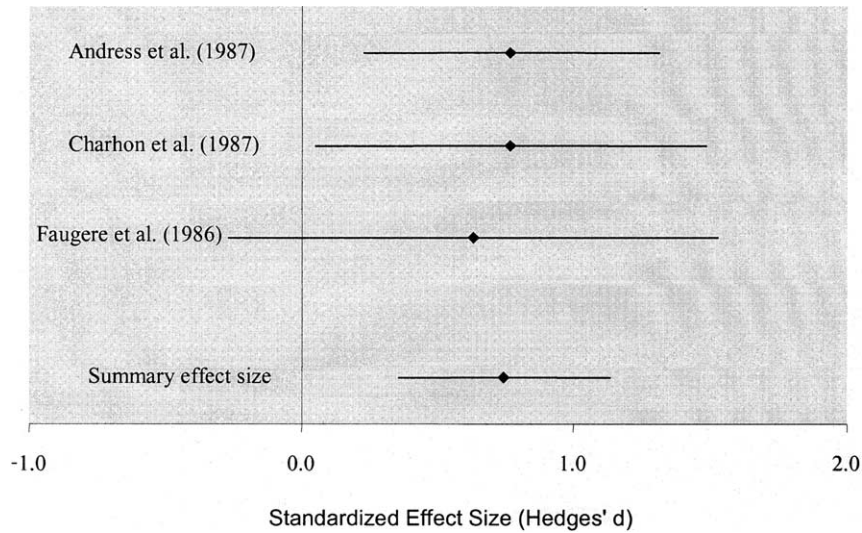


Fig 8. Individual Study and Summary Effect Sizes for the Effect of DFO Therapy on Bone Formation Rate

ance 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 $506 \pm 253 \mu\text{g/L}$ to $121 \pm 46 \mu\text{g/L}$ (mean \pm SD). The first DFO infusion test (5 mg/kg) was given during the last hour of dialysis; the increment of serum aluminum was $300 \mu\text{g/L}$ in

11 patients, seven of whom developed neurological symptoms (headache, hallucinations, or myoclonic jerks) and two developed ophthalmological symptoms (transiently blurred vision) after the DFO test; 30 patients had increments of serum aluminum $<300 \mu\text{g/L}$, only three of whom had developed neurological symptoms. These three symptomatic patients and the 11 patients with a post-DFO aluminum increment $<300 \mu\text{g/L}$ received DFO treatment given via a periph-

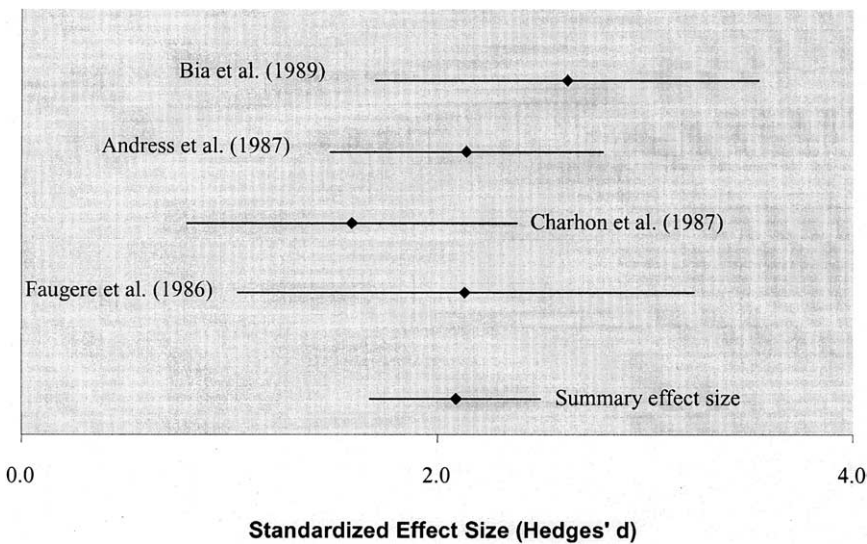


Fig 9. Individual Study and Summary Effect Sizes for the Effect of DFO Therapy on Bone Surface Aluminum Stain

eral 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 serum aluminum was $<60 \mu\text{g/L}$ and the increment after DFO was $<50 \mu\text{g/L}$, 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 cross-over 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 serum 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 serum PTH levels in both groups.⁵⁰⁹

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,^{465,495,496,510,511} while reports of mucormycosis among dialysis patients not receiving DFO are unusual.⁴²⁰ An international registry collected 59 cases of mucormycosis among dialysis patients⁴⁶⁵; 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.^{493,494,512} Increased susceptibility to mucormycosis was found to occur because of persistence of significant concentrations of feroxamine, the iron chelate with DFO, in CKD 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.⁴²⁰ The clearance of feroxamine by a standard dialyzer is quite low, and three to four dialysis treatments may be required to clear this substance from the blood.⁵⁰⁵

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 1986-1989 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 U.S. with interest in aluminum toxicity and use of DFO, no recent cases of mucormycosis associated with DFO therapy could be identified.⁵¹³

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, aluminoferoxamine, are removed more effectively.⁵⁰³ Hemoperfusion with a sorbent cartridge has also been very effective⁵⁰⁵; however, such cartridges are not presently available in the U.S. In addition, there has been a reduction of the DFO dose from 20-40 mg/kg to 5-10 mg/kg, with the DFO dose given 4-6 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.⁵⁰⁸ Also, DFO should only be given every 7-10 days,⁵⁰⁸ with three to four dialysis procedures between each dose of DFO.⁵⁰⁸ 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 10-15 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 20-40 mg/kg BW. Despite this, the numbers of patients in prospective trials were 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.⁴⁹⁹ 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 one death (due to hyperkalemia) among 42 patients who followed the recommended protocol.⁴³⁴ Small studies suggest that doses of DFO as low as 1 mg/kg and 0.5 mg/kg can raise the ultrafilterable aluminum in serum, 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 evidence 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 DFO⁴⁹⁷ has not been critically evaluated. There was a small number of dialysis patients with elevated serum aluminum levels and histological features of aluminum bone disease, who had repeat biopsies approximately 12 months after all aluminum was withdrawn.^{498,499} The close association between the

reduction of surface stainable aluminum and the improvement of bone formation and mineralization rate⁴⁹⁹ 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 parathyroidectomy⁴⁹⁹ is consistent with failure of bone histomorphometry to improve in DFO-treated patients with symptomatic aluminum bone disease.⁴⁶⁰

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 20-40 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.¹⁷⁴

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 serum aluminum levels during such treatment.⁴⁶⁸ Others have shown that DFO in doses of 0.5-1.0 mg/kg increases the ultrafilterable (and hence the dialyzable) level of serum aluminum in dialysis patients with elevated serum aluminum levels.⁴⁶⁷ 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 binders.

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 14. TREATMENT OF BONE DISEASE IN CKD

The treatment of bone disease in CKD is based on its specific type. This Guideline encompasses three parts: Guideline 14A deals with high-turnover bone disease; Guideline 14B with rickets/osteomalacia; and Guideline 14C with adynamic bone disease.

GUIDELINE 14A. HYPERPARATHYROID (HIGH-TURNOVER) BONE DISEASE

- 14A.1** In CKD patients who have serum PTH levels >70 pg/mL (Stages 2-3) or >110 pg/mL (Stage 4), dietary phosphate intake should be modified according to Guidelines 5 and 6, and dietary calcium should be modified according to Guideline 7. Nutritional vitamin D insufficiency or deficiency should be corrected according to Guideline 8. If a repeat 1st PTH-IMA after 3 months of dietary intervention shows that PTH levels remain elevated, then patients should be treated with calcitriol or 1- α -vitamin D₂ (EVIDENCE), to prevent or ameliorate high-turnover bone disease.
- 14A.2** In CKD Stage 5 patients who have elevated serum PTH levels (>300 pg/mL) despite modification of dietary phosphate intake according to Guidelines 5 and 6, calcitriol or 1- α -vitamin D₂ (EVIDENCE) should be used to reverse the bone features of hyperparathyroidism (i.e., high-turnover bone disease).

BACKGROUND

In the untreated patient, studies in adults and children with CKD Stage 5 have shown that high-turnover bone disease is often associated with serum levels of PTH >300 pg/mL. High-turnover bone disease may also be seen at similar PTH values despite treatment with daily low-dose calcitriol or intermittent high-dose calcitriol therapy in CKD Stage 5.

RATIONALE

The understanding of bone disease in CKD has evolved dramatically over the years. The recognition that hyperparathyroidism is a compli-

cation of kidney failure may predate by many years the initiation of dialysis treatment. Early studies of osteodystrophy focused largely on understanding the pathophysiology and the prevention of severe hyperparathyroid bone disease. The development of more specific 1st PTH-IMA facilitated more accurate classification of the different forms of renal osteodystrophy.

LIMITATIONS

See the corresponding section in Guidelines 8A and 8B. There are no published data on the correlation between PTH levels and bone histology in children with CKD Stages 2-4. At this time, there are no data to support the use of bisphosphonates in children with renal osteodystrophy (see Guideline 16).

RECOMMENDATIONS FOR RESEARCH

Studies are needed to evaluate the changes in bone histology, iPTH, and PTH fragments with the available vitamin D analogs and other therapeutic approaches for the treatment of renal osteodystrophy. The relationship among iPTH, PTH fragments, vitamin D therapies, and linear growth needs to be established in children with CKD. The influence of GH in osteodystrophy is incompletely known at this time and needs further study. Randomized clinical trials should be conducted in order to determine the effects of vitamin D therapies on bone histology and growth in children on maintenance dialysis.

GUIDELINE 14B. RICKETS/OSTEOMALACIA

- 14B.1** Rickets and osteomalacia due to aluminum toxicity should be prevented in dialysis patients by maintaining aluminum concentration in dialysate fluid at <10 μ g/L and by avoiding the use of aluminum-containing compounds. (OPINION)
- 14B.2** Rickets and osteomalacia due to vitamin D deficiency should be treated according to Guideline 7. (EVIDENCE)
- 14B.3** Rickets and osteomalacia due to hypophosphatemia should be treated with neutral sodium phosphate salts. Concomitant active vitamin D therapy should be considered. See Guidelines 7 and 8. (EVIDENCE)

BACKGROUND

As aluminum accumulates on bone surfaces, it impairs bone formation, leading to either rickets, 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 pre-existing tubular defects of phosphate depletion, or vitamin D₂ or D₃ deficiency. While the incidence of aluminum bone disease has been greatly reduced it still may occur and its diagnosis and treatment should be addressed. Osteomalacia may occur in the absence of aluminum exposure and is often related to hypophosphatemia or vitamin D deficiency.

RATIONALE

In the late 1970s, it was documented that rickets or osteomalacia occurred in patients with CKD secondary to aluminum intoxication. The clinical manifestations in children include bone pain, bone deformities, deranged mineral ion homeostasis, and reduced linear growth. In children, aluminum toxicity may cause neurological manifestations, including seizures, microcephaly, development delays, and encephalopathy. When marked aluminum loading occurs, brain abnormalities develop which, if untreated, are usually lethal. Treatment with a chelating agent, such as DFO, may improve patients' bone disease and neurological abnormalities in children with CKD. Rickets and osteomalacia occur in children with CKD in the absence of aluminum intoxication. 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, hypophosphatemia or metabolic acidosis, 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 rickets and

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 of its treatment are possible.

CLINICAL APPLICATION

A DFO challenge test (see Guidelines 12 and 13) can often identify aluminum overload, but is not specific for the presence of bone lesions. The 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 to the underlying mechanism. Treatment should be continued until clinical laboratory indicators of osteomalacia and the associated metabolic acidosis have disappeared.

RECOMMENDATIONS FOR RESEARCH

Aluminum accumulation in bone has become much less frequent as the use of aluminum-containing phosphate binders has declined. Unfortunately, the calcium-based binders which have largely replaced aluminum-containing phosphate binders may be associated with calcium overload, hypercalcemia, and vascular calcification. Studies need to evaluate the safety and efficacy of non-metal-containing phosphate binders.

GUIDELINE 14C. ADYNAMIC BONE DISEASE

14C.1 In CKD Stage 5, adynamic bone disease not related to aluminum (as determined either by bone biopsy or suggested by PTH <150 pg/mL) should be treated by allowing serum levels of PTH to rise in order to increase bone turnover. (OPINION)

14C.1.a The increase in PTH levels can be accomplished by discontinuing treatment with activated vitamin D analogs, decreasing or eliminating the use of calcium-based phosphate binders, reducing the dialysate calcium concen-

tration (see Guideline 8) (EVIDENCE), and/or using a metal-free phosphate binder. (OPINION)

BACKGROUND

The prevalence of adynamic bone disease has increased with more frequent use of vitamin D analogs and calcium-based phosphate binders. Adynamic bone disease has been reported in children and adolescents receiving hemodialysis or peritoneal dialysis. The clinical sequelae of adynamic bone disease are the risk of bone fractures, impairment of linear growth, and the inability of adynamic bone to contribute to overall mineral ion homeostasis.

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 as demonstrated by bone histomorphometric studies.⁵¹⁴ The disease has been ascribed to insufficient levels of PTH (<150 pg/mL in patients with CKD Stage 5) due to the use of active vitamin D analogs, chronic positive calcium in excess of that needed for growth, or following subtotal parathyroidectomy.^{22,327,515}

Although blood levels of PTH (<150 pg/mL) strongly suggest the presence of adynamic bone disease, adynamic bone disease may occur at higher levels of PTH often associated with hypercalcemia or hyperphosphatemia. Bone biopsy may therefore be required to establish or rule out the diagnosis of adynamic bone disease. Accumulating data in adults with CKD Stage 5 suggest that evidence for adynamic bone disease by histology is not benign. In this dialysis population, there is a four-fold increase in hip fracture risk compared to the general population.^{516,517} Age, duration of dialysis, female sex, and diabetes appear to confer an increased risk for fracture in such patients. In children with CKD Stage 5, the clinical manifestations of adynamic bone disease are not well characterized. The single study in children that included bone histomorphology demonstrated that adynamic bone disease in the setting of high-dose calcitriol therapy was associated with impaired linear growth.⁵¹⁸ The relatively inert, adynamic bone does not

allow an appropriate deposition of calcium into bone and thus leads to impaired regulation of blood calcium. Because of the inability to deposit calcium into bone, calcium loading (for example, by oral calcium-containing phosphate binders or by loading through dialysate calcium) often leads to marked hypercalcemia. In addition, with the failure of the bone to accrue calcium, other tissues such as the vascular system become vulnerable to its accumulation in the form of metastatic calcification. Indeed, it has been demonstrated that a greater degree of arterial calcification in those patients with adynamic osteodystrophy is also evident in patients with low bone turnover.³⁷³

STRENGTH OF EVIDENCE

Calcium kinetic studies clearly show that adult CKD Stage 5 patients with adynamic bone disease have decreased calcium accretion in bone, despite the fact that intestinal calcium absorption is similar in these patients and those with high bone turnover.²⁰⁷ There are no controlled studies on treatment of adynamic bone disease, though its consequences are troublesome. Indeed, more severe growth retardation has been described in those children that developed adynamic bone after treatment with calcium-containing binders and intermittent calcitriol therapy. Recommendations for therapy should be of the current understanding of the pathogenetic mechanisms of the bone abnormalities as well as the abnormalities of the growth plate described in experimental models of adynamic bone.

Bone densitometry and its relationship to fracture is incompletely defined in adult CKD Stage 5 patients, though data continue to suggest that bone density is reduced and fracture rates increased. In the healthy population, there is a strong association between decreased bone density and fractures. While adult patients with osteoporosis and normal renal function benefit from treatment with intermittent PTH injections, it is not clear whether this approach would be effective in the context of CKD Stage 5. Furthermore, treatment with daily PTH injections should not be pursued in pediatric patients with CKD due to the risk of osteosarcoma, which was observed in rats treated intermittently with extremely high doses of synthetic PTH (see package insert, Forteo™, Lilly Laboratories).

LIMITATIONS

Much of the data described above suggest a relationship between relatively low PTH levels, bone mass, and low bone turnover in the adult dialysis population, leading to an increased risk for fractures. In addition, a greater degree of arterial calcifications has been described in adult patients treated with hemodialysis and adynamic bone. However, there are no published data of increased fracture rate in children, but adynamic bone disease appears to be associated with further impairment in longitudinal growth in children with CKD Stage 5 after treatment with calcium-containing binders and intermittent calcitriol therapy.³¹²

CLINICAL APPLICATION

Adynamic bone should be treated by increasing bone turnover by allowing the serum PTH concentration to rise to 200-300 pg/mL. This can best be accomplished by discontinuation of the use of active vitamin D analogs and lowering doses of calcium-based phosphate binders as described in Guideline 8. The lowering of bath calcium (1.0-2.0 mEq/L) has also been suggested as a possible approach. One published study of

this therapy in a small number of adult patients undergoing peritoneal dialysis did lead to a substantial increase in PTH levels³⁶⁶; however, this approach must be considered experimental at this point. Furthermore, the use of non-calcium, non-metal containing phosphate binders should be considered in those patients especially with evidence of vascular calcifications, in order to diminish the potential role of the exogenous calcium load in its progression.

RECOMMENDATIONS FOR RESEARCH

The long-term safety of lower dialysate calcium concentration for treatment of adynamic bone disease needs to be carefully studied. The use of new phosphate binders should be carefully studied in pediatric patients with CKD. Moreover, agents with a potential to increase bone turnover such as rhGH or PTH need to be studied for the treatment of adynamic bone disease in children with CKD Stage 5. Manipulation of the calcium receptor with either calcilytics (which stimulate PTH release and are not yet FDA approved) or calcimimetics (which suppress PTH, but may lead to intermittent PTH release) may also become an important therapeutic approach.

GUIDELINE 15. PARATHYROIDECTOMY IN PATIENTS WITH CKD

- 15.1** Parathyroidectomy should be considered in patients with severe hyperparathyroidism (persistent serum levels of PTH >1,000 pg/mL [1,000 ng/L]), and disabling bone deformities associated with hypercalcemia and/or hyperphosphatemia that are refractory to medical therapy. (OPINION)
- 15.2** Effective surgical therapy of severe hyperparathyroidism can be accomplished by subtotal parathyroidectomy or total parathyroidectomy with parathyroid tissue autotransplantation. (EVIDENCE)
- 15.2a** 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.
- 15.3** In patients who undergo parathyroidectomy the following should be done:
- 15.3.a** In the 72 hours prior to parathyroidectomy, consideration should be given to administration of calcitriol or other active vitamin D sterols, to lessen postoperative hypocalcemia.
- 15.3.b** The blood level of ionized calcium should be measured every 4-6 hours for the first 24 hours after surgery, and then less frequently until less stable. (OPINION)
- 15.3.c** If the level of ionized calcium falls below normal (<1 mM or <4 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 1-2 mg elemental calcium per kilogram body weight per hour and adjusted to maintain an ionized calcium in the normal range (1.15-1.36 mM or 4.6-5.4 mg/dL). (OPINION) A 10-mL ampule of 10% calcium gluconate contains 90 mg of elemental calcium.
- 15.3.d** The calcium infusion should be gradually reduced when the level of ionized calcium attains the normal range and remains stable. (OPINION)
- 15.3.e** When oral intake is possible, the patient should receive elemental calcium 1-2 g, three times a day, as well as calcitriol 1-2 µg/day, and these therapies should be adjusted as necessary to maintain the level of ionized calcium in the normal range. (OPINION)
- 15.3.f** 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)
- 15.4** Imaging of parathyroid glands with ⁹⁹Tc-Sestamibi scan, ultrasound, CT scan, or Magnetic Resonance Imaging (MRI) should be done prior to re-exploration parathyroid surgery. (OPINION)

BACKGROUND

Hyperparathyroidism is a common complication of CKD 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 2° HPT. Accordingly, some patients require surgical parathyroidectomy to correct the problem. Hyperparathyroidism is currently most often assessed using PTH measurements from 1st PTH-IMA. Newer assays which are more specific for the 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. The presence and magnitude of the disabling bone deformities should be an additional consideration in the decision for parathyroidectomy. (See Table 1 in Introduction.) In these circumstances, surgical ablation of the parathyroid glands can provide effective therapy. The efficacy of surgical parathyroidectomy is well documented.⁵¹⁹⁻⁵²⁵ 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.⁵¹⁹⁻⁵²⁵ 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, a portion of the smallest parathyroid gland (i.e., one less likely to have severe nodular hyperplasia) should be reimplanted. 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.⁵²⁶ Parathyroid imaging is not usually required, preoperatively, although it may be helpful in cases where re-exploration is required, such as persistent hypercalcemia or recurrent hyperparathyroidism.⁵²⁷⁻⁵²⁹ Of the methods

used, ⁹⁹Tc-sestamibi with or without subtraction techniques appears to have the highest sensitivity, although MRI, CT, and ultrasound have also been regarded to be useful.^{526-528,530-538}

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 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.⁵³⁹

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. There are no data about the use of calcimimetics in children with CKD Stage 5.

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 PTH assays 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 with calcimimetic agents.

GUIDELINE 16. METABOLIC ACIDOSIS

16.1 In CKD Stages 1-5, the serum level of total CO₂ should be measured.

16.1.a The frequency of these measurements should be based on the stage of CKD as shown in Table 19. (OPINION)

16.2 In patients >2 years of age, serum levels of total CO₂ should be maintained at ≥22 mEq/L (22 mmol/L); in neonates and young infants below age two, serum levels of total CO₂ should be maintained at ≥20 mEq/L (20 mmol/L). (EVIDENCE) If necessary, supplemental alkali salts should be given to achieve this goal. Elevation of the bicarbonate concentration in the hemodialysis bath is an additional or alternative strategy. (OPINION)

BACKGROUND

Acidosis is a common component of many diseases of the kidney that affect the proximal or distal tubules, and is often present even when glomerular function is relatively intact (CKD Stages 1-2). Such diseases include inherited and genetic tubulopathies or acquired dysfunction of the tubules through, for example, the presence of obstructive uropathies or recurrent pyelonephritis. As glomerular function declines, acidosis may become more common and is uniformly present in CKD Stages 4-5. There is a developmental regulation of serum bicarbonate, such that values of ≥20 mEq/L (20 mmol/L) are normal for neonates and infants below two years of age, and values of 22 mEq/L (22 mmol/L) represent the lower limit of normal after age 2 years.

Chronic metabolic acidosis is a major component of the linear growth failure associated with CKD in infants and children with relatively pre-

served GFR. The mechanisms whereby acidosis blunts linear growth involve its effects on bone mineral on the growth hormone-IGF-I axis, and on renal synthesis of 1,25-(OH)₂D, among others.

Classical studies in humans demonstrated the powerful effect of chronic metabolic acidosis, induced experimentally or resulting from CKD, on the loss of bone mineral. 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. Cellular functions within bone are changed by chronic metabolic acidosis, such that matrix gene expression associated with osteoblastic activity is inhibited, while osteoclastic activities are increased. Additionally, the trophic effects of the growth hormone-IGF-I axis on bone growth and structure are blunted with chronic metabolic acidosis. Chronic metabolic acidosis reduces the kidney proximal tubule synthesis of 1,25(OH)₂D, and may thereby limit the supply of calcium absorbed from the diet. Chronic metabolic acidosis alters the homeostatic relationships between blood ionized calcium, PTH, and 1,25(OH)₂D such that bone dissolution is exaggerated.

Chronic metabolic acidosis contributes, in part, to the renal osteodystrophy in patients with CKD. Rickets is the most common manifestation of chronic metabolic acidosis in the bone of children with CKD Stages 1-3. The rickets may be cured by provision of alkali salts in some cases, but require supplemental vitamin D or its analogs in others. In adults,

Table 19. Frequency for Measurement of Serum Levels of Total CO₂

CKD Stage	GFR Range mL/min/1.73 m ²	Frequency of Measurement
1	>90	At least every 12 months
2	60-89	At least every 12 months
3	30-59	At least every 6 months
4	15-29	At least every 3 months
5	<15	At least every 3 months
	Dialysis	At least every month

bone fractures are a relatively common manifestation of chronic metabolic acidosis. More recent studies in adults have demonstrated a reduction in bone mineral density, and in BFRs, by dynamic histomorphometry.⁵⁴⁰ Additional 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 and successful treatment restores linear growth potential.⁵⁴¹

RATIONALE

There is scant evidence *per se*, in patients with kidney failure (adult or pediatric) and undergoing maintenance dialysis, that either amelioration or improvement of renal osteodystrophy occurs through elimination of chronic metabolic acidosis. However, a cross-sectional study of 76 adult patients studied with percutaneous, transiliac bone biopsy demonstrated that those with a normal biopsy result had a serum bicarbonate level ≥ 23 mM while those with either mild or advanced mixed osteodystrophy had serum bicarbonate levels < 20 mM.⁵⁴² It appears that the absence of acidosis renders therapy of renal osteodystrophy with a vitamin D metabolite more effective. Correction of metabolic acidosis allows normalization of linear growth in children with isolated renal tubular acidosis.⁵⁴¹

CLINICAL APPLICATIONS

Measurement and monitoring of the serum bicarbonate level is warranted in patients with proximal or distal tubulopathies or acquired tubulo-interstitial renal disease (such as from obstructive uropathies or recurrent pyelonephritis) regardless of glomerular filtration rates, in CKD Stages 1-5, and with maintenance dialysis. Measures to keep the bicarbonate level ≥ 22 mM (20 mM for the neonate and young infant below two years of age) are warranted for improvement in bone histology, and to improve linear growth. The clinician is reminded that the use of exogenous alkali salts containing citrate increases the absorption of aluminum in patients, and should be avoided as GFR declines into CKD Stage 3 and below (see Guideline 12).

RECOMMENDATIONS FOR RESEARCH

Areas for future research into the effects of chronic metabolic acidosis and renal osteodystrophy include a fuller understanding of the calcium-vitamin D-PTH and the growth hormone-IGF-I axes in humans with CKD at the level of bone, especially at the growth plate. The role of newer therapeutic agents for treatment of osteoporosis in adults, such as bisphosphonates, selective estrogen-receptor modulators, or isoflavones in patients with CKD, with or without chronic metabolic acidosis, remains unknown.

GUIDELINE 17. BONE DISEASE IN THE PEDIATRIC KIDNEY TRANSPLANT RECIPIENT

- 17.1 Serum levels of calcium, phosphorus, total CO₂ and PTH should be monitored following kidney transplantation. (OPINION)**
 - 17.1.a The frequency of these measurements should be at least as often as shown in Table 20. (OPINION)**
 - 17.1.b Six months after transplantation, the frequency of measurements should follow the recommendations of Table 2, Guideline 1, depending on the stage of CKD.**
- 17.2 The care of osteodystrophy in kidney transplant patients reaching CKD Stage 2 and below should follow the guidelines established for native CKD. (OPINION)**
- 17.3 Kidney transplant recipients who develop persistent hypophosphatemia (below the age-appropriate lower limits) should be treated with phosphate supplementation. (OPINION)**
- 17.4 To minimize bone mass loss and osteonecrosis, the lowest effective dose of glucocorticoids should be used. (OPINION)**

BACKGROUND

Successful renal transplantation corrects many of the underlying abnormalities contributing to bone disease in children with CKD. However, hypophosphatemia, pre-existing hyperparathyroidism, and glucocorticoid therapy may impair healing of renal bone disease and lead to bone loss. In addition, progressive damage to the transplanted kidney will result in CKD and bone and mineral disorders comparable to the effects of CKD in the native kidney. Therefore, the kidney transplant recipient is at risk for multifactorial, progressive bone disease.

Hypophosphatemia

Hypophosphatemia is a frequent, early complication of renal transplantation. The primary cause is increased urinary phosphate loss and persistent hyperparathyroidism.⁵⁴³ A recent series in adults demonstrated that as many as 93% of patients develop moderate to severe hypophosphatemia (serum phosphate concentration 0.9-2.25 mg/dL), an average of 5 weeks following transplantation.⁵⁴⁴ In the setting of good allograft function, gradual decreases in serum PTH and improvements in allograft tubular function result in normalization of serum phosphate concentrations within months. Hypophosphatemia may persist as a late complication in patients with prolonged hyperparathyroidism.¹⁸⁸ Numerous adult studies have demonstrated incomplete resolution of hyperparathyroidism and persistently increased bone turnover in long-term recipients with good renal function.^{545,546}

Corticosteroid-Induced Osteopenia

The pathogenesis of corticosteroid-induced bone loss is multifactorial and has been reviewed extensively in the adult literature.⁵⁴⁷ The primary mechanism of glucocorticoid-induced osteopenia is decreased bone formation by osteoblasts due to a decreased work rate and a decreased active life span of osteoblasts. Animal data from a rat model suggest that cyclosporine may induce a high-turnover osteopenia with loss of trabecular bone,⁵⁴⁸ potentially compounding the bone toxicities of glucocorticoid therapy and hyperparathyroidism. It is well-recognized that corticosteroids result in rapid loss of trabecular bone in adults; however, the effects of corticosteroids, cyclosporin A and tacrolimus on trabecular and cortical bone mineral accretion during growth are not known.

Table 20. Frequency of Measurement of Calcium, Phosphorus, PTH, and Total CO₂ after Kidney Transplantation

Parameter	First Week	First 2 Months	From 2-6 months
Calcium	Daily	Weekly	Monthly
Phosphorus	Daily	Weekly	Monthly
PTH	Optional	Once at one month, thereafter optional	Optional if normal initially
Total CO ₂	Daily	Every 1 week	Monthly

RATIONALE

Hypophosphatemia

Severe hypophosphatemia may result in hemolytic anemia, impaired cardiac contractility and respiratory insufficiency. Therefore, it is common practice to supplement with oral phosphate salts in patients with severe hypophosphatemia. In adults, a preliminary study assessed phosphate replacement for moderate hypophosphatemia in the early post-transplant period, and the impact on serum calcium, PTH, and acid/base metabolism. Oral supplementation with neutral sodium phosphate (Na_2HPO_4) effectively corrected hypophosphatemia, increased muscular ATP and phosphodiester content, and improved renal acid excretion without any adverse effect on serum PTH levels.

CKD in the Transplanted Kidney

There are no available data on the clinical sequelae of bone disease in children with progressive CKD due to allograft failure in the setting of renal transplantation. However, progressive CKD in the allograft will likely set in motion the same pathophysiological abnormalities observed with CKD in the native kidney. In addition, the combination of glucocorticoid-induced suppression of bone formation and hyperparathyroid-induced increases in bone resorption result in uncoupling of bone. This likely has particularly devastating effects on bone modeling and bone mineral accrual during growth. Glucocorticoids may impair gastrointestinal calcium absorption, resulting in negative calcium balance and exacerbating 2° HPT. Therefore, the child with progressive CKD and a kidney transplant requires ongoing assessment and treatment of serum calcium, phosphorus, PTH, serum bicarbonate and 25(OH)D concentrations, consistent with the guidelines for CKD in the native kidney.

STRENGTH OF EVIDENCE

Hypophosphatemia

We are unaware of any investigations examining the incidence of hypophosphatemia in the weeks immediately following transplantation in children. One study recently described a series of 16 children evaluated at 3, 6, and 12 months following transplantation. Serum phosphate concentrations were not decreased at these inter-

vals.⁵⁴⁹ The median serum phosphate concentration at 3 months was 3.99 mg/dL, range 3.16–5.54 mg/dL.

Impaired Bone Mineralization Following Transplantation in Children

While there are numerous DXA studies of bone following transplantation in children, only one included bone histomorphometry.³⁷² This study evaluated 47 children and adolescents with stable renal function an average of 3.2 years after transplantation.³⁷² Eleven of 47 children had PTH values >65 pg/mL and four exceeded 100 pg/mL. Bone biopsies revealed that 31 transplant recipients had normal bone formation, 11 had mild hyperparathyroidism, and five had adynamic skeletal lesions. Neither the interval since transplantation, serum PTH, serum creatinine, nor the cumulative prednisone doses differed according to histological subgroups. Despite normal bone formation rates (BFRs) in many children, all three subgroups demonstrated increased eroded bone perimeter, increased osteoid area, and increased osteoid perimeter. Hyperparathyroidism improved or resolved after transplantation in all 14 subjects with high-turnover bone disease prior to transplantation; however, one patient developed an adynamic lesion following transplantation. Bone histology did not change following transplantation among those with normal bone formation prior to transplantation. Bone formation improved in two of the three children with adynamic bone disease prior to transplantation. In summary, most—but not all—skeletal lesions improve substantially in pediatric patients undergoing successful transplantation; however, concern is raised over residual hyperparathyroidism or development of adynamic bone disease in a few.

Studies of bone using DXA in children following transplantation have yielded conflicting results, largely related to the difficulties in interpreting DXA results in children with delayed growth and development.^{35,372,549-551} One study first described bone loss in children following renal transplantation.⁵⁵² Bone mineral content (BMC) z-scores were less than -2.0 in 11 of 18 (62%) children. Children receiving daily steroid demonstrated significantly greater bone loss than children on alternate-day steroid treatment. A subsequent longitudinal study of DXA measures of whole body BMC following renal transplanta-

tion in 16 children showed that BMC decreased from the initial z-score of 0.98 to a z-score of -0.55 three months after transplant.⁵⁴⁹ A further decrease was noted at the end of month 6 (-1.34 SD) and month 12 (-1.32 SD). These studies related bone mineralization to chronologic age. Others have investigated the possible influence of height and weight retardation on the measurement of BMD in pediatric transplantation recipients.³⁵ Only one patient had low values for vertebral BMD when the data were corrected for height or weight. The authors concluded that BMD among pediatric renal transplantation recipients is not diminished when the data are corrected for height or weight, rather than age. Another study reported similar results³⁷²: BMD z-scores for age were significantly decreased (-0.67 ± 1.2); however, BMD z-scores for height were above normal in all three histological subgroups (0.68 ± 1.0). This may be a misleading approach since shorter controls will be less mature than the patients with CKD. With the exception of a case series of fractures in children with cystinosis,⁵⁵³ there are no data on fractures following transplantation in children.

Corticosteroid-Induced Osteopenia

There are currently no data available addressing the impact of different corticosteroid doses or formulations on bone mineral accretion in children with a kidney transplant. None of the DXA studies reviewed above demonstrated a consistent relationship between glucocorticoid therapy and bone mass. However, glucocorticoid therapy is a major factor in the development of osteopenia in adult transplantation recipients, as reviewed in the adult guidelines. Therefore, it is recommended that clinicians use the lowest effective dose of corticosteroids necessary to preserve renal function.

Prior studies have suggested that calcium and active vitamin D therapy may lessen corticosteroid-induced bone loss in non-transplant patients.^{554,555} A recent randomized clinical trial in 111 adult renal transplant recipients demonstrated that low-dose (0.25 $\mu\text{g}/\text{day}$) 1- α -hydroxyvitamin D plus calcium (1,000 mg/day) partially prevented the bone loss at the lumbar spine and proximal femur during the first six

months following renal transplantation.⁵⁵⁶ There are no data in children.

Bisphosphonate Therapy

The effects of bisphosphonate therapy on skeletal modeling and bone mineral accretion have not been adequately addressed in children with CKD. There are no data assessing the safety and efficacy of these drugs in children with CKD or glucocorticoid-induced osteoporosis.

LIMITATIONS

As outlined above, DXA studies of bone in children following transplantation have yielded conflicting results, largely related to the difficulties in interpreting DXA results in children with delayed growth and development. Furthermore, there are no data assessing the prevalence and timing of hypophosphatemia in the immediate post-transplant interval, risk factors for hypophosphatemia in children, or the efficacy of phosphate supplementation. Finally, there are no controlled studies, either clinical trials or controlled observational studies, examining bone disease in the pediatric renal transplant recipient.

RESEARCH RECOMMENDATIONS

Bone disease may not regress completely in children following successful kidney transplantation. Future research is needed to address the following issues:

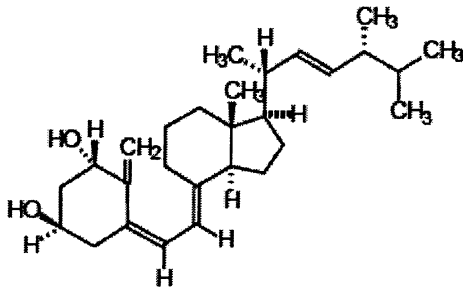
- Do children with renal osteodystrophy recover cortical bone dimensions and trabecular architecture following transplantation with a functioning allograft?
- What is the impact of transplantation during childhood and adolescence on peak bone mass?
- Does supplementation with calcium and vitamin D following transplantation decrease progressive bone loss?
- Are the bisphosphonates safe and effective in children following transplantation? What are the effects of bisphosphonates on bone modeling and growth in children?
- Does GH following transplantation affect bone mineral accretion?
- What is the best method to evaluate bone mineralization in children? Do DXA results predict fracture risk?

AFTERWORD

Since the time of our last committee meetings, long and frequent telecommunications, and late-night E-mail communiqués, additional drugs have become available for the treatment of secondary hyperparathyroidism and hyperphosphatemia that will have an impact in the field of renal osteodystrophy in children with chronic kidney disease. We would like to highlight such developments and suggest that the next group of experts who reviews the care of pediatric osteodystrophy will be forthcoming with guidelines about these subjects.

VITAMIN D ANALOGUES

A) Doxercalciferol (**Hectorol**®, Bone Care International^R, Madison, WI) was approved by the Food and Drug Administration for the treatment of osteodystrophy in adult patients with chronic kidney disease stages 2-5, in April 2004. Oral soft gelatin formulations (2.5 mcg; 0.5 mcg) and a parenteral formulation (2 mcg/mL) are available. Its structure is shown below:

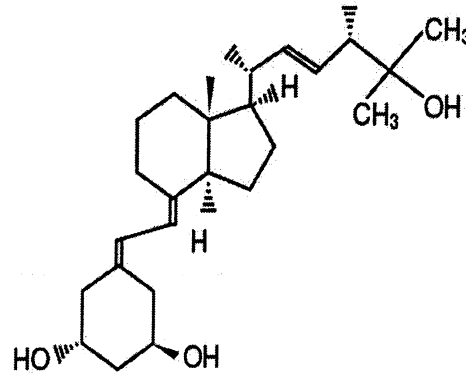


Doxercalciferol acts as a pro-hormone, needing 25-hydroxylation in the liver for bioactivation into 1 α , 25-hydroxyvitamin D₂. Pivotal studies in adults on dialysis have demonstrated control of secondary hyperparathyroidism that is superior to placebo therapy, without undue suppression of 1st IMA-PTH < 300 pg/mL, or occurrences of hypercalcemia. Doxercalciferol has been shown to be effective in controlling secondary hyperparathyroidism of adult patients with CKD stages 3-4.

Use in children is not yet FDA approved, but recent data demonstrated that oral doxercalciferol given thrice-weekly is as effective as calcitriol in reducing PTH levels and improv-

ing the skeletal lesions of secondary hyperparathyroidism in children treated with peritoneal dialysis.^{163a}

B) Paricalcitol (**Zemlar**®, or 19-nor-1 α ,25-dihydroxyvitamin D₃, Abbot Laboratories, Chicago, IL) has been available as a parenteral formulation for some time for patients with CKD stage 5, and is now available as 1-4 micrograms tablets. Its structure is shown below.



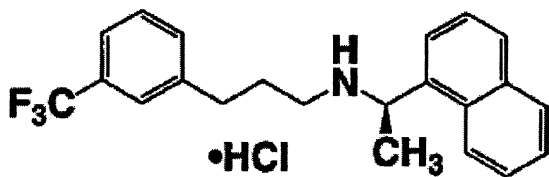
Paricalcitol is a synthetic, biologically active vitamin D analog of calcitriol with modification to the side chain (D₂) and the A (19-nor) ring. Its biological actions are mediated through binding of the vitamin D receptor, which results in selective activation of vitamin D-responsive pathways. Paricalcitol has been shown to reduce 1st IMA-PTH by inhibiting PTH synthesis and secretion in adult patients undergoing maintenance hemodialysis.³²¹ Use in children remains unpublished.

CALCIMIMETIC AGENTS

Cinacalcet hydrochloride (**Sensipar**®, Amgen, Thousand Oaks, CA) is a calcimimetic, the first of a new class of pharmacologic agents that modulate the actions of the membrane-anchored calcium-sensing receptor (CaSR) located on the parathyroid cells. The CaSR is also located in the kidney tubules, as well as many other cells within the body. Activation of the CaSR, whether by calcium or by a calcimimetic agent, reduces PTH secretion. The reduction in PTH diminishes bone resorption and is thus associated with a

concomitant decrease in serum calcium and phosphorus levels.

Its structure is shown below.



Cinacalcet hydrochloride has been approved for the treatment of secondary hyperparathyroidism of stage 5 CKD (maintenance dialysis) in adults. Its pharmacokinetics are being studied in children on maintenance dialysis, but no data are yet available. At present, there is no recommendation regarding the use of cinacalcet hydrochloride in children with CKD. As the eCaSR is expressed at the level of the growth plate, the safety of cinacalcet hydrochloride in growing children remains to be demonstrated.

PHOSPHATE BINDER

Lanthanum carbonate (Fosrenol®, Shire US Inc., Wayne, PA) contains lanthanum carbonate (2:3) hydrate with a molecular formula of $\text{La}_2(\text{CO}_3)_3 \cdot x\text{H}_2\text{O}$ (on average, $x=4-5$) and serves as a dietary phosphate binder. Lanthanum carbonate inhibits absorption of phosphate by forming highly insoluble lanthanum-phosphate complexes and thereby reduces both serum phosphorus and the $\text{Ca} \times \text{P}$ product in patients with CKD.

In 105 adults with kidney failure treated with lanthanum carbonate for up to 4-5 years, rising levels of lanthanum were noted over time. Estimates of elimination half-life from bone ranged from 2-3.6 years. Steady-state bone concentrations were not reached during the period studied.

There are no studies in children on maintenance dialysis. Further, the current FDA-approved label for lanthanum carbonate indicates that lanthanum can be found in the growth plate.⁵⁵⁷ Therefore, we do not recommend use of lanthanum carbonate for the chronic treatment of hyperphosphatemia in children.

BIOGRAPHICAL SKETCHES OF WORK GROUP MEMBERS

Craig B. Langman, MD (Work Group Co-Chair), is the Isaac A. Abt MD Professor of Kidney Disease at the Feinberg School of Medicine at Northwestern University and Head of Kidney Diseases 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. He has pioneered the use of noninvasive testing in children to assess bone cell function. Dr Langman has published more than 160 articles, chapters, and reviews in his discipline and currently serves as the Senior Associate Editor for the *American Journal of Nephrology* and on the Editorial Board for the *Journal for Bone and Mineral Research*. He previously served on the Editorial Advisory Board of Pediatric Nephrology, Advances in Chronic Kidney Disease and Pediatric Endocrinology. Dr Langman has served as 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 Scientific Advisory Board, Public Policy, and the Executive Committee of the Council of Pediatric Urology and Nephrology Committees, among others, of the National Kidney Foundation. He has also served on the Growth Advisory Board of the North American Pediatric Renal Transplant Cooperative Study. He serves as a consultant for many pharmaceutical laboratories, health care companies, and health care related Foundations, including Merck USA, Roche Pharmaceuticals, Novartis, Genentech, Amgen, Bone Care International, Abbott Laboratories, and the Oxalosis and Hyperoxaluria Foundation.

Isidro B. Salusky, MD, FAAP (Work Group Co-Chair), 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. Dr Salusky has published more than 150 papers and is very active in many professional societies. During the course of these studies, Dr Salusky has been successful in obtaining funding from the National Institutes of Health, as well as from other profit and nonprofit organizations. He is a consultant for Genzyme, Inc, Bone Care International, and Abbott Laboratories.

Larry Greenbaum, MD, PhD, is the Associate Professor of Pediatrics and Vice Chair of the Pediatric IRB at the Medical College of Wisconsin in Milwaukee, WI. He has been a principal investigator for multicenter studies in the areas of pediatric dialysis and transplantation. He co-edited the textbook *Practical Strategies in Pediatric Diagnosis and Therapy* and has written the "Pathophysiology of Body Fluids and Fluid Therapy" section for the next edition of *Nelson Textbook of Pediatrics*. His research on nutritional rickets has led to policy changes in the Wisconsin WIC program. He has received multiple teaching awards at the Medical College of Wisconsin and UCLA. He has been a reviewer for numerous journals, including the *American Journal of Kidney Disease*, *Pediatric Nephrology* and *Peritoneal Dialysis International*. He serves on the Medical Advisory Board of the Oxalosis and Hyperoxaluria Foundation and the Medical Advisory Committee of the NKF of Wisconsin.

Harald Jueppner, MD, is the Associate Professor of Pediatrics at Harvard Medical School in Boston, Massachusetts. A researcher interested in areas such as bone and mineral homeostasis, cartilage and bone development and uremic bone disease, Dr Jueppner also serves as Associate Biologist and Associate Pediatrician at the Massachusetts General Hospital in Boston. He has served as an invited guest speaker in numerous international symposiums including the European Renal Association–European Dialysis and Transplantation Association in Geneva, Switzerland and the International Bone Forum in Yokohama, Japan. Dr Jueppner is the author of numerous scientific papers in his field and is the President of Advance in Mineral Metabolism.

Mary Leonard, MD, is the Assistant Professor of Pediatrics and Epidemiology at The Children's Hospital of Philadelphia. She is also a Senior Scholar at Center for Clinical Epidemiology and Biostatistics (CCEB) and serves on the United States Renal Data System Scientific Advisory Committee. Dr Leonard has special research interest in the assessment of bone mineralization in children, glucocorticoid-induced osteoporosis in children, structural effects of renal osteodystrophy during growth, and dialysis outcomes in children. She has received grants for her research in areas such as Structural Effects of Renal Osteodystrophy During Growth and Glucocorticoid-Induced Osteoporosis in Children. She is also an active member several organizations including the American Society of Pediatric Nephrology, the International Pediatric Nephrology Association and the American Society of Nephrology.

Pauline Nelson, RD, is the Pediatric Renal Dietitian at the UCLA Center for the Health Sciences, working with children in the inpatient and outpatient settings on all modalities of end-stage renal disease (ESRD) care. She has participated in many clinical research studies related to growth and nutrition, especially in the areas of recombinant human growth hormone and peritoneal dialysis. Ms Nelson has written numerous professional and lay papers on various aspects of nutrition in ESRD, with a particular emphasis on practical approaches to the delivery of nutrients. She has been active in the American Dietetic Association and the Council on Renal Nutrition of the National Kidney Foundation on local and national levels.

Anthony Portale, MD, is Professor of Pediatrics, Chief of Pediatric Nephrology, and Director of the Pediatric Dialysis Program at the University of California San Francisco Children's Hospital. Dr Portale's clinical and research focus is

inherited and acquired disorders of phosphorus and vitamin D metabolism, renal osteodystrophy, and metabolic bone disease in infants and children. He has done extensive work to characterize the physiologic regulation of phosphorus and vitamin D metabolism in individuals and in experimental models. Dr Portale has published numerous scientific papers and book chapters in his field, and serves on the editorial boards for the *Journal of Bone and Mineral Research*, the *American Journal of Nephrology*, and *Clinical Pediatric Endocrinology*.

Bradley A. Warady, MD, is Chief of Nephrology and Director of Dialysis and Transplantation at The Children's Mercy Hospital, and Professor of Pediatrics at the University of Missouri-Kansas City School of Medicine. Dr Warady's clinical and research focus is end-stage renal disease with particular emphasis on peritoneal dialysis. He established the Pediatric Peritoneal Dialysis Study Consortium, and he is on the executive committee of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). He currently directs or co-directs research projects on a number of topics including: growth hormone usage in pediatric dialysis patients; peritoneal dialysis adequacy in children; intravenous iron therapy in pediatric patients receiving hemodialysis, and anemia management in children on dialysis. He co-edited the book *CAPD/CCPD in Children* and has published more than 180 articles and book chapters. Dr Warady serves on the executive committees of the American Society of Pediatric Nephrology and the Nephrology section of the American Academy of Pediatrics. Dr Warady also serves as an Associate Editor for *Peritoneal Dialysis International*, an Assistant Editor for *Advances in Chronic Kidney Disease*, and sits on the Editorial Board for *Pediatric Nephrology*.

REFERENCES

1. Bachrach LK: Acquisition of optimal bone mass in childhood and adolescence. *Trends Endocrinol Metab* 12:22-28, 2001
2. Klaus G, Jux C, Leiber K, Hugel U, Mehls O: Interaction between insulin-like growth factor I, growth hormone, parathyroid hormone, 1 alpha,25-dihydroxyvitamin D3 and steroids on epiphyseal chondrocytes. *Acta Paediatr Suppl* 417:69-71, 1996
3. Langman CB, Mazur AT, Baron R, Norman ME: 25-hydroxyvitamin D3 (calcifediol) therapy of juvenile renal osteodystrophy: beneficial effect on linear growth velocity. *J Pediatr* 100:815-820, 1982
4. Krempien B, Mehls O, Ritz E: Morphological studies on pathogenesis of epiphyseal slipping in uremic children. *Virchows Arch A Pathol Anat Histol* 362:129-143, 1974
5. Schober HC, Han ZH, Foldes AJ, Shih MS, Rao DS, Balena R, Parfitt AM: Mineralized bone loss at different sites in dialysis patients: implications for prevention. *J Am Soc Nephrol* 9:1225-1233, 1998
6. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. *Am J Kidney Dis* 39:S1-S000, 2002 (suppl 1)
7. Manjunath G, Sarnak MJ, Levey AS: Estimating the glomerular filtration rate. Dos and don'ts for assessing kidney function. *Postgrad Med. Dec*;110:55-62, 2001
8. Malluche HH, Faugere MC: Effects of 1,25(OH)2D3 administration on bone in patients with renal failure. *Kidney Int Suppl* 29:S48-S53, 1990
9. Malluche H, Faugere MC: Renal bone disease 1990: an unmet challenge for the nephrologist. *Kidney Int* 38:193-211, 1990
10. Hamdy NA, Kanis JA, Beneton MN, Brown CB, Juttman JR, Jordans JG, Josse S, Meyrier A, Lins RL, Fairey IT: Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure. *BMJ* 310:358-363, 1995
11. Goodman WG, Coburn JW: The use of 1,25-dihydroxyvitamin D3 in early renal failure. *Annu Rev Med* 43:227-237, 1992
12. de Caestecker MP, Bottomley M, Telfer BA, Hutchinson IV, Vose BM, Ballardie FW: Detection of abnormal peripheral blood mononuclear cell cytokine networks in human IgA nephropathy. *Kidney Int* 44:1298-1308, 1993
13. Feldman HI, Held PJ, Hutchinson JT, Stoiber E, Hartigan MF, Berlin JA: Hemodialysis vascular access morbidity in the United States. *Kidney Int* 43:1091-1096, 1993
14. Hutchison AJ, Whitehouse RW, Boulton HF, Adams JE, Mawer EB, Freemont TJ, Gokal R: Correlation of bone histology with parathyroid hormone, vitamin D3, and radiology in end-stage renal disease. *Kidney Int* 44:1071-1077, 1993
15. Gerakis A, Hutchison AJ, Apostolou T, Freemont AJ, Billis A: Biochemical markers for non-invasive diagnosis of hyperparathyroid bone disease and adynamic bone in patients on haemodialysis. *Nephrol Dial Transplant* 11:2430-2438, 1996
16. Quigg RJ, Brathwaite M, Gardner DF, Gretch DR, Ruddy S: Successful cyclophosphamide treatment of cryoglobulinemic membranoproliferative glomerulonephritis associated with hepatitis C virus infection. *Am J Kidney Dis* 25:798-800, 1995
17. Qi Q, Monier-Faugere MC, Geng Z, Malluche HH: Predictive value of serum parathyroid hormone levels for bone turnover in patients on chronic maintenance dialysis. *Am J Kidney Dis* 26:622-631, 1995
18. Block GA, Port FK: Re-evaluation of risks associated with hyperphosphatemia and hyperparathyroidism in dialysis patients: recommendations for a change in management. *Am J Kidney Dis* 35:1226-1237, 2000
19. Urena P, Ferreira A, Kung VT, Morieux C, Simon P, Ang KS, Souberbielle JC, Segre GV, Druke TB, De Vernejoul MC: Serum pyridinoline as a specific marker of collagen breakdown and bone metabolism in hemodialysis patients. *J Bone Miner Res* 10:932-939, 1995
20. Norman ME, Mazur AT, Borden S 4th, Gruskin A, Anast C, Baron R, Rasmussen H: Early diagnosis of juvenile renal osteodystrophy. *J Pediatr* 97:226-232, 1980
21. Martinez I, Saracho R, Montenegro J, Llach F: The importance of dietary calcium and phosphorus in the secondary hyperparathyroidism of patients with early renal failure. *Am J Kidney Dis* 29:496-502, 1997
22. Salusky IB, Ramirez JA, Oppenheim W, Gales B, Segre GV, Goodman WG: Biochemical markers of renal osteodystrophy in pediatric patients undergoing CAPD/CCPD. *Kidney Int* 45:253-258, 1994
23. Mathias R, Salusky I, Harman W, Paredes A, Emans J, Segre G, Goodman W: Renal bone disease in pediatric and young adult patients on hemodialysis in a children's hospital. *J Am Soc Nephrol* 3:1938-1946, 1993
24. Ziolkowska H, Paniczyk-Tomaszewska M, Debinski A, Polowicz Z, Sawicki A, Sieniawska M: Bone biopsy results and serum bone turnover parameters in uremic children. *Acta Paediatr* 89:666-671, 2000
25. Solal ME, Sebert JL, Boudailliez B, Marie A, Moriniere P, Guerin J, Bouillon R, Fournier A: Comparison of intact, midregion, and carboxy terminal assays of parathyroid hormone for the diagnosis of bone disease in hemodialyzed patients. *J Clin Endocrinol Metab* 73:516-524, 1991
26. Wang M, Hercz G, Sherrard DJ, Maloney NA, Segre GV, Pei Y: Relationship between intact 1-84 parathyroid hormone and bone histomorphometric parameters in dialysis patients without aluminum toxicity. *Am J Kidney Dis* 26:836-844, 1995
27. Huraib S, Souqqiyeh MZ, Aswad S, al-Swailem AR: Pattern of renal osteodystrophy in haemodialysis patients in Saudi Arabia. *Nephrol Dial Transplant* 8:603-608, 1993
28. DeVita MV, Rasenas LL, Bansal M, Gleim GW, Zabetakis PM, Gardenswartz MH, Michelis MF: Assessment of renal osteodystrophy in hemodialysis patients. *Medicine (Baltimore)* 71:284-290, 1992
29. Eastwood JB: Quantitative bone histology in 38 patients with advanced renal failure. *J Clin Pathol* 35:125-134, 1982
30. Hasselblad V, Hedges LV: Meta-analysis of screening and diagnostic tests. *Psychol Bull* 117:167-178, 1995

31. World Health Organization diagnostic criteria for osteoporosis and trends in Europe and USA. *Nippon Rinsho. Japanese Journal of Clinical Medicine* Feb;62:235-239, 2004 (Suppl 2)
32. Leonard MB, Feldman HI, Zemel BS, Berlin JA, Barden EM, Stallings VA: Evaluation of low density spine software for the assessment of bone mineral density in children. *J Bone Miner Res* 13:1687-1690, 1998
33. Leonard MB, Propert KJ, Zemel BS, Stallings VA, Feldman HI: Discrepancies in pediatric bone mineral density reference data: potential for misdiagnosis of osteopenia. *J Pediatr* 135:182-188, 1999
34. Molgaard C, Thomsen BL, Prentice A, Cole TJ, Michaelsen KF: Whole body bone mineral content in healthy children and adolescents. *Arch Dis Child* 76:9-15, 1997
35. Klaus G, Paschen C, Wuster C, Kovacs GT, Barden J, Mehls O, Scharer K: Weight-/height-related bone mineral density is not reduced after renal transplantation. *Pediatr Nephrol* 12:343-348, 1998
36. Kim MS, Kim YS, Lim SK, Kim SI, Moon JI, Park K: Effect of deflazacort on bone mineral density in renal transplant recipients. *Transplant Proc* 30:3041-3042, 1998
37. Hurst G, Alloway R, Hathaway D, Somerville T, Hughes T, Gaber A: Stabilization of bone mass after renal transplant with preemptive care. *Transplant Proc* 30:1327-1328, 1998
38. Aroldi A, Tarantino A, Montagnino G, Cesana B, Cocucci C, Ponticelli C: Effects of three immunosuppressive regimens on vertebral bone density in renal transplant recipients: a prospective study. *Transplantation* 63:380-386, 1997
39. Pichette V, Bonnardeaux A, Prudhomme L, Gagne M, Cardinal J, Ouimet D: Long-term bone loss in kidney transplant recipients: a cross-sectional and longitudinal study. *Am J Kidney Dis* 28:105-114, 1996
40. Setterberg L, Sandberg J, Elinder CG, Nordenstrom J: Bone demineralization after renal transplantation: contribution of secondary hyperparathyroidism manifested by hypercalcaemia. *Nephrol Dial Transplant* 11:1825-1828, 1996
41. Yazawa K, Ishikawa T, Ichikawa Y, Shin J, Usui Y, Hanafusa T, Fukunishi T, Sakai R, Nagano S, Fujita N, Mizuno K: Positive effects of kidney transplantation on bone mass. *Transplant Proc* 30:3031-3033, 1998
42. Torres A, Lorenzo V, Gonzalez-Posada JM: Comparison of histomorphometry and computerized tomography of the spine in quantitating trabecular bone in renal osteodystrophy. *Nephron* 44:282-287, 1986
43. Glorieux FH, Travers R, Taylor A, Bowen JR, Rauch F, Norman M, Parfitt AM: Normative data for iliac bone histomorphometry in growing children. *Bone* 26:103-109, 2000
44. Mehls O, Ritz E, Gilli G, Kreusser W: Growth in renal failure. *Nephron* 21:237-247, 1978
45. Castaneda C, Gordon PL, Uhlin KL, Levey AS, Kehayias JJ, Dwyer JT, Fielding RA, Roubenoff R, Singh MF: Resistance training to counteract the catabolism of a low-protein diet in patients with chronic renal insufficiency. A randomized, controlled trial. *Ann Intern Med* 135:965-976, 2001
46. Davids JR, Fisher R, Lum G, Von Glinski S: Angular deformity of the lower extremity in children with renal osteodystrophy. *J Pediatr Orthop* 12:291-299, 1992
47. Oppenheim WL, Fischer SR, Salusky IB: Surgical correction of angular deformity of the knee in children with renal osteodystrophy. *J Pediatr Orthop* 17:41-49, 1997
48. Apel DM, Millar EA, Moel DI: Skeletal disorders in a pediatric renal transplant population. *J Pediatr Orthop* 9:505-511, 1989
49. Barrett IR, Papadimitriou DG: Skeletal disorders in children with renal failure. *J Pediatr Orthop* 16:264-272, 1996
50. Beskin JL, Burke SW, Johnston CE 2nd, Roberts JM: Clinical basis for a mechanical etiology in adolescent Blount's disease. *Orthopedics* 9:365-370, 1986
51. Blockey NJ, Murphy AV, Mocan H: Management of rachitic deformities in children with chronic renal failure. *J Bone Joint Surg Br* 68:791-794, 1986
52. Evans GA, Arulanantham K, Gage JR: Primary hypophosphatemic rickets. Effect of oral phosphate and vitamin D on growth and surgical treatment. *J Bone Joint Surg Am* 62:1130-1138, 1980
53. Fine RN, Isaacson AS, Payne V, Grushkin CM: Renal osteodystrophy in children: the effect of hemodialysis and renal homotransplantation. *J Pediatr* 80:243-249, 1972
54. Mehls O, Ritz E, Oppermann HC, Guignard JP: Femoral head necrosis in uremic children without steroid treatment or transplantation. *J Pediatr* 99:926-929, 1981
55. Rubinovitch M, Said SE, Glorieux FH, Cruess RL, Rogala E: Principles and results of corrective lower limb osteotomies for patients with vitamin D-resistant hypophosphatemic rickets. *Clin Orthop*:264-270, 1988
56. Salenius P, Vankka E: The development of the tibiofemoral angle in children. *J Bone Joint Surg Am* 57:259-261, 1975
57. Loder RT, Hensinger RN: Slipped capital femoral epiphysis associated with renal failure osteodystrophy. *J Pediatr Orthop* 17:205-211, 1997
58. Mehls O, Ritz E, Krempien B, Gilli G, Link K, Willich E, Scharer K: Slipped epiphyses in renal osteodystrophy. *Arch Dis Child* 50:545-554, 1975
59. Swierstra BA, Diepstraten AF, vd Heyden BJ: Distal femoral physiolysis in renal osteodystrophy. Successful nonoperative treatment of 3 cases followed for 5 years. *Acta Orthop Scand* 64:382-384, 1993
60. Tebor GB, Ehrlich MG, Herrin J: Slippage of the distal tibial epiphysis. *J Pediatr Orthop* 3:211-215, 1983
61. Hartjen CA, Koman LA: Treatment of slipped capital femoral epiphysis resulting from juvenile renal osteodystrophy. *J Pediatr Orthop* 10:551-554, 1990
62. Oppenheim WL, Bowen RE, McDonough PW, Funahashi TT, Salusky IB: Outcome of slipped capital femoral epiphysis in renal osteodystrophy. *J Pediatr Orthop* 23:169-174, 2003
63. Boechat MI, Winters WD, Hogg RJ, Fine RN, Watkins SL: Avascular necrosis of the femoral head in children with chronic renal disease. *Radiology* 218:411-413, 2001
64. Watkins SL: Bone disease in patients receiving growth hormone. *Kidney Int Suppl* 53:S126-S127, 1996

65. Harrington KD, Murray WR, Kountz SL, Belzer FO: Avascular necrosis of bone after renal transplantation. *J Bone Joint Surg Am* 53:203-215, 1971
66. Ibels LS, Alfrey AC, Huffer WE, Weil R 3rd: Aseptic necrosis of bone following renal transplantation: experience in 194 transplant recipients and review of the literature. *Medicine (Baltimore)* 57:25-45, 1978
67. Stern PJ, Watts HG: Osteonecrosis after renal transplantation in children. *J Bone Joint Surg Am* 61:851-856, 1979
68. Davidson JK, Tsakiris D, Briggs JD, Junor BJ: Osteonecrosis and fractures following renal transplantation. *Clin Radiol* 36:27-35, 1985
69. Murray WR: Hip problems associated with organ transplants. *Clin Orthop* 90:57-69, 1973
70. Brodehl J, Gellissen K, Weber HP: Postnatal development of tubular phosphate reabsorption. *Clin Nephrol* 17:163-171, 1982
71. Burritt MF, Slockbower JM, Forsman RW, Offord KP, Bergstrahl EJ, Smithson WA: Pediatric reference intervals for 19 biologic variables in healthy children. *Mayo Clin Proc* 65:329-336, 1990
72. Arnaud SB, Goldsmith RS, Stickler GB, McCall JT, Arnaud CD: Serum parathyroid hormone and blood minerals: interrelationships in normal children. *Pediatr Res* 7:485-493, 1973
73. Greenberg BG, Winters RW, Graham JB: The normal range of serum inorganic phosphorus and its utility as a discriminant in the diagnosis of congenital hypophosphatemia. *J Clin Endocrinol Metab* 20:364-379, 1960
74. Portale AA, Booth BE, Halloran BP, Morris RC Jr: Effect of dietary phosphorus on circulating concentrations of 1,25-dihydroxyvitamin D and immunoreactive parathyroid hormone in children with moderate renal insufficiency. *J Clin Invest* 73:1580-1589, 1984
75. Portale AA, Halloran BP, Morris RC Jr: Dietary intake of phosphorus modulates the circadian rhythm in serum concentration of phosphorus. Implications for the renal production of 1,25-dihydroxyvitamin D. *J Clin Invest* 80:1147-1154, 1987
76. Markowitz ME, Rosen JF, Laxminarayan S, Mizruchi M: Circadian rhythms of blood minerals during adolescence. *Pediatr Res* 18:456-462, 1984
77. Naveh-Manly T, Rahamimov R, Livni N, Silver J: Parathyroid cell proliferation in normal and chronic renal failure rats. The effects of calcium, phosphate, and vitamin D. *J Clin Invest* 96:1786-1793, 1995
78. Slatopolsky E, Finch J, Denda M, Ritter C, Zhong M, Dusso A, MacDonald PN, Brown AJ: Phosphorus restriction prevents parathyroid gland growth. High phosphorus directly stimulates PTH secretion in vitro. *J Clin Invest* 97:2534-2540, 1996
79. Kimura K, Saika Y, Otani H, Fujii R, Mune M, Yukawa S: Factors associated with calcification of the abdominal aorta in hemodialysis patients. *Kidney Int Suppl* 71:S238-S241, 1999
80. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB: Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 342:1478-1483, 2000
81. Mazhar AR, Johnson RJ, Gillen D, Stivelman JC, Ryan MJ, Davis CL, Stehman-Breen CO: Risk factors and mortality associated with calciphylaxis in end-stage renal disease. *Kidney Int* 60:324-332, 2001
82. Ahmed S, O'Neill KD, Hood AF, Evan AP, Moe SM: Calciphylaxis is associated with hyperphosphatemia and increased osteopontin expression by vascular smooth muscle cells. *Am J Kidney Dis* 37:1267-1276, 2001
83. Marchais SJ, Metivier F, Guerin AP, London GM: Association of hyperphosphatemia with haemodynamic disturbances in end-stage renal disease. *Nephrol Dial Transplant* 14:2178-2183, 1999
84. Guerin AP, London GM, Marchais SJ, Metivier F: Arterial stiffening and vascular calcifications in end-stage renal disease. *Nephrol Dial Transplant* 15:1014-1021, 2000
85. Block GA, Hulbert-Shearon TE, Levin NW, Port FK: Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 31:607-617, 1998
86. Lowrie EG, Lew NL: Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* 15:458-482, 1990
87. Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM: Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension* 38:938-942, 2001
88. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK: Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol* 12:2131-2138, 2001
89. Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, Morii H, Giachelli CM: Phosphate regulation of vascular smooth muscle cell calcification. *Circ Res* 87:E10-E17, 2000
90. Rostand SG, Sanders C, Kirk KA, Rutsky EA, Fraser RG: Myocardial calcification and cardiac dysfunction in chronic renal failure. *Am J Med* 85:651-657, 1988
91. Katz AI, Hampers CL, Merrill JP: Secondary hyperparathyroidism and renal osteodystrophy in chronic renal failure. Analysis of 195 patients, with observations on the effects of chronic dialysis, kidney transplantation and subtotal parathyroidectomy. *Medicine (Baltimore)* 48:333-374, 1969
92. Raggi P, Reinmuller R, Chertow GM: Cardiac calcification is prevalent and severe in ESRD patients as measured by electron beam CT scanning. *J Am Soc Nephrol Abstract* A0405:75A, 2000
93. Oh J, Wunsch R, Turzer M, Bahner M, Raggi P, Querfeld U, Mehls O, Schaefer F: Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. *Circulation* 106:100-105, 2002
94. Greene SV, Falciglia G, Rademacher R: Relationship between serum phosphorus levels and various outcome measures in adult hemodialysis patients. *J Ren Nutr* 8:77-82, 1998
95. Greenbaum LA: Pathophysiology of Body Fluids and Fluid Therapy, 17th ed. Philadelphia, PA, Elsevier Science, 2004

96. Portale AA, Booth BE, Tsai HC, Morris RC, Jr.: Reduced plasma concentration of 1,25-dihydroxyvitamin D in children with moderate renal insufficiency. *Kidney Int* 21:627-632, 1982
97. Massry SG, Coburn JW, Popovtzer MM, Shinaberger JH, Maxwell MH, Kleeman CR: Secondary hyperparathyroidism in chronic renal failure. The clinical spectrum in uremia, during hemodialysis, and after renal transplantation. *Arch Intern Med* 124:431-441, 1969
98. Llach F, Massry SG, Singer FR, Kurokawa K, Kaye JH, Coburn JW: Skeletal resistance to endogenous parathyroid hormone in patients with early renal failure. A possible cause for secondary hyperparathyroidism. *J Clin Endocrinol Metab* 41:339-345, 1975
99. von Lilienfeld-Toal H, Gerlach I, Klehr HU, Issa S, Keck E: Immunoreactive parathyroid hormone in early and advanced renal failure. *Nephron* 31:116-122, 1982
100. Llach F, Massry SG: On the mechanism of secondary hyperparathyroidism in moderate renal insufficiency. *J Clin Endocrinol Metab* 61:601-606, 1985
101. Wilson L, Felsenfeld A, Drezner MK, Llach F: Altered divalent ion metabolism in early renal failure: role of 1,25(OH)₂D. *Kidney Int* 27:565-573, 1985
102. Tessitore N, Venturi A, Adami S, Roncari C, Ruggiu C, Corgnati A, Bonucci E, Maschio G: Relationship between serum vitamin D metabolites and dietary intake of phosphate in patients with early renal failure. *Miner Electrolyte Metab* 13:38-44, 1987
103. Pitts TO, Piraino BH, Mitro R, Chen TC, Segre GV, Greenberg A, Puschett JB: Hyperparathyroidism and 1,25-dihydroxyvitamin D deficiency in mild, moderate, and severe renal failure. *J Clin Endocrinol Metab* 67:876-881, 1988
104. Malluche HH, Ritz E, Lange HP, Kutschera L, Hodgson M, Seiffert U, Schoeppe W: Bone histology in incipient and advanced renal failure. *Kidney Int* 9:355-362, 1976
105. Hodson EM, Evans RA, Dunstan CR, Hills EE, Shaw PF: Quantitative bone histology in children with chronic renal failure. *Kidney Int* 21:833-839, 1982
106. Friis T, Hahnemann S, Weeke E: Serum calcium and serum phosphorus in uraemia during administration of sodium phytate and aluminium hydroxide. *Acta Med Scand* 183:497-505, 1968
107. Coburn JW, Koppel MH, Brickman AS, Massry SG: Study of intestinal absorption of calcium in patients with renal failure. *Kidney Int* 3:264-272, 1973
108. Taylor A, Norman ME: Interrelationship of serum 25-hydroxyvitamin D₃ and 1,25-dihydroxyvitamin D in juvenile renal osteodystrophy after therapy with 25-hydroxyvitamin D₃. *Metab Bone Dis Relat Res* 4:255-261, 1982
109. Chesney RW, Hamstra AJ, Mazess RB, Rose P, DeLuca HF: Circulating vitamin D metabolite concentrations in childhood renal diseases. *Kidney Int* 21:65-69, 1982
110. Mason RS, Lissner D, Wilkinson M, Posen S: Vitamin D metabolites and their relationship to azotaemic osteodystrophy. *Clin Endocrinol (Oxf)* 13:375-385, 1980
111. Christiansen C, Christensen MS, Melsen F, Rodbro P, DeLuca HF: Mineral metabolism in chronic renal failure with special reference to serum concentrations of 1,25(OH)₂D and 24,25(OH)₂D. *Clin Nephrol* 15:18-22, 1981
112. Juttmann JR, Visser TJ, Buurman C, de Kam E, Birkenhager JC: Seasonal fluctuations in serum concentrations of vitamin D metabolites in normal subjects. *Br Med J (Clin Res Ed)* 282:1349-1352, 1981
113. Tessitore N, Lund B, Bonucci E, Sorensen OH, Maschio G: Vitamin D metabolites in early renal failure. *Minerva Nefrol* 28:293-297, 1981
114. Cheung AK, Manolagas SC, Catherwood BD, Mosely CA Jr, Mitas JA 2nd, Blantz RC, Deftos LJ: Determinants of serum 1,25(OH)₂D levels in renal disease. *Kidney Int* 24:104-109, 1983
115. Lucas PA, Brown RC, Bloodworth L, Jones CR, Woodhead JS: Effects of chronic renal failure, renal transplantation and unilateral nephrectomy on 1,25-dihydroxycholecalciferol. Berlin, Walter de Gruyter, 1985
116. Prince RL, Hutchison BG, Kent JC, Kent GN, Retallack RW: Calcitriol deficiency with retained synthetic reserve in chronic renal failure. *Kidney Int* 33:722-728, 1988
117. Ishimura E, Nishizawa Y, Inaba M, Matsumoto N, Emoto M, Kawagishi T, Shoji S, Okuno S, Kim M, Miki T, Morii H: Serum levels of 1,25-dihydroxyvitamin D, 24,25-dihydroxyvitamin D, and 25-hydroxyvitamin D in nondialyzed patients with chronic renal failure. *Kidney Int* 55:1019-1027, 1999
118. Turner C, Compston J, Mak RH, Vedi S, Mellish RW, Haycock GB, Chantler C: Bone turnover and 1,25-dihydroxycholecalciferol during treatment with phosphate binders. *Kidney Int* 33:989-995, 1988
119. Tenenhouse HS, Murer H: Disorders of Renal Tubular Phosphate Transport. *J Am Soc Nephrol* 14:240-247, 2003
120. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G: The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med* 330:877-884, 1994
121. The Modification of Diet in Renal Disease Study: design, methods, and results from the feasibility study. *Am J Kidney Dis* 20:18-33, 1992
122. Malvy D, Maingourd C, Pengloan J, Bagros P, Nivet H: Effects of severe protein restriction with ketoanalogues in advanced renal failure. *J Am Coll Nutr* 18:481-486, 1999
123. Wingen AM, Fabian-Bach C, Schaefer F, Mehls O: Randomised multicentre study of a low-protein diet on the progression of chronic renal failure in children. European Study Group of Nutritional Treatment of Chronic Renal Failure in Childhood. *Lancet* 349:1117-1123, 1997
124. Herselman MG, Albertse EC, Lombard CJ, Swanepoel CR, Hough FS: Supplemented low-protein diets—are they superior in chronic renal failure? *S Afr Med J* 85:361-365, 1995
125. D'Amico G, Gentile MG, Fellin G, Manna G, Cofano F: Effect of dietary protein restriction on the progression of renal failure: a prospective randomized trial. *Nephrol Dial Transplant* 9:1590-1594, 1994
126. Dullaart RP, Beusekamp BJ, Meijer S, van Doormaal JJ, Sluiter WJ: Long-term effects of protein-restricted diet on albuminuria and renal function in IDDM patients without

clinical nephropathy and hypertension. *Diabetes Care* 16:483-492, 1993

128. Kist-van Holthe tot Echten JE, Nauta J, Hop WC, de Jong MC, Reitsma-Bierens WC, Ploos van Amstel SL, van Acker KJ, Noordzij CM, Wolff ED: Protein restriction in chronic renal failure. *Arch Dis Child* 68:371-375, 1993

129. Williams PS, Stevens ME, Fass G, Irons L, Bone JM: Failure of dietary protein and phosphate restriction to retard the rate of progression of chronic renal failure: a prospective, randomized, controlled trial. *Q J Med* 81:837-855, 1991

130. Locatelli F, Alberti D, Graziani G, Bucciatti G, Redaelli B, Giangrande A: Prospective, randomised, multi-centre trial of effect of protein restriction on progression of chronic renal insufficiency. Northern Italian Cooperative Study Group. *Lancet* 337:1299-1304, 1991

131. Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson HR: Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 324:78-84, 1991

132. Forget D, Caranhac G, Quillot MJ, Besnier MO: Compliance with very low protein diet and ketoanalogues in chronic renal failure. The French Multicentric Trial IRCCA. *Contrib Nephrol* 81:79-86, 1990

133. Ihle BU, Becker GJ, Whitworth JA, Charlwood RA, Kincaid-Smith PS: The effect of protein restriction on the progression of renal insufficiency. *N Engl J Med* 321:1773-1777, 1989

134. Mahmoud MD, Bouche V, Collin P, Girault A: Effects of keto-analogues on phosphocalcic and aminoacid metabolism in dialysed patients: a crossover study. *Int J Artif Organs* 12:692-696, 1989

135. Ando A, Orita Y, Nakata K, Fukuhara Y, Mikami H, Fujii M, Nakajima Y, Ueda N, Abe H: The effect of essential amino acid supplementation therapy on prognosis of patients with chronic renal failure estimated on the basis of the Markov process. *Med J Osaka Univ* 32:31-37, 1981

136. Barsotti G, Lazzeri M, Polloni A, Morelli E, Giovannetti E, Lupetti S, Cupisti A, Dani L, Giovannetti S: Effects of the impairment of renal function and of the pH of gastric secretion on the efficacy of $Al(OH)_3$ to reduce serum inorganic phosphorus. *Adv Exp Med Biol* 208:493-499, 1986

137. Meisinger E, Strauch M: Controlled trial of two keto acid supplements on renal function, nutritional status, and bone metabolism in uremic patients. *Kidney Int Suppl* 22:S170-S173, 1987

138. Schmicker R, Vetter K, Lindenau K, Frohling PT, Kokot F: Conservative long-term treatment of chronic renal failure with keto acid and amino acid supplementation. *Infusionsther Klin Ernahr* 14:34-38, 1987 (suppl 5)

139. Gentile MG, Manna GM, Ferrario L, D'Amico G: Preliminary experience on dietary management of chronic renal failure. *Contrib Nephrol* 53:102-108, 1986

140. Druke TB: Primary and secondary uraemic hyperparathyroidism: from initial clinical observations to recent findings. *Nephrol Dial Transplant* 13:1384-1387, 1998

141. Recker RR, Saville PD: Calcium absorption in renal failure: its relationship to blood urea nitrogen, dietary calcium intake, time on dialysis, and other variables. *J Lab Clin Med* 78:380-388, 1971

142. Hosking DJ, Chamberlain MJ: Calcium balance in chronic renal failure. A study using in vivo neutron activation analysis. *Q J Med* 42:467-479, 1973

143. Popovtzer MM, Massry SG, Makoff DL, Maxwell MH, Kleeman CR: Renal handling of phosphate in patients with chronic renal failure. The role of variations in serum phosphorus and parathyroid activity. *Isr J Med Sci* 5:1018-1023, 1969

144. Suzuki M, Hirasawa Y: Renal osteodystrophy in early chronic renal failure. *Contrib Nephrol* 22:28-38, 1980

145. Better OS, Kleeman CR, Gonick HC, Varrady PD, Maxwell MH: Renal handling of calcium, magnesium and inorganic phosphate in chronic renal failure. *Isr J Med Sci* 3:60-79, 1967

146. Cochran M, Bulusu L, Horsman A, Stasiak L, Nordin BE: Hypocalcaemia and bone disease in renal failure. *Nephron* 10:113-140, 1973

147. Duursma SA, Visser WJ, Mees EJ, Njio L: Serum calcium, phosphate and alkaline phosphatase and morphometric bone examinations in 30 patients with renal insufficiency. *Calcif Tissue Res* 16:129-138, 1974

148. London GM, Pannier B, Marchais SJ, Guerin AP: Calcification of the aortic valve in the dialyzed patient. *J Am Soc Nephrol* 11:778-783, 2000

149. Milas NC, Nowalk MP, Akpele L, Castaldo L, Coyne T, Doroshenko L, Kigawa L, Korzec-Ramirez D, Scherch LK, Snetselaar L: Factors associated with adherence to the dietary protein intervention in the Modification of Diet in Renal Disease Study. *J Am Diet Assoc* 95:1295-1300, 1995

150. Foret M, Renversez JC, Meftahi H, Kuentz F, Milongo R, Hachache T, Vallin J, Dechelette E, Cordonnier D: How far can plasmatic levels of beta-2-microglobulin in hemodialysis be relied upon? *Contrib Nephrol* 62:54-59, 1988

151. Jureidini KF, Hogg RJ, van Renen MJ, Southwood TR, Henning PH, Cobiac L, Daniels L, Harris S: Evaluation of long-term aggressive dietary management of chronic renal failure in children. *Pediatr Nephrol* 4:1-10, 1990

152. Uauy RD, Hogg RJ, Brewer ED, Reisch JS, Cunningham C, Holliday MA: Dietary protein and growth in infants with chronic renal insufficiency: a report from the Southwest Pediatric Nephrology Study Group and the University of California, San Francisco. *Pediatr Nephrol* 8:45-50, 1994

153. Kopple JD, Levey AS, Greene T, Chumlea WC, Gassman JJ, Hollinger DL, Maroni BJ, Merrill D, Scherch LK, Schulman G, Wang SR, Zimmer GS: Effect of dietary protein restriction on nutritional status in the Modification of Diet in Renal Disease Study. *Kidney Int* 52:778-791, 1997

154. Coggins CH, Dwyer JT, Greene T, Petot G, Snetselaar LG, Van Lente F: Serum lipid changes associated with modified protein diets: results from the feasibility phase of the Modification of Diet in Renal Disease Study. *Am J Kidney Dis* 23:514-523, 1994

155. Combe C, Deforges-Lasseur C, Caix J, Pommereau A, Marot D, Aparicio M: Compliance and effects of nutritional treatment on progression and metabolic disorders of chronic renal failure. *Nephrol Dial Transplant* 8:412-418, 1993

156. Cianciaruso B, Capuano A, D'Amario E, Ferrara N, Nastasi A, Conte G, Bellizzi V, Andreucci VE: Dietary compliance to a low protein and phosphate diet in patients

- with chronic renal failure. *Kidney Int Suppl* 27:S173-176, 1989
157. Clinical practice guidelines for nutrition in chronic renal failure. K/DOQI, National Kidney Foundation. *Am J Kidney Dis* 35:S1-S140, 2000
158. Wallot M, Bonzel KE, Winter A, Georger B, Lettgen B, Bald M: Calcium acetate versus calcium carbonate as oral phosphate binder in pediatric and adolescent hemodialysis patients. *Pediatr Nephrol* 10:625-630, 1996
159. Sieniawska M, Roszkowska-Blaim M, Weglarska J, Jablczynska A, Welc-Dobies J: Calcium carbonate as a phosphate binder in children on continuous ambulatory peritoneal dialysis and hemodialysis. *Mater Med Pol* 23:203-208, 1991
160. Tamanaha K, Mak RH, Rigden SP, Turner C, Start KM, Haycock GB, Chantler C: Long-term suppression of hyperparathyroidism by phosphate binders in uremic children. *Pediatr Nephrol* 1:145-149, 1987
161. Andreoli SP, Dunson JW, Bergstein JM: Calcium carbonate is an effective phosphorus binder in children with chronic renal failure. *Am J Kidney Dis* 9:206-210, 1987
162. Salusky IB, Coburn JW, Foley J, Nelson P, Fine RN: Effects of oral calcium carbonate on control of serum phosphorus and changes in plasma aluminum levels after discontinuation of aluminum-containing gels in children receiving dialysis. *J Pediatr* 108:767-770, 1986
163. Mahdavi H, Kuizon BD, Gales B, Wang HJ, Elashoff RM, Salusky IB: Sevelamer hydrochloride: an effective phosphate binder in dialyzed children. *Pediatr Nephrol* 18:1260-1264, 2003
- 163a. Salusky IB, Goodman WG, Sahney S, Gales B, Perilloux A, Wang HJ, Elashoff RM, Juppner H: Sevelamer controls parathyroid hormone-induced bone disease as efficiently as calcium carbonate without increasing serum calcium levels during therapy with active vitamin D sterols. *J Am Soc Nephrol* 16:2501-2508, 2005
164. Sedman AB, Wilkening GN, Warady BA, Lum GM, Alfrey AC: Encephalopathy in childhood secondary to aluminum toxicity. *J Pediatr* 105:836-838, 1984
165. Sedman AB, Miller NL, Warady BA, Lum GM, Alfrey AC: Aluminum loading in children with chronic renal failure. *Kidney Int* 26:201-204, 1984
166. Salusky IB, Foley J, Nelson P, Goodman WG: Aluminum accumulation during treatment with aluminum hydroxide and dialysis in children and young adults with chronic renal disease. *N Engl J Med* 324:527-531, 1991
167. Lefebvre A, de Vernejoul MC, Gueris J, Goldfarb B, Graulet AM, Morieux C: Optimal correction of acidosis changes progression of dialysis osteodystrophy. *Kidney Int* 36:1112-1118, 1989
168. Mauro LS, Kuhl DA, Kirchoff JR, Mauro VF, Hamilton RW: Impact of oral bases on aluminum absorption. *Am J Ther* 8:21-25, 2001
169. Mai ML, Emmett M, Sheikh MS, Santa Ana CA, Schiller L, Fordtran JS: Calcium acetate, an effective phosphorus binder in patients with renal failure. *Kidney Int* 36:690-695, 1989
170. Schiller LR, Santa Ana CA, Sheikh MS, Emmett M, Fordtran JS: Effect of the time of administration of calcium acetate on phosphorus binding. *N Engl J Med* 320:1110-1113, 1989
171. Slatopolsky E, Weerts C, Lopez-Hilker S, Norwood K, Zink M, Windus D, Delmez J: Calcium carbonate as a phosphate binder in patients with chronic renal failure undergoing dialysis. *N Engl J Med* 315:157-161, 1986
172. Balasa RW, Murray RL, Kondelis NP, Bischel MD: Phosphate-binding properties and electrolyte content of aluminum hydroxide antacids. *Nephron* 45:16-21, 1987
173. Emmett M, Sirmon MD, Kirkpatrick WG, Nolan CR, Schmitt GW, Cleveland MB: Calcium acetate control of serum phosphorus in hemodialysis patients. *Am J Kidney Dis* 17:544-550, 1991
174. Sheikh MS, Maguire JA, Emmett M, Santa Ana CA, Nicar MJ, Schiller LR, Fordtran JS: Reduction of dietary phosphorus absorption by phosphorus binders. A theoretical, in vitro, and in vivo study. *J Clin Invest* 83:66-73, 1989
175. Rosenbaum DP, Holmes-Farley SR, Mandeville WH, Pitruzzello M, Goldberg DI: Effect of RenaGel, a non-absorbable, cross-linked, polymeric phosphate binder, on urinary phosphorus excretion in rats. *Nephrol Dial Transplant* 12:961-964, 1997
176. Tom A, McCauley L, Bell L, Rodd C, Espinosa P, Yu G, Yu J, Girardin C, Sharma A: Growth during maintenance hemodialysis: impact of enhanced nutrition and clearance. *J Pediatr* 134:464-471, 1999
177. Raj DS, Charra B, Pierratos A, Work J: In search of ideal hemodialysis: is prolonged frequent dialysis the answer? *Am J Kidney Dis* 34:597-610, 1999
178. Mucsi I, Hercz G, Uldall R, Ouwendyk M, Francoeur R, Pierratos A: Control of serum phosphate without any phosphate binders in patients treated with nocturnal hemodialysis. *Kidney Int* 53:1399-1404, 1998
179. Alfrey AC: Aluminum intoxication. *N Engl J Med* 310:1113-1115, 1984
180. Andreoli SP, Bergstein JM, Sherrard DJ: Aluminum intoxication from aluminum-containing phosphate binders in children with azotemia not undergoing dialysis. *N Engl J Med* 310:1079-1084, 1984
181. Alon U, Davidai G, Bentur L, Berant M, Better OS: Oral calcium carbonate as phosphate-binder in infants and children with chronic renal failure. *Miner Electrolyte Metab* 12:320-325, 1986
182. Birck R, Zimmermann E, Wassmer S, Nowack R, van der Woude FJ: Calcium ketoglutarate versus calcium acetate for treatment of hyperphosphataemia in patients on maintenance haemodialysis: a cross-over study. *Nephrol Dial Transplant* 14:1475-1479, 1999
183. Lerner A, Kramer M, Goldstein S, Caruana R, Epstein S, Raja R: Calcium carbonate. A better phosphate binder than aluminum hydroxide. *ASAIO Trans* 32:315-318, 1986
184. Bleyer AJ, Burke SK, Dillon M, Garrett B, Kant KS, Lynch D, Rahman SN, Schoenfeld P, Teitelbaum I, Zeig S, Slatopolsky E: A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients. *Am J Kidney Dis* 33:694-701, 1999
185. Janssen MJ, van der Kuy A, ter Wee PM, van Boven WP: Aluminum hydroxide, calcium carbonate and calcium acetate in chronic intermittent hemodialysis patients. *Clin Nephrol* 45:111-119, 1996

186. Pflanz S, Henderson IS, McElduff N, Jones MC: Calcium acetate versus calcium carbonate as phosphate-binding agents in chronic haemodialysis. *Nephrol Dial Transplant* 9:1121-1124, 1994
187. Ring T, Nielsen C, Andersen SP, Behrens JK, Sodemann B, Kornerup HJ: Calcium acetate versus calcium carbonate as phosphorus binders in patients on chronic haemodialysis: a controlled study. *Nephrol Dial Transplant* 8:341-346, 1993
188. Caravaca F, Fernandez MA, Ruiz-Calero R, Cubero J, Aparicio A, Jimenez F, Garcia MC: Effects of oral phosphorus supplementation on mineral metabolism of renal transplant recipients. *Nephrol Dial Transplant* 13:2605-2611, 1998
189. Chertow GM, Burke SK, Lazarus JM, Stenzel KH, Wombolt D, Goldberg D, Bonventre JV, Slatopolsky E: Poly[allylamine hydrochloride] (RenaGel): a noncalcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure. *Am J Kidney Dis* 29:66-71, 1997
190. Delmez JA, Kelber J, Norword KY, Giles KS, Slatopolsky E: Magnesium carbonate as a phosphorus binder: a prospective, controlled, crossover study. *Kidney Int* 49:163-167, 1996
191. van den Bergh JP, Gelens MA, Klaassen HA, Kaufmann BG, Bottger WM, Verstappen VM: Efficacy and tolerance of three different calcium acetate formulations in hemodialysis patients. *Neth J Med* 55:222-228, 1999
192. Tan SY, Irish A, Winearls CG, Brown EA, Gower PE, Clutterbuck EJ, Madhoo S, Lavender JP, Pepys MB, Hawkins PN: Long term effect of renal transplantation on dialysis-related amyloid deposits and symptomatology. *Kidney Int* 50:282-289, 1996
193. Ittel TH, Schafer C, Schmitt H, Gladziwa U, Sieberth HG: Calcium carbonate as a phosphate binder in dialysis patients: evaluation of an enteric-coated preparation and effect of additional aluminium hydroxide on hyperalbuminaemia. *Klin Wochenschr* 69:59-67, 1991
194. Bro S, Rasmussen RA, Handberg J, Olgaard K, Feldt-Rasmussen B: Randomized crossover study comparing the phosphate-binding efficacy of calcium ketoglutarate versus calcium carbonate in patients on chronic hemodialysis. *Am J Kidney Dis* 31:257-262, 1998
195. Jespersen B, Jensen JD, Nielsen HK, Lauridsen IN, Andersen MJ, Poulsen JH, Gammelgaard B, Pedersen EB: Comparison of calcium carbonate and aluminium hydroxide as phosphate binders on biochemical bone markers, PTH(1-84), and bone mineral content in dialysis patients. *Nephrol Dial Transplant* 6:98-104, 1991
196. Bame SI, Petersen N, Wray NP: Variation in hemodialysis patient compliance according to demographic characteristics. *Soc Sci Med* 37:1035-1043, 1993
197. Coyne T, Olson M, Bradham K, Garcon M, Gregory P, Scherch L: Dietary satisfaction correlated with adherence in the Modification of Diet in Renal Disease Study. *J Am Diet Assoc* 95:1301-1306, 1995
198. Cleary DJ, Matzke GR, Alexander AC, Joy MS: Medication knowledge and compliance among patients receiving long-term dialysis. *Am J Health Syst Pharm* 52:1895-1900, 1995
199. Morduchowicz G, Sulkes J, Aizic S, Gabbay U, Winkler J, Boner G: Compliance in hemodialysis patients: a multivariate regression analysis. *Nephron* 64:365-368, 1993
200. Weed-Collins M, Hogan R: Knowledge and health beliefs regarding phosphate-binding medication in predicting compliance. *Anna J* 16:278-282, 285; discussion 286, 1989
201. Cummings KM, Becker MH, Kirscht JP, Levin NW: Psychosocial factors affecting adherence to medical regimens in a group of hemodialysis patients. *Med Care* 20:567-580, 1982
202. Blackburn SL: Dietary compliance of chronic hemodialysis patients. *J Am Diet Assoc* 70:31-37, 1977
203. Coburn JW, Mischel MG, Goodman WG, Salusky IB: Calcium citrate markedly enhances aluminum absorption from aluminum hydroxide. *Am J Kidney Dis* 17:708-711, 1991
204. Chertow GM, Dillon M, Burke SK, Steg M, Bleyer AJ, Garrett BN, Domoto DT, Wilkes BM, Wombolt DG, Slatopolsky E: A randomized trial of sevelamer hydrochloride (RenaGel) with and without supplemental calcium. Strategies for the control of hyperphosphatemia and hyperparathyroidism in hemodialysis patients. *Clin Nephrol* 51:18-26, 1999
205. Chertow GM, Dillon MA, Amin N, Burke SK: Sevelamer with and without calcium and vitamin D: observations from a long-term open-label clinical trial. *J Ren Nutr* 10:125-132, 2000
206. Slatopolsky E, Finch J, Clay P, Martin D, Sicard G, Singer G, Gao P, Cantor T, Dusso A: A novel mechanism for skeletal resistance in uremia. *Kidney Int* 58:753-761, 2000
207. Kurz P, Monier-Faugere MC, Bognar B, Werner E, Roth P, Vlachojannis J, Malluche HH: Evidence for abnormal calcium homeostasis in patients with adynamic bone disease. *Kidney Int* 46:855-861, 1994
208. Chertow GM, Burke SK, Raggi P: Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int* 62:245-252, 2002
209. Nordin BEC: Nutritional consideration, in Calcium, Phosphate and Magnesium Metabolism, Nordin BEC (ed). New York, Churchill Livingstone, 1976, pp 3-35
210. Portale AA: Blood calcium, phosphorus, and magnesium, in *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, Favus MJ (ed). Philadelphia, Lippincott, Williams & Wilkins, 1999, pp 115-118
211. Elin RJ: Laboratory reference intervals and values, in *Cecil Textbook of Medicine*, Goldman L, Bennett JC (eds), 21st ed. Philadelphia, W. B. Saunders Co., 2000, pp 2299-2308
212. Enders DB, Rude RK: Mineral and bone metabolism, in *Tietz Fundamentals of Clinical Chemistry*, Burtis CA, Ashwood ER (eds), 5th ed. Philadelphia, W. B. Saunders Co., 2001, pp 795-821
213. Institute of Medicine. Dietary references intakes: calcium, phosphorus, magnesium, vitamin D3, and fluoride. Washington, DC, National Academy Press, 2000
214. Lemann J, Favus MJ: The intestinal absorption of calcium, magnesium, and phosphate, in *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, Favus MJ (ed). Philadelphia, Lippincott, Williams & Wilkins, 1999, pp 63-67

215. Brickman AS, Coburn JW, Massry SG, Norman AW: 1,25 Dihydroxy-vitamin D3 in normal man and patients with renal failure. *Ann Intern Med* 80:161-168, 1974
216. Shane E: Hypercalcemia; pathogenesis, clinical manifestation, differential diagnosis and management, in *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, Favus MJ (ed). Philadelphia, Lippincott, Williams & Wilkins, 1999, pp 183-187
217. Massry SG, Smogorzewski M: Dyscalcemias, in *Massry and Glasscock's Textbook of Nephrology*, Massry SG, Glasscock RJ (eds), Philadelphia, Lippincott, Williams & Wilkins, 2001, pp 326-340
218. Fernandez E, Montoliu J: Successful treatment of massive uraemic tumoral calcinosis with daily haemodialysis and very low calcium dialysate. *Nephrol Dial Transplant* 9:1207-1209, 1994
219. Baker SS, Cochran WJ, Flores CA, Georgieff MK, Jacobson MS, Jaksic T, Krebs NF: American Academy of Pediatrics. Committee on Nutrition. Calcium requirements of infants, children, and adolescents. *Pediatrics* 104:1152-1157, 1999
220. Raper NR, Zissa C, Rourke J: Nutrient Content of the US Food Supply, 1909-1988, in *Home Economics Research Report No. 50*. Washington, DC, US Dept of Agriculture, 1992
221. Hsu CH: Are we mismanaging calcium and phosphate metabolism in renal failure? *Am J Kidney Dis* 29:641-649, 1997
222. Andon MB, Peacock M, Kanerva RL, De Castro JA: Calcium absorption from apple and orange juice fortified with calcium citrate malate (CCM). *J Am Coll Nutr* 15:313-316, 1996
223. Gonzalez E, Martin K: Calcium, phosphorus and vitamin D. Philadelphia, PA, Lippincott-Raven, 1998
224. Weaver CM: Calcium bioavailability and its relation to osteoporosis. *Proc Soc Exp Biol Med* 200:157-160, 1992
225. Weaver CM, Proulx WR, Heaney R: Choices for achieving adequate dietary calcium with a vegetarian diet. *Am J Clin Nutr* 70:543S-548S, 1999
226. Weaver CM, Plawewski KL: Dietary calcium: adequacy of a vegetarian diet. *Am J Clin Nutr* 59:1238S-1241S, 1994
227. Clase CM, Norman GL, Beecroft ML, Churchill DN: Albumin-corrected calcium and ionized calcium in stable haemodialysis patients. *Nephrol Dial Transplant* 15:1841-1846, 2000
228. Morton AR, Hercz G: Hypercalcemia in dialysis patients: comparison of diagnostic methods. *Dial Transplant* 20:661-667, 1991
229. Rix M, Andreassen H, Eskildsen P, Langdahl B, Olgaard K: Bone mineral density and biochemical markers of bone turnover in patients with predialysis chronic renal failure. *Kidney Int* 56:1084-1093, 1999
230. Coburn JW, Popovtzer MM, Massry SG, Kleeman CR: The physicochemical state and renal handling of divalent ions in chronic renal failure. *Arch Intern Med* 124:302-311, 1969
231. Wasler M: The separate effects of hyperparathyroidism, hypercalcemia of malignancy, renal failure and acidosis on the state of calcium phosphate and other ions in plasma. *J Clin Invest* 41:1454-1464, 1962
232. Campos C, Arata RO, Mautalen CA: Parathyroid hormone and vertebral osteosclerosis in uremic patients. *Metabolism* 25:495-501, 1976
233. Fuss M, De Backer M, Brauman J, Nijs-Dewolf N, Manderlier T, Brauman H, Corvilain J: Parathyroid hormone plasma level in untreated chronic renal failure and in hemodialyzed patients. *Nephron* 17:144-154, 1976
234. Malhotra KK, Gaddekar NG, Umashankar P, Bhargava S: Bone disease in chronic renal failure. *Indian J Med Res* 56:1687-1695, 1968
235. Foley RN, Parfrey PS, Harnett JD, Kent GM, Hu L, O'Dea R, Murray DC, Barre PE: Hypocalcemia, morbidity, and mortality in end-stage renal disease. *Am J Nephrol* 16:386-393, 1996
236. Reichel H, Deibert B, Schmidt-Gayk H, Ritz E: Calcium metabolism in early chronic renal failure: implications for the pathogenesis of hyperparathyroidism. *Nephrol Dial Transplant* 6:162-169, 1991
237. Malluche HH, Werner E, Ritz E: Intestinal calcium absorption and whole-body calcium retention incipient and advanced renal failure. *Miner Electrolyte Metab* 1:263-270, 1978
238. Wiegmann TB, Kaye M: Malabsorption of calcium and phosphate in chronic renal failure: 32P and 45Ca studies in dialysis patients. *Clin Nephrol* 34:35-41, 1990
239. Mountokalakis TH, Singhellakis PN, Alevizaki CC, Virvidakis K, Ikkos DG: Relationship between degree of renal failure and impairment of intestinal calcium absorption. *Nephron* 16:20-30, 1976
240. Kopple JD, Coburn JW: Metabolic studies of low protein diets in uremia. II. Calcium, phosphorus and magnesium. *Medicine (Baltimore)* 52:597-607, 1973
241. Popovtzer MM, Michael UF, Johnson-Dial KS, Ronstadt C, Nelson D, Ogden DA: Dietary calcium deprivation and secondary hyperparathyroidism in patients treated with chronic dialysis. *Miner Electrolyte Metab* 12:298-302, 1986
242. Trachtman H, Chan JC, Boyle R, Farina D, Baluarte HJ, Chinchilli VM, Dresner IG, Feld LG: The relationship between calcium, phosphorus, and sodium intake, race, and blood pressure in children with renal insufficiency: a report of the Growth Failure in Children with Renal Diseases (GFRD) Study. *J Am Soc Nephrol* 6:126-131, 1995
243. Clarkson EM, Eastwood JB, Koutsaimanis KG, de Wardener HE: Net intestinal absorption of calcium in patients with chronic renal failure. *Kidney Int* 3:258-263, 1973
244. Hercz G, Kraut JA, Andress DA, Howard N, Roberts C, Shinaberger JH, Sherrard DJ, Coburn JW: Use of calcium carbonate as a phosphate binder in dialysis patients. *Miner Electrolyte Metab* 12:314-319, 1986
245. Moriniere P, Fournier A, Leflon A, Herve M, Sebert JL, Gregoire I, Bataille P, Gueris J: Comparison of 1 alpha-OH-vitamin D3 and high doses of calcium carbonate for the control of hyperparathyroidism and hyperaluminemia in patients on maintenance dialysis. *Nephron* 39:309-315, 1985
246. Petersen LJ, Rudnicki M, Hojsted J: Long-term oral calcium supplementation reduces diastolic blood pressure in end stage renal disease. A randomized, double-blind, placebo controlled study. *Int J Artif Organs* 17:37-40, 1994

247. Saha H, Pietila K, Mustonen J, Pasternack A, Morsky P, Seppala E, Reinikainen P: Acute effects of calcium carbonate and citrate on secondary hyperparathyroidism in chronic renal failure. *Am J Nephrol* 11:465-469, 1991
248. Maher ER, Young G, Smyth-Walsh B, Pugh S, Curtis JR: Aortic and mitral valve calcification in patients with end-stage renal disease. *Lancet* 2:875-877, 1987
249. Fernandez-Reyes MJ, Auxiliadora Bajo M, Robles P, Selgas R, Oliver J, Del Peso G, Garcia G, Jimenez C, Garcia-Gallego F: Mitral annular calcification in CAPD patients with a low degree of hyperparathyroidism. An analysis of other possible risk factors. *Nephrol Dial Transplant* 10:2090-2095, 1995
250. Valentzas C, Meindok H, Oreopoulos DG, Meema HK, Rabinovich S, Jones M, Sutton D, Rapaport A, deVeber GA: Visceral calcification and Ca - P product. *Adv Exp Med Biol* 103:187-193, 1978
251. Ribeiro S, Ramos A, Brandao A, Rebelo JR, Guerra A, Resina C, Vila-Lobos A, Carvalho F, Remedio F, Ribeiro F: Cardiac valve calcification in haemodialysis patients: role of calcium-phosphate metabolism. *Nephrol Dial Transplant* 13:2037-2040, 1998
252. Cassidy MJ, Owen JP, Ellis HA, Dewar J, Robinson CJ, Wilkinson R, Ward MK, Kerr DN: Renal osteodystrophy and metastatic calcification in long-term continuous ambulatory peritoneal dialysis. *Q J Med* 54:29-48, 1985
253. Milliner DS, Zinsmeister AR, Lieberman E, Landing B: Soft tissue calcification in pediatric patients with end-stage renal disease. *Kidney Int* 38:931-936, 1990
254. Bouillon RA, Auwerx JH, Lissens WD, Pelemans WK: Vitamin D status in the elderly: seasonal substrate deficiency causes 1,25-dihydroxycholecalciferol deficiency. *Am J Clin Nutr* 45:755-763, 1987
255. Ooms ME, Roos JC, Bezemer PD, van der Vijgh WJ, Bouter LM, Lips P: Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double-blind trial. *J Clin Endocrinol Metab* 80:1052-1058, 1995
256. Khaw KT, Sneyd MJ, Compston J: Bone density, parathyroid hormone and 25-hydroxyvitamin D concentrations in middle aged women. *Br Med J* 305:373-376, 1992
257. Eastwood JB, Stamp TC, De Wardener HE, Bordier PJ, Arnaud CD: The effect of 25-hydroxy vitamin D3 in the osteomalacia of chronic renal failure. *Clin Sci Mol Med* 52:499-508, 1977
258. Eastwood JB, Stamp TC, Harris E, de Wardener HE: Vitamin-D deficiency in the osteomalacia of chronic renal failure. *Lancet* 2:1209-1211, 1976
259. Chapuy MC, Meunier PJ: Vitamin D insufficiency in adults and the elderly, in Vitamin D, Feldman D, Glorieux FH, Pike JW (eds). San Diego, Academic Press, 1997, pp 679-693
260. Thomas MK, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, Vamvakas EC, Dick IM, Prince RL, Finkelstein JS: Hypovitaminosis D in medical inpatients. *N Engl J Med* 338:777-783, 1998
261. LeBoff MS, Kohlmeier L, Hurwitz S, Franklin J, Wright J, Glowacki J: Occult vitamin D deficiency in postmenopausal US women with acute hip fracture. *JAMA* 281:1505-1511, 1999
262. Koenig KG, Lindberg JS, Zerwekh JE, Padalino PK, Cushner HM, Copley JB: Free and total 1,25-dihydroxyvitamin D levels in subjects with renal disease. *Kidney Int* 41:161-165, 1992
263. Messa P, Vallone C, Mioni G, Geatti O, Turrin D, Passoni N, Cruciatti A: Direct in vivo assessment of parathyroid hormone-calcium relationship curve in renal patients. *Kidney Int* 46:1713-1720, 1994
264. Papapoulos SE, Clemens TL, Fraher LJ, Glead J, O'Riordan JL: Metabolites of vitamin D in human vitamin-D deficiency: effect of vitamin D3 or 1,25-dihydroxycholecalciferol. *Lancet* 2:612-615, 1980
265. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. *Am J Kidney Dis* 42:S1-S202, 2003 (suppl 3)
267. Holick MF: Vitamin D and the kidney. *Kidney Int* 32:912-929, 1987
268. Holick MF, Matsuoka LY, Wortsman J: Age, vitamin D, and solar ultraviolet. *Lancet* 2:1104-1105, 1989
269. Clemens TL, Adams JS, Henderson SL, Holick MF: Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. *Lancet* 1:74-76, 1982
270. Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, Meunier PJ: Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporos Int* 7:439-443, 1997
271. Saha H: Calcium and vitamin D homeostasis in patients with heavy proteinuria. *Clin Nephrol* 41:290-296, 1994
272. Kinyamu HK, Gallagher JC, Balhorn KE, Petranick KM, Rafferty KA: Serum vitamin D metabolites and calcium absorption in normal young and elderly free-living women and in women living in nursing homes. *Am J Clin Nutr* 65:790-797, 1997
273. Webb AR, Pilbeam C, Hanafin N, Holick MF: An evaluation of the relative contributions of exposure to sunlight and of diet to the circulating concentrations of 25-hydroxyvitamin D in an elderly nursing home population in Boston. *Am J Clin Nutr* 51:1075-1081, 1990
274. Ghazali A, Fardellone P, Pruna A, Atik A, Achard JM, Oprisiu R, Brazier M, Remond A, Moriniere P, Garabedian M, Eastwood J, Fournier A: Is low plasma 25-(OH)vitamin D a major risk factor for hyperparathyroidism and Looser's zones independent of calcitriol? *Kidney Int* 55:2169-2177, 1999
275. Lambert PW, Stern PH, Avioli RC, Brackett NC, Turner RT, Greene A, Fu IY, Bell NH: Evidence for extrarenal production of 1 alpha, 25-dihydroxyvitamin D in man. *J Clin Invest* 69:722-725, 1982
276. Dusso A, Lopez-Hilker S, Rapp N, Slatopolsky E: Extra-renal production of calcitriol in chronic renal failure. *Kidney Int* 34:368-375, 1988
277. Dusso AS, Finch J, Brown A, Ritter C, Delmez J, Schreiner G, Slatopolsky E: Extrarenal production of calcitriol in normal and uremic humans. *J Clin Endocrinol Metab* 72:157-164, 1991
278. Food and Nutrition Board. National Research Council. National Academy of Sciences. Recommended Daily Allowances. 10 ed. Washington, DC, National Academy Press, 1989
279. Food and Nutrition Board. National Research Council. National Academy of Sciences. Dietary Reference

- Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Washington, DC, National Academy Press, 1997
280. Shah BR, Finberg L: Single-day therapy for nutritional vitamin D-deficiency rickets: a preferred method. *J Pediatr* 125:487-490, 1994
281. Kruse K: Pathophysiology of calcium metabolism in children with vitamin D-deficiency rickets. *J Pediatr* 126:736-741, 1995
282. Combe C, Aparicio M: Phosphorus and protein restriction and parathyroid function in chronic renal failure. *Kidney Int* 46:1381-1386, 1994
283. Lafage MH, Combe C, Fournier A, Aparicio M: Ketodiet, physiological calcium intake and native vitamin D improve renal osteodystrophy. *Kidney Int* 42:1217-1225, 1992
284. Coburn JW, Tan AU Jr, Levine BS, Mazess RB, Kyllö DM, Knutson JC, Bishop CW: 1 alpha-Hydroxyvitamin D₂: a new look at an 'old' compound. *Nephrol Dial Transplant* 11:153-157, 1996 (suppl 3)
285. Harrington DD, Page EH: Acute vitamin D₃ toxicosis in horses: case reports and experimental studies of the comparative toxicity of vitamins D₂ and D₃. *J Am Vet Med Assoc* 182:1358-1369, 1983
286. van der Wielen RP, Lowik MR, van den Berg H, de Groot LC, Haller J, Moreiras O, van Staveren WA: Serum vitamin D concentrations among elderly people in Europe. *Lancet* 346:207-210, 1995
287. Lips P, van Ginkel FC, Jongen MJ, Rubertus F, van der Vijgh WJ, Netelenbos JC: Determinants of vitamin D status in patients with hip fracture and in elderly control subjects. *Am J Clin Nutr* 46:1005-1010, 1987
288. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, Delmas PD, Meunier PJ: Vitamin D₃ and calcium to prevent hip fractures in the elderly women. *N Engl J Med* 327:1637-1642, 1992
289. Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, Wong C, Stehman-Breen C: Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int* 58:396-399, 2000
290. Rickers H, Christiansen C, Christensen P, Christensen M, Rodbro P: Serum concentrations of vitamin D metabolites in different degrees of impaired renal function. Estimation of renal and extrarenal secretion rate of 24,25-dihydroxyvitamin D. *Nephron* 39:267-271, 1985
291. Martinez I, Saracho R, Montenegro J, Llach F: A deficit of calcitriol synthesis may not be the initial factor in the pathogenesis of secondary hyperparathyroidism. *Nephrol Dial Transplant* 11:22-28, 1996 (suppl 3)
292. Nordal KP, Dahl E: Low dose calcitriol versus placebo in patients with predialysis chronic renal failure. *J Clin Endocrinol Metab* 67:929-936, 1988
293. Coen G, Mazzaferro S, Bonucci E, Ballanti P, Massimetti C, Donato G, Landi A, Smacchi A, Della Rocca C, Cinotti GA, et al: Treatment of secondary hyperparathyroidism of predialysis chronic renal failure with low doses of 1,25(OH)₂D₃: humoral and histomorphometric results. *Miner Electrolyte Metab* 12:375-382, 1986
294. Bianchi ML, Colantonio G, Campanini F, Rossi R, Valenti G, Ortolani S, Buccioni G: Calcitriol and calcium carbonate therapy in early chronic renal failure. *Nephrol Dial Transplant* 9:1595-1599, 1994
295. Silver J, Naveh-Manly T, Mayer H, Schmelzer HJ, Popovtzer MM: Regulation by vitamin D metabolites of parathyroid hormone gene transcription in vivo in the rat. *J Clin Invest* 78:1296-1301, 1986
296. Przedlacki J, Manelius J, Huttunen K: Bone mineral density evaluated by dual-energy X-ray absorptiometry after one-year treatment with calcitriol started in the predialysis phase of chronic renal failure. *Nephron* 69:433-437, 1995
297. Baker LR, Abrams L, Roe CJ, Faugere MC, Fanti P, Subayti Y, Malluche HH: 1,25(OH)₂D₃ administration in moderate renal failure: a prospective double-blind trial. *Kidney Int* 35:661-669, 1989
298. Nordal KP, Dahl E, Halse J, Attramadal A, Flatmark A: Long-term low-dose calcitriol treatment in predialysis chronic renal failure: can it prevent hyperparathyroid bone disease? *Nephrol Dial Transplant* 10:203-206, 1995
299. Chesney RW, Moorthy AV, Eisman JA, Jax DK, Mazess RB, DeLuca HF: Increased growth after long-term oral 1alpha,25-vitamin D₃ in childhood renal osteodystrophy. *N Engl J Med* 298:238-242, 1978
300. Chan JC, McEnery PT, Chinchilli VM, Abitbol CL, Boineau FG, Friedman AL, Lum GM, Roy S, 3rd, Ruley EJ, Strife CF: A prospective, double-blind study of growth failure in children with chronic renal insufficiency and the effectiveness of treatment with calcitriol versus dihydroxycholesterol. The Growth Failure in Children with Renal Diseases Investigators. *J Pediatr* 124:520-528, 1994
301. Schmitt CP, Ardissino G, Testa S, Claris-Appiani A, Mehls O: Growth in children with chronic renal failure on intermittent versus daily calcitriol. *Pediatr Nephrol* 18:440-444, 2003
302. Kuizon BD, Goodman WG, Juppner H, Boechat I, Nelson P, Gales B, Salusky IB: Diminished linear growth during intermittent calcitriol therapy in children undergoing CCPD. *Kidney Int* 53:205-211, 1998
303. Waller S, Ledermann S, Trompeter R, van't Hoff W, Ridout D, Rees L: Catch-up growth with normal parathyroid hormone levels in chronic renal failure. *Pediatr Nephrol* 18:1236-1241, 2003
304. Coen G, Mazzaferro S, Manni M, Napoletano I, Fondi G, Sardella D, Perruzza I, Pasquali M, Taggi F: Treatment with small doses of 1,25-dihydroxyvitamin D in predialysis chronic renal failure may lower the rate of decline of renal function. *Ital J Miner Electrolyte Metab* 8:117-121, 1994
305. Jensen GF, Christiansen C, Transbol I: 1,25(OH)₂D₃ and renal function. A controlled clinical study in normal elderly women. *Acta Med Scand* 211:51-54, 1982
306. Bertoli M, Luisetto G, Ruffatti A, Urso M, Romagnoli G: Renal function during calcitriol therapy in chronic renal failure. *Clin Nephrol* 33:98-102, 1990
307. Perez A, Raab R, Chen TC, Turner A, Holick MF: Safety and efficacy of oral calcitriol (1,25-dihydroxyvitamin D₃) for the treatment of psoriasis. *Br J Dermatol* 134:1070-1078, 1996
308. Kanis JA, Cundy T, Earnshaw M, Henderson RG, Heynen G, Naik R, Russell RG, Smith R, Woods CG: Treatment of renal bone disease with 1 alpha-hydroxylated derivatives of vitamin D₃. Clinical, biochemical, radio-

graphic and histological responses. *Q J Med* 48:289-322, 1979

309. Naik RB, Cundy T, Robinson BH, Russell RG, Kanis JA: Effects of vitamin D metabolites and analogues on renal function. *Nephron* 28:17-25, 1981

310. Nielsen HE, Romer FK, Melsen F, Christensen MS, Hansen HE: 1 alpha-hydroxy vitamin D3 treatment of non-dialyzed patients with chronic renal failure. Effects on bone, mineral metabolism and kidney function. *Clin Nephrol* 13:103-108, 1980

311. Goodman WG, Salusky IB: Evolution of secondary hyperparathyroidism during oral calcitriol therapy in pediatric renal osteodystrophy. *Contrib Nephrol* 90:189-195, 1991

312. Salusky IB, Kuizon BD, Belin TR, Ramirez JA, Gales B, Segre GV, Goodman WG: Intermittent calcitriol therapy in secondary hyperparathyroidism: a comparison between oral and intraperitoneal administration. *Kidney Int* 54:907-914, 1998

313. Brickman AS, Coburn JW, Sherrard DJ, Wong EG, Norman AW, Singer FR: Clinical effects of 1,25-dihydroxyvitamin D3 in uremic patients with overt osteodystrophy. *Contrib Nephrol* 18:29-41, 1980

314. Kanis JA, Russell RG, Cundy T, Earnshaw M, Woods CG, Smith R, Heynen G: An evaluation of 1 alpha-hydroxy- and 1,25-dihydroxyvitamin D3 in the treatment of renal bone disease. *Contrib Nephrol* 18:12-28, 1980

315. Berl T, Berns AS, Huffer WE, Alfrey AC, Arnaud CD, Schrier RR: Controlled trial of the effects of 1,25-dihydroxycholecalciferol in patients treated with regular dialysis. *Contrib Nephrol* 18:72-81, 1980

316. Peacock M, Aaron JE, Walker GS, Davison AM: Bone disease and hyperparathyroidism in chronic renal failure: the effect of 1alpha-hydroxyvitamin D3. *Clin Endocrinol (Oxf)* 7 Suppl:73s-81s, 1977

317. Herrmann P, Ritz E, Schmidt-Gayk H, Schafer I, Geyer J, Nonnast-Daniel B, Koch KM, Weber U, Horl W, Haas-Worle A, et al.: Comparison of intermittent and continuous oral administration of calcitriol in dialysis patients: a randomized prospective trial. *Nephron* 67:48-53, 1994

318. Papapoulos SE, Brownjohn AM, Junor BJ, Marsh FP, Goodwin FJ, Hatley W, Lewin IG, Tomlinson S, Hendy GN, O'Riordan JL: Hyperparathyroidism in chronic renal failure. *Clin Endocrinol (Oxf)* 7 Suppl:59s-65s, 1977

319. Moriniere P, Esper NE, Viron B, Judith D, Bourgeon B, Farquet C, Gheerbrandt JD, Chapuy MC, Orshoven AV, Pamphile R, Fournier A: Improvement of severe secondary hyperparathyroidism in dialysis patients by intravenous 1-alpha(OH) vitamin D3, oral CaCo3 and low dialysate calcium. *Kidney Int* 43:S121-S124, 1993 (suppl 41)

320. Morii H, Ogura Y, Koshikawa S, Mimura N, Suzuki M, Kurokawa K, Marumo F, Kawaguchi Y, Maeda K, Nishizawa Y, Inoue S, Fujimi S: Efficacy and safety of oral falecalcitriol in reducing parathyroid hormone in hemodialysis patients with secondary hyperparathyroidism. *J Bone Miner Metab* 16, 1988

321. Martin KJ, Gonzalez EA, Gellens M, Hamm LL, Abboud H, Lindberg J: 19-Nor-1-alpha-25-dihydroxyvitamin D2 (Paricalcitol) safely and effectively reduces the levels of intact parathyroid hormone in patients on hemodialysis. *J Am Soc Nephrol* 9:1427-1432, 1998

322. Frazao JM, Elangovan L, Maung HM, Chesney RW, Acchiardo SR, Bower JD, Kelley BJ, Rodriguez HJ, Norris KC, Robertson JA, Levine BS, Goodman WG, Gentile D, Mazess RB, Kylo DM, Douglass LL, Bishop CW, Coburn JW: Intermittent doxercalciferol (1alpha-hydroxyvitamin D(2)) therapy for secondary hyperparathyroidism. *Am J Kidney Dis* 36:550-561, 2000

323. Maung HM, Elangovan L, Frazao JM, Bower JD, Kelley BJ, Acchiardo SR, Rodriguez HJ, Norris KC, Sigala JF, Rutkowski M, Robertson JA, Goodman WG, Levine BS, Chesney RW, Mazess RB, Kylo DM, Douglass LL, Bishop CW, Coburn JW: Efficacy and side effects of intermittent intravenous and oral doxercalciferol (1alpha-hydroxyvitamin D(2)) in dialysis patients with secondary hyperparathyroidism: a sequential comparison. *Am J Kidney Dis* 37:532-543, 2001

324. Sherrard DJ, Coburn JW, Brickman AS, Singer FR, Maloney N: Skeletal response to treatment with 1,25-dihydroxyvitamin D in renal failure. *Contrib Nephrol* 18:92-97, 1980

325. Krempien B, Ritz E, Tschope W: The effect of 1,25 (OH)2D3 on bone mineralization: ultrastructural studies in patients with renal osteodystrophy. *Contrib Nephrol* 18:122-134, 1980

326. Tan AU Jr, Levine BS, Mazess RB, Kylo DM, Bishop CW, Knutson JC, Kleinman KS, Coburn JW: Effective suppression of parathyroid hormone by 1 alpha-hydroxyvitamin D2 in hemodialysis patients with moderate to severe secondary hyperparathyroidism. *Kidney Int* 51:317-323, 1997

327. Sherrard DJ, Hercz G, Pei Y, Maloney NA, Greenwood C, Manuel A, Saiphoo C, Fenton SS, Segre GV: The spectrum of bone disease in end-stage renal failure—an evolving disorder. *Kidney Int* 43:436-442, 1993

328. Goodman WG, Ramirez JA, Belin TR, Chon Y, Gales B, Segre GV, Salusky IB: Development of adynamic bone in patients with secondary hyperparathyroidism after intermittent calcitriol therapy. *Kidney Int* 46:1160-1166, 1994

329. Quarles LD, Lobaugh B, Murphy G: Intact parathyroid hormone overestimates the presence and severity of parathyroid-mediated osseous abnormalities in uremia. *J Clin Endocrinol Metab* 75:145-150, 1992

330. Sprague SM, Moe SM: Safety and efficacy of long-term treatment of secondary hyperparathyroidism by low-dose intravenous calcitriol. *Am J Kidney Dis* 19:532-539, 1992

331. Cannella G, Bonucci E, Rolla D, Ballanti P, Moriero E, De Grandi R, Augeri C, Claudiani F, Di Maio G: Evidence of healing of secondary hyperparathyroidism in chronically hemodialyzed uremic patients treated with long-term intravenous calcitriol. *Kidney Int* 46:1124-1132, 1994

332. Dressler R, Laut J, Lynn RI, Ginsberg N: Long-term high dose intravenous calcitriol therapy in end-stage renal disease patients with severe secondary hyperparathyroidism. *Clin Nephrol* 43:324-331, 1995

333. Llach F, Hervas J, Cerezo S: The importance of dosing intravenous calcitriol in dialysis patients with severe hyperparathyroidism. *Am J Kidney Dis* 26:845-851, 1995

334. Fukuda N, Tanaka H, Tominaga Y, Fukagawa M, Kurokawa K, Seino Y: Decreased 1,25-dihydroxyvitamin

- D3 receptor density is associated with a more severe form of parathyroid hyperplasia in chronic uremic patients. *J Clin Invest* 92:1436-1443, 1993
335. Slatopolsky E, Weerts C, Thielan J, Horst R, Harter H, Martin KJ: Marked suppression of secondary hyperparathyroidism by intravenous administration of 1,25-dihydroxycholecalciferol in uremic patients. *J Clin Invest* 74:2136-2143, 1984
336. Fukagawa M, Kitaoka M, Yi H, Fukuda N, Matsumoto T, Ogata E, Kurokawa K: Serial evaluation of parathyroid size by ultrasonography is another useful marker for the long-term prognosis of calcitriol pulse therapy in chronic dialysis patients. *Nephron* 68:221-228, 1994
337. Fukagawa M, Okazaki R, Takano K, Kaname S, Ogata E, Kitaoka M, Harada S, Sekine N, Matsumoto T, Kurokawa K: Regression of parathyroid hyperplasia by calcitriol-pulse therapy in patients on long-term dialysis. *N Engl J Med* 323:421-422, 1990
338. Tsukamoto Y, Nomura M, Takahashi Y, Takagi Y, Yoshida A, Nagaoka T, Togashi K, Kikawada R, Marumo F: The 'oral 1,25-dihydroxyvitamin D3 pulse therapy' in hemodialysis patients with severe secondary hyperparathyroidism. *Nephron* 57:23-28, 1991
339. Muramoto H, Haruki K, Yoshimura A, Mimo N, Oda K, Tofuku Y: Treatment of refractory hyperparathyroidism in patients on hemodialysis by intermittent oral administration of 1,25(OH)₂vitamin D₃. *Nephron* 58:288-294, 1991
340. Baker LR, Muir JW, Sharman VL, Abrams SM, Greenwood RN, Cattell WR, Goodwin FJ, Marsh FP, Adami S, Hately W: Controlled trial of calcitriol in hemodialysis patients. *Clin Nephrol* 26:185-191, 1986
341. Memmos DE, Eastwood JB, Talner LB, Gower PE, Curtis JR, Phillips ME, Carter GD, Alagband-Zadeh J, Roberts AP, de Wardener HE: Double-blind trial of oral 1,25-dihydroxy vitamin D₃ versus placebo in asymptomatic hyperparathyroidism in patients receiving maintenance haemodialysis. *Br Med J (Clin Res Ed)* 282:1919-1924, 1981
342. Bacchini G, Fabrizi F, Pontoriero G, Marcelli D, Di Filippo S, Locatelli F: 'Pulse oral' versus intravenous calcitriol therapy in chronic hemodialysis patients. A prospective and randomized study. *Nephron* 77:267-272, 1997
343. Indridason OS, Quarles LD: Comparison of treatments for mild secondary hyperparathyroidism in hemodialysis patients. *Durham Renal Osteodystrophy Study Group. Kidney Int* 57:282-292, 2000
344. Fischer ER, Harris DC: Comparison of intermittent oral and intravenous calcitriol in hemodialysis patients with secondary hyperparathyroidism. *Clin Nephrol* 40:216-220, 1993
345. Liou HH, Chiang SS, Huang TP, Shieh SD, Akmal M: Comparative effect of oral or intravenous calcitriol on secondary hyperparathyroidism in chronic hemodialysis patients. *Miner Electrolyte Metab* 20:97-102, 1994
346. Caravaca F, Cubero JJ, Jimenez F, Lopez JM, Aparicio A, Cid MC, Pizarro JL, Liso J, Santos I: Effect of the mode of calcitriol administration on PTH-ionized calcium relationship in uremic patients with secondary hyperparathyroidism. *Nephrol Dial Transplant* 10:665-670, 1995
347. Quarles LD, Yohay DA, Carroll BA, Spritzer CE, Minda SA, Bartholomay D, Lobaugh BA: Prospective trial of pulse oral versus intravenous calcitriol treatment of hyperparathyroidism in ESRD. *Kidney Int* 45:1710-1721, 1994
348. Levine BS, Song M: Pharmacokinetics and efficacy of pulse oral versus intravenous calcitriol in hemodialysis patients. *J Am Soc Nephrol* 7:488-496, 1996
349. Gallieni M, Brancaccio D, Padovese P, Rolla D, Bedani P, Colantonio G, Bronzieri C, Bagni B, Tarolo G: Low-dose intravenous calcitriol treatment of secondary hyperparathyroidism in hemodialysis patients. Italian Group for the Study of Intravenous Calcitriol. *Kidney Int* 42:1191-1198, 1992
350. Moe SM, Kraus MA, Gassensmith CM, Fineberg NS, Gannon FH, Peacock M: Safety and efficacy of pulse and daily calcitriol in patients on CAPD: a randomized trial. *Nephrol Dial Transplant* 13:1234-1241, 1998
351. Brown AJ, Slatopolsky E: Vitamin D analogs: perspectives for treatment. *Miner Electrolyte Metab* 25:337-341, 1999
352. Slatopolsky E, Dusso A, Brown A: New analogs of vitamin D₃. *Kidney Int Suppl* 73:S46-S51, 1999
353. Kurokawa K, Akizawa T, Suzuki M, Akiba T, Ogata E, Slatopolsky E: Effect of 22-oxacalcitriol on hyperparathyroidism of dialysis patients: results of a preliminary study. *Nephrol Dial Transplant* 11:121-124, 1996 (suppl 3)
354. Akiba T, Marumo F, Owada A, Kurihara S, Inoue A, Chida Y, Ando R, Shinoda T, Ishida Y, Ohashi Y: Controlled trial of falecalcitriol versus alfalcidol in suppression of parathyroid hormone in hemodialysis patients with secondary hyperparathyroidism. *Am J Kidney Dis* 32:238-246, 1998
355. Taga T: The signal transducer gp130 is shared by interleukin-6 family of haematopoietic and neurotrophic cytokines. *Ann Med* 29:63-72, 1997
356. Slatopolsky E, Finch J, Ritter C, Denda M, Morrissey J, Brown A, DeLuca H: A new analog of calcitriol, 19-nor-1,25-(OH)₂D₂, suppresses parathyroid hormone secretion in uremic rats in the absence of hypercalcemia. *Am J Kidney Dis* 26:852-860, 1995
357. Nishii Y, Abe J, Mori T, Brown AJ, Dusso AS, Finch J, Lopez-Hilker S, Morrissey J, Slatopolsky E: The noncalcemic analogue of vitamin D, 22-oxacalcitriol, suppresses parathyroid hormone synthesis and secretion. *Contrib Nephrol* 91:123-128, 1991
358. Sjoden G, Lindgren JU, DeLuca HF: Antirachitic activity of 1 alpha-hydroxyergocalciferol and 1 alpha-hydroxycholecalciferol in rats. *J Nutr* 114:2043-2046, 1984
359. Sjoden G, Smith C, Lindgren U, DeLuca HF: 1 alpha-Hydroxyvitamin D₂ is less toxic than 1 alpha-hydroxyvitamin D₃ in the rat. *Proc Soc Exp Biol Med* 178:432-436, 1985
360. Gallagher JC, Bishop CW, Knutson JC, Mazess RB, DeLuca HF: Effects of increasing doses of 1 alpha-hydroxyvitamin D₂ on calcium homeostasis in postmenopausal osteopenic women. *J Bone Miner Res* 9:607-614, 1994
361. Weber K, Goldberg M, Stangassinger M, Erben RG: 1alpha-hydroxyvitamin D₂ is less toxic but not bone selective relative to 1alpha-hydroxyvitamin D₃ in ovariectomized rats. *J Bone Miner Res* 16:639-651, 2001
362. Vlassopoulos D, Noussias C, Revenas K, Hadjilouka-Mantaka A, Arvanitis D, Tzortzis G, Hadjicostantinou V:

- Long-term effects of small doses of calcitriol in hemodialysis patients with moderate secondary hyperparathyroidism. *Ren Fail* 21:199-207, 1999
363. Martinez ME, Selgas R, Miguel JL, Balaguer G, Sanchez-Cabezudo MJ, Llach F: Osteocalcin levels in uremic patients: influence of calcitriol treatment through two different routes and type of dialysis. *Nephron* 59:429-433, 1991
364. Morita A, Tabata T, Inoue T, Nishizawa Y, Morii H: The effect of oral 1 alpha-hydroxycalciferol treatment on bone mineral density in hemodialysis patients. *Clin Nephrol* 46:389-393, 1996
365. Shimamatsu K, Maeda T, Harada A, Nishitani H, Onoyama K, Fujimi S, Omae T: 1-year controlled trial of 1 alpha-hydroxycholecalciferol in patients on maintenance hemodialysis. *Nephron* 28:70-75, 1981
366. Hercz G, Pei Y, Greenwood C, Manuel A, Saiphoo C, Goodman WG, Segre GV, Fenton S, Sherrard DJ: Aplastic osteodystrophy without aluminum: the role of "suppressed" parathyroid function. *Kidney Int* 44:860-866, 1993
367. Address DL, Norris KC, Coburn JW, Slatopolsky EA, Sherrard DJ: Intravenous calcitriol in the treatment of refractory osteitis fibrosa of chronic renal failure. *N Engl J Med* 321:274-279, 1989
368. Kanis JA, Russell RG, Naik RB, Earnshaw M, Smith R, Heynen G, Woods CG: Factors influencing the response to 1alpha-hydroxyvitamin D3 in patients with renal bone disease. *Clin Endocrinol (Oxf)* 7 Suppl:51s-57s, 1977
369. Malluche HH, Goldstein DA, Massry SG: Effects of 6 months therapy with 1,25 (OH)2D3 on bone disease of dialysis patients. *Contrib Nephrol* 18:98-104, 1980
370. Delling G, Luhmann H, Bulla M, Fuchs C, Henning HV, Jansen JL, Kohnle W, Schulz W: The action of 1,25 (OH)2D3 on turnover kinetic, remodelling surfaces and structure of trabecular bone in chronic renal failure. *Contrib Nephrol* 18:105-121, 1980
371. Johnson WJ, Goldsmith RS, Beabout JW, Jowsey J, Kelly PJ, Arnaud CD: Prevention and reversal of progressive secondary hyperparathyroidism in patients maintained by hemodialysis. *Am J Med* 56:827-832, 1974
372. Sanchez CP, Salusky IB, Kuizon BD, Ramirez JA, Gales B, Ettenger RB, Goodman WG: Bone disease in children and adolescents undergoing successful renal transplantation. *Kidney Int* 53:1358-1364, 1998
373. London GM, Marty C, Marchais SJ, Guerin AP, Metivier F, de Vernejoul MC: Arterial calcifications and bone histomorphometry in end-stage renal disease. *J Am Soc Nephrol* 15:1943-1951, 2004
374. Piraino B, Bernardini J, Holley J, Johnston JR, Perlmutter JA, Martis L: Calcium mass transfer in peritoneal dialysis patients using 2.5 mEq/l calcium dialysate. *Clin Nephrol* 37:48-51, 1992
375. Malberti F, Corradi B, Imbasciati E: Calcium mass transfer and kinetics in CAPD using calcium-free solutions. *Adv Perit Dial* 9:274-279, 1993
376. Weinreich T, Colombi A, Echterhoff HH, Mielke G, Nebel M, Ziegelmayer C, Passlick-Deetjen J: Transperitoneal calcium mass transfer using dialysate with a low calcium concentration (1.0 mM). *Perit Dial Int* 13:S467-S470, 1993 (suppl 2)
377. Sieniawska M, Roszkowska-Blaim M, Wojciechowska B: The influence of dialysate calcium concentration on the PTH level in children undergoing CAPD. *Perit Dial Int* 16:S567-S569, 1996 (suppl 1)
378. Banalagay EE, Bernardini J, Piraino B: Calcium mass transfer with 10-hour dwell time using 1.25 versus 1.75 mmol/L calcium dialysate. *Adv Perit Dial* 9:271-273, 1993
379. Fabrizi F, Bacchini G, Di Filippo S, Pontoriero G, Locatelli F: Intradialytic calcium balances with different calcium dialysate levels. Effects on cardiovascular stability and parathyroid function. *Nephron* 72:530-535, 1996
380. Fernandez E, Borrás M, Pais B, Montoliu J: Low-calcium dialysate stimulates parathormone secretion and its long-term use worsens secondary hyperparathyroidism. *J Am Soc Nephrol* 6:132-135, 1995
381. Honkanen E, Kala AR, Gronhagen-Riska C, Ikaheimo R: CAPD with low calcium dialysate and calcium carbonate: results of a 24-week study. *Adv Perit Dial* 8:356-361, 1992
382. Bro S, Brandi L, Olgaard K: High-normal calcium (1.35 mmol/l) dialysate in patients on CAPD: efficient and safe long-term control of plasma calcium, phosphate, and parathyroid hormone. *Nephrol Dial Transplant* 11:1586-1591, 1996
383. Hutchison AJ, Freemont AJ, Boulton HF, Gokal R: Low-calcium dialysis fluid and oral calcium carbonate in CAPD. A method of controlling hyperphosphataemia whilst minimizing aluminium exposure and hypercalcaemia. *Nephrol Dial Transplant* 7:1219-1225, 1992
384. Sawyer N, Noonan K, Altmann P, Marsh F, Cunningham J: High-dose calcium carbonate with stepwise reduction in dialysate calcium concentration: effective phosphate control and aluminium avoidance in haemodialysis patients. *Nephrol Dial Transplant* 4:105-109, 1989
385. Carozzi S, Nasini MG, Santoni O, Pietrucci A: Low- and high-turnover bone disease in continuous ambulatory peritoneal dialysis: effects of low-Ca²⁺ peritoneal dialysis solution. *Perit Dial Int* 13:S473-S475, 1993 (suppl 2)
386. Brandi L, Nielsen PK, Bro S, Daugaard H, Olgaard K: Long-term effects of intermittent oral alphacalcidol, calcium carbonate and low-calcium dialysis (1.25 mmol L⁻¹) on secondary hyperparathyroidism in patients on continuous ambulatory peritoneal dialysis. *J Intern Med* 244:121-131, 1998
387. Buijsen CG, Struijk DG, Huijgen HJ, Boeschoten EW, Wilink JM: Can low-calcium peritoneal dialysis solution safely replace the standard calcium solution in the majority of chronic peritoneal dialysis patients? *Perit Dial Int* 16:497-504, 1996
388. Shigematsu T, Kawaguchi Y, Kubo H, Nakayama M, Kato N, Yamamoto H, Osaka N, Hayakawa H, Ogawa A, Sakai O: Low calcium (1.25 mmol/L) dialysate can normalize relative hypoparathyroidism in CAPD patients with low bone turnover. *Adv Perit Dial* 12:250-256, 1996
389. Chertow GM, Burke SK, Dillon MA, Slatopolsky E: Long-term effects of sevelamer hydrochloride on the calcium x phosphate product and lipid profile of haemodialysis patients. *Nephrol Dial Transplant* 14:2907-2914, 1999
390. Slatopolsky E, Weerts C, Norwood K, Giles K, Fryer P, Finch J, Windus D, Delmez J: Long-term effects of

- calcium carbonate and 2.5 mEq/liter calcium dialysate on mineral metabolism. *Kidney Int* 36:897-903, 1989
391. Goldberg DI, Dillon MA, Slatopolsky EA, Garrett B, Gray JR, Marbury T, Weinberg M, Wombolt D, Burke SK: Effect of RenaGel, a non-absorbed, calcium- and aluminium-free phosphate binder, on serum phosphorus, calcium, and intact parathyroid hormone in end-stage renal disease patients. *Nephrol Dial Transplant* 13:2303-2310, 1998
392. Morrison G, Michelson EL, Brown S, Morganroth J: Mechanism and prevention of cardiac arrhythmias in chronic hemodialysis patients. *Kidney Int* 17:811-819, 1980
393. Nappi SE, Virtanen VK, Saha HH, Mustonen JT, Pasternack AI: QTc dispersion increases during hemodialysis with low-calcium dialysate. *Kidney Int* 57:2117-2122, 2000
394. Nappi SE, Saha HH, Virtanen VK, Mustonen JT, Pasternack AI: Hemodialysis with high-calcium dialysate impairs cardiac relaxation. *Kidney Int* 55:1091-1096, 1999
395. Kyriazis J, Stamatiadis D, Mamouna A: Intradialytic and interdialytic effects of treatment with 1.25 and 1.75 mmol/L of calcium dialysate on arterial compliance in patients on hemodialysis. *Am J Kidney Dis* 35:1096-1103, 2000
396. Weinreich T, Passlick-Deetjen J, Ritz E: Low dialysate calcium in continuous ambulatory peritoneal dialysis: a randomized controlled multicenter trial. The Peritoneal Dialysis Multicenter Study Group. *Am J Kidney Dis* 25:452-460, 1995
397. Wadhwa NK, Howell N, Suh H, Cabralda T: Low calcium (2.5 mEq/l) and high calcium (3.5 mEq/l) dialysate in peritoneal dialysis patients. *Adv Perit Dial* 8:385-388, 1992
398. Stein A, Baker F, Moorhouse J, Walls J: Peritonitis rate: traditional versus low calcium dialysate. *Am J Kidney Dis* 26:632-633, 1995
399. Weinreich T, Ritz E, Passlick-Deetjen J: Long-term dialysis with low-calcium solution (1.0 mmol/L) in CAPD: effects on bone mineral metabolism. Collaborators of the Multicenter Study Group. *Perit Dial Int* 16:260-268, 1996
400. Van der Niepen P, Sennesael J, Louis O, Verbeelen D: Effect of treatment with 1.25 and 1.75 mmol/l calcium dialysate on bone mineral density in haemodialysis patients. *Nephrol Dial Transplant* 10:2253-2258, 1995
401. Hamdy NA, Boletis J, Charlesworth D, Kanis JA, Brown CB: Low calcium dialysate increases the tolerance to vitamin D in peritoneal dialysis. *Contrib Nephrol* 89:190-198, 1991
402. Holgado R, Haire H, Ross D, Sprague S, Pahl M, Jara A, Martin-Malo A, Rodriguez M, Almaden Y, Felsenfeld AJ: Effect of a low calcium dialysate on parathyroid hormone secretion in diabetic patients on maintenance hemodialysis. *J Bone Miner Res* 15:927-935, 2000
403. Johnson DW, Rigby RJ, McIntyre HD, Brown A, Freeman J: A randomized trial comparing 1.25 mmol/l calcium dialysate to 1.75 mmol/l calcium dialysate in CAPD patients. *Nephrol Dial Transplant* 11:88-93, 1996
404. Armstrong A, Beer J, Noonan K, Cunningham J: Reduced calcium dialysate in CAPD patients: efficacy and limitations. *Nephrol Dial Transplant* 12:1223-1228, 1997
405. Fine RN, Kohaut EC, Brown D, Perlman AJ: Growth after recombinant human growth hormone treatment in children with chronic renal failure: report of a multicenter randomized double-blind placebo-controlled study. Genentech Cooperative Study Group. *J Pediatr* 124:374-382, 1994
406. Schaefer F, Wuhl E, Haffner D, Mehls O: Stimulation of growth by recombinant human growth hormone in children undergoing peritoneal or hemodialysis treatment. German Study Group for Growth Hormone Treatment in Chronic Renal Failure. *Adv Perit Dial* 10:321-326, 1994
407. Haffner D, Schaefer F, Nissel R, Wuhl E, Tonshoff B, Mehls O: Effect of growth hormone treatment on the adult height of children with chronic renal failure. German Study Group for Growth Hormone Treatment in Chronic Renal Failure. *N Engl J Med* 343:923-930, 2000
408. Van Dyck M, Bilem N, Proesmans W: Conservative treatment for chronic renal failure from birth: a 3-year follow-up study. *Pediatr Nephrol* 13:865-869, 1999
409. Nixon JV, Narahara KA, Smitherman TC: Estimation of myocardial involvement in patients with acute myocardial infarction by two-dimensional echocardiography. *Circulation* 62:1248-1255, 1980
410. Prasad V, Greig F, Bastian W, Castells S, Juan C, AvRuskin TW: Slipped capital femoral epiphysis during treatment with recombinant growth hormone for isolated, partial growth hormone deficiency. *J Pediatr* 116:397-399, 1990
411. Fine RN, Kohaut E, Brown D, Kuntze J, Attie KM: Long-term treatment of growth retarded children with chronic renal insufficiency, with recombinant human growth hormone. *Kidney Int* 49:781-785, 1996
412. Mehls O, Broyer M: Growth response to recombinant human growth hormone in short prepubertal children with chronic renal failure with or without dialysis. The European/Australian Study Group. *Acta Paediatr Suppl* 399:81-87, 1994
413. Van Dyck M, Gyssels A, Proesmans W, Nijs J, Eeckels R: Growth hormone treatment enhances bone mineralisation in children with chronic renal failure. *Eur J Pediatr* 160:359-363, 2001
414. van der Sluis IM, Boot AM, Nauta J, Hop WC, de Jong MC, Lilien MR, Groothoff JW, van Wijk AE, Pols HA, Hokken-Koelega AC, de Muinck Keizer-Schrama SM: Bone density and body composition in chronic renal failure: effects of growth hormone treatment. *Pediatr Nephrol* 15:221-228, 2000
415. Lanes R, Gunczler P, Orta N, Bosquez M, Scovino R, Dominguez L, Esaa S, Weisinger JR: Changes in bone mineral density, growth velocity and renal function of prepubertal uremic children during growth hormone treatment. *Horm Res* 46:263-268, 1996
416. Fujisawa Y, Kida K: Effect of growth hormone (GH) therapy on parathyroid hormone metabolism in a girl with GH deficient short stature and chronic renal failure. *J Pediatr Endocrinol Metab* 9:555-558, 1996
417. Sieniawska M, Panczyk-Tomaszewska M, Ziolkowska H: The influence of growth hormone treatment on bone metabolism in dialysis patients. *Br J Clin Pract Suppl* 85:61-63, 1996
418. Kaufman DB: Growth hormone and renal osteodystrophy: a case report. *Pediatr Nephrol* 12:157-159, 1998
419. Milliner DS, Shinaberger JH, Shuman P, Coburn JW: Inadvertent aluminum administration during plasma ex-

- change due to aluminum contamination of albumin-replacement solutions. *N Engl J Med* 312:165-167, 1985
420. Daly AL, Velazquez LA, Bradley SF, Kauffman CA: Mucormycosis: association with deferoxamine therapy. *Am J Med* 87:468-471, 1989
421. Alfrey AC: The toxicity of the aluminum burden. *Semin Nephrol* 3:329-334, 1983
422. Graf H, Stummvoll HK, Meisinger V, Kovarik J, Wolf A, Pinggera WF: Aluminum removal by hemodialysis. *Kidney Int* 19:587-592, 1981
423. Trapp GA: Plasma aluminum is bound to transferrin. *Life Sci* 33:311-316, 1983
424. Alfrey AC: Aluminum metabolism in uremia. *Neurotoxicol* 1:43-53, 1980
425. Alfrey AC, Hegg A, Craswell P: Metabolism and toxicity of aluminum in renal failure. *Am J Clin Nutr* 33:1509-1516, 1980
426. Alfrey AC, LeGendre GR, Kaehny WD: The dialysis encephalopathy syndrome. Possible aluminum intoxication. *N Engl J Med* 294:184-188, 1976
427. Kerr DN, Ward MK, Arze RS, Ramos JM, Grekas D, Parkinson IS, Ellis HA, Owen JP, Simpson W, Dewar J, et al: Aluminum-induced dialysis osteodystrophy: the demise of "Newcastle bone disease"? *Kidney Int Suppl* 18:S58-S64, 1986
428. Ward MK, Feest TG, Ellis HA, Parkinson IS, Kerr DN: Osteomalacic dialysis osteodystrophy: Evidence for a water-borne aetiological agent, probably aluminium. *Lancet* 1:841-845, 1978
429. Parkinson IS, Ward MK, Feest TG, Fawcett RW, Kerr DN: Fracturing dialysis osteodystrophy and dialysis encephalopathy. An epidemiological survey. *Lancet* 1:406-409, 1979
430. Parkinson IS, Ward MK, Kerr DN: Dialysis encephalopathy, bone disease and anaemia: the aluminum intoxication syndrome during regular haemodialysis. *J Clin Pathol* 34:1285-1294, 1981
431. McGonigle RJ, Parsons V: Aluminium-induced anaemia in haemodialysis patients. *Nephron* 39:1-9, 1985
432. O'Hare JA, Murnaghan DJ: Reversal of aluminum-induced hemodialysis anemia by a low-aluminum dialysate. *N Engl J Med* 306:654-656, 1982
433. Berkseth RO, Shapiro FL: An epidemic of dialysis encephalopathy and exposure to high aluminum dialysate, in *Controversies in Nephrology*, Schreiner GE, Winchester JF (eds), Washington, DC, Georgetown University Press, 1980, pp 42-51
434. Simoes J, Barata JD, D'Haese PC, De Broe ME: Cela n'arrive qu'aux autres (aluminium intoxication only happens in the other nephrologist's dialysis centre). *Nephrol Dial Transplant* 9:67-68, 1994
435. LeGendre GR, Alfrey AC: Measuring picogram amounts of aluminum in biological tissue by flameless atomic absorption analysis of a chelate. *Clin Chem* 22:53-56, 1976
436. Bakir AA, Hryhorczuk DO, Berman E, Dunea G: Acute fatal hyperaluminemic encephalopathy in undialyzed and recently dialyzed uremic patients. *ASAIO Trans* 32:171-176, 1986
437. Kirschbaum BB, Schoolwerth AC: Acute aluminum toxicity associated with oral citrate and aluminum-containing antacids. *Am J Med Sci* 297:9-11, 1989
438. Molitoris BA, Froment DH, Mackenzie TA, Huffer WH, Alfrey AC: Citrate: a major factor in the toxicity of orally administered aluminum compounds. *Kidney Int* 36:949-953, 1989
439. Nolan CR, Califano JR, Butzin CA: Influence of calcium acetate or calcium citrate on intestinal aluminum absorption. *Kidney Int* 38:937-941, 1990
440. Sherrard DJ, Walker JV, Boykin JL: Precipitation of dialysis dementia by deferoxamine treatment of aluminum-related bone disease. *Am J Kidney Dis* 12:126-130, 1988
441. McCauley J, Sorkin MI: Exacerbation of aluminium encephalopathy after treatment with desferrioxamine. *Nephrol Dial Transplant* 4:110-114, 1989
442. Alfrey AC, Mishell JM, Burks J, Contiguglia SR, Rudolph H, Lewin E, Holmes JH: Syndrome of dyspraxia and multifocal seizures associated with chronic hemodialysis. *Trans Am Soc Artif Intern Organs* 18:257-261, 266-257, 1972
443. Dunea G, Mahurkar SD, Mamdani B, Smith EC: Role of aluminum in dialysis dementia. *Ann Intern Med* 88:502-504, 1978
444. Hodsman AB, Sherrard DJ, Wong EG, Brickman AS, Lee DB, Alfrey AC, Singer FR, Norman AW, Coburn JW: Vitamin-D-resistant osteomalacia in hemodialysis patients lacking secondary hyperparathyroidism. *Ann Intern Med* 94:629-637, 1981
445. Hodsman AB, Sherrard DJ, Alfrey AC, Ott S, Brickman AS, Miller NL, Maloney NA, Coburn JW: Bone aluminum and histomorphometric features of renal osteodystrophy. *J Clin Endocrinol Metab* 54:539-546, 1982
446. Kaehny WD, Hegg AP, Alfrey AC: Gastrointestinal absorption of aluminum from aluminum-containing antacids. *N Engl J Med* 296:1389-1390, 1977
447. Monier-Faugere MC, Malluche HH: Trends in renal osteodystrophy: a survey from 1983 to 1995 in a total of 2248 patients. *Nephrol Dial Transplant* 11:111-120, 1996 (suppl 3)
448. Puschett JB, Piraino B, Greenberg A, Rault R: Hypercalcemia in a dialysis patient. *Am J Nephrol* 6:388-395, 1986
449. Norris KC, Crooks PW, Nebeker HG, Hercz G, Milliner DS, Gerszi K, Slatopolsky E, Andress DL, Sherrard DJ, Coburn JW: Clinical and laboratory features of aluminum-related bone disease: differences between sporadic and "epidemic" forms of the syndrome. *Am J Kidney Dis* 6:342-347, 1985
450. Sherrard DJ, Ott SM, Andress DL: Pseudohyperparathyroidism. Syndrome associated with aluminum intoxication in patients with renal failure. *Am J Med* 79:127-130, 1985
451. Andress DL, Ott SM, Maloney NA, Sherrard DJ: Effect of parathyroidectomy on bone aluminum accumulation in chronic renal failure. *N Engl J Med* 312:468-473, 1985
452. Recker R, Schoenfeld P, Letteri J, Slatopolsky E, Goldsmith R, Brickman A: The efficacy of calcifediol in renal osteodystrophy. *Arch Intern Med* 138 Spec No:857-863, 1978

453. Kausz AT, Antonsen JE, Hercz G, Pei Y, Weiss NS, Emerson S, Sherrard DJ: Screening plasma aluminum levels in relation to aluminum bone disease among asymptomatic dialysis patients. *Am J Kidney Dis* 34:688-693, 1999
454. Milliner DS, Nebeker HG, Ott SM, Andress DL, Sherrard DJ, Alfrey AC, Slatopolsky EA, Coburn JW: Use of the deferoxamine infusion test in the diagnosis of aluminum-related osteodystrophy. *Ann Intern Med* 101:775-779, 1984
455. Nebeker HG, Andress DL, Milliner DS, Ott SM, Alfrey AC, Slatopolsky EA, Sherrard DJ, Coburn JW: Indirect methods for the diagnosis of aluminum bone disease: plasma aluminum, the desferrioxamine infusion test, and serum iPTH. *Kidney Int Suppl* 18:S96-S99, 1986
456. Malluche HH, Smith AJ, Abreo K, Faugere MC: The use of deferoxamine in the management of aluminium accumulation in bone in patients with renal failure. *N Engl J Med* 311:140-144, 1984
457. Fournier A, Fohrer P, Leflon P, Moriniere P, Tolani M, Lambrey G, Demontis R, Sebert JL, Van Devyver F, Debroe M: The desferrioxamine test predicts bone aluminium burden induced by Al(OH)₃ in uraemic patients but not mild histological osteomalacia. *Proc Eur Dial Transplant Assoc Eur Ren Assoc* 21:371-376, 1985
458. Ott SM, Maloney NA, Coburn JW, Alfrey AC, Sherrard DJ: The prevalence of bone aluminum deposition in renal osteodystrophy and its relation to the response to calcitriol therapy. *N Engl J Med* 307:709-713, 1982
459. Andress DL, Maloney NA, Coburn JW, Endres DB, Sherrard DJ: Osteomalacia and aplastic bone disease in aluminum-related osteodystrophy. *J Clin Endocrinol Metab* 65:11-16, 1987
460. Andress DL, Nebeker HG, Ott SM, Endres DB, Alfrey AC, Slatopolsky EA, Coburn JW, Sherrard DJ: Bone histologic response to deferoxamine in aluminum-related bone disease. *Kidney Int* 31:1344-1350, 1987
461. Pei Y, Hercz G, Greenwood C, Sherrard D, Segre G, Manuel A, Saiphoo C, Fenton S: Non-invasive prediction of aluminum bone disease in hemo- and peritoneal dialysis patients. *Kidney Int* 41:1374-1382, 1992
462. Alfrey AC: Aluminum metabolism. *Kidney Int Suppl* 18:S8-S11, 1986
463. Bene C, Manzler A, Bene D, Kranias G: Irreversible ocular toxicity from single "challenge" dose of deferoxamine. *Clin Nephrol* 31:45-48, 1989
464. Pengloan J, Dantal J, Rossazza C, Abazza M, Nivet H: Ocular toxicity after a single intravenous dose of desferrioxamine in 2 hemodialyzed patients. *Nephron* 46:211-212, 1987
465. Boelaert JR, Fenves AZ, Coburn JW: Deferoxamine therapy and mucormycosis in dialysis patients: report of an international registry. *Am J Kidney Dis* 18:660-667, 1991
466. D'Haese PC, Couutenye MM, Goodman WG, Lemoniatiou E, Digenis P, Sotornik I, Fagalde A, Barsoum RS, Lamberts LV, De Broe ME: Use of the low-dose desferrioxamine test to diagnose and differentiate between patients with aluminium-related bone disease, increased risk for aluminium toxicity, or aluminium overload. *Nephrol Dial Transplant* 10:1874-1884, 1995
467. Canteros A, Diaz-Corte C, Fernandez-Martin JL, Gago E, Fernandez-Merayo C, Cannata J: Ultrafiltrable aluminium after very low doses of desferrioxamine. *Nephrol Dial Transplant* 13:1538-1542, 1998
468. Jorge C, Gil C, Possante M, Catarino MC, Cruz A, Andrade R, Teixeira R, Santos N, Ferreira A: Use of a desferrioxamine "microdose" to chelate aluminum in hemodialysis patients. *Clin Nephrol* 52:335-336, 1999
469. Salusky IB, Coburn JW, Paunier L, Sherrard DJ, Fine RN: Role of aluminum hydroxide in raising serum aluminum levels in children undergoing continuous ambulatory peritoneal dialysis. *J Pediatr* 105:717-720, 1984
470. Rozas VV, Port FK, Rutt WM: Progressive dialysis encephalopathy from dialysate aluminum. *Arch Intern Med* 138:1375-1377, 1978
471. Burwen DR, Olsen SM, Bland LA, Arduino MJ, Reid MH, Jarvis WR: Epidemic aluminum intoxication in hemodialysis patients traced to use of an aluminum pump. *Kidney Int* 48:469-474, 1995
472. D'Haese PC, Clement JP, Elseviers MM, Lamberts LV, Van de Vyver FL, Visser WJ, De Broe ME: Value of serum aluminium monitoring in dialysis patients: a multicentre study. *Nephrol Dial Transplant* 5:45-53, 1990
473. Pei Y, Hercz G, Greenwood C, Segre G, Manuel A, Saiphoo C, Fenton S, Sherrard D: Risk factors for renal osteodystrophy: a multivariate analysis. *J Bone Miner Res* 10:149-156, 1995
474. Heaf JG, Podenphant J, Andersen JR: Bone aluminium deposition in maintenance dialysis patients treated with aluminium-free dialysate: role of aluminium hydroxide consumption. *Nephron* 42:210-216, 1986
475. Channon SM, Arfeen S, Ward MK: Long-term accumulation of aluminum in patients with renal failure. *Trace Elements Med* 5:147-157, 1988
476. Costantini S, Giordano R, Vernillo I, Piccioni A, Zapponi GA: Predictive value of serum aluminium levels for bone accumulation in haemodialyzed patients. *Ann Ist Super Sanita* 25:457-461, 1989
477. Sherrard DJ: Aluminum—much ado about something. *N Engl J Med* 324:558-559, 1991
478. Cases A, Kelly J, Sabater J, Campistol JM, Torras A, Montoliu J, Lopez I, Revert L: Acute visual and auditory neurotoxicity in patients with end-stage renal disease receiving desferrioxamine. *Clin Nephrol* 29:176-178, 1988
479. Janssen MJ, van Boven WP: Efficacy of low-dose desferrioxamine for the estimation of aluminium overload in haemodialysis patients. *Pharm World Sci* 18:187-191, 1996
480. Ott SM, Andress DL, Nebeker HG, Milliner DS, Maloney NA, Coburn JW, Sherrard DJ: Changes in bone histology after treatment with desferrioxamine. *Kidney Int Suppl* 18:S108-S113, 1986
481. Faugere MC, Arnala IO, Ritz E, Malluche HH: Loss of bone resulting from accumulation of aluminum in bone of patients undergoing dialysis. *J Lab Clin Med* 107:481-487, 1986
482. Charhon SA, Chavassieux P, Boivin G, Parisien M, Chapuy MC, Traeger J, Meunier PJ: Deferoxamine-induced bone changes in haemodialysis patients: a histomorphometric study. *Clin Sci (Lond)* 73:227-234, 1987
483. Bia MJ, Cooper K, Schnall S, Duffy T, Hendler E, Malluche H, Solomon L: Aluminum induced anemia: pathogenesis and treatment in patients on chronic hemodialysis. *Kidney Int* 36:852-858, 1989

484. Felsenfeld AJ, Rodriguez M, Coleman M, Ross D, Llach F: Desferrioxamine therapy in hemodialysis patients with aluminum-associated bone disease. *Kidney Int* 35:1371-1378, 1989
485. McCarthy JT, Milliner DS, Johnson WJ: Clinical experience with desferrioxamine in dialysis patients with aluminium toxicity. *Q J Med* 74:257-276, 1990
486. Ackrill P, Ralston AJ, Day JP, Hodge KC: Successful removal of aluminium from patient with dialysis encephalopathy. *Lancet* 2:692-693, 1980
487. Hood SA, Clark WF, Hodsman AB, Bolton CF, Cordy PE, Anderson C, Leung F: Successful treatment of dialysis osteomalacia and dementia, using desferrioxamine infusions and oral 1-alpha hydroxycholecalciferol. *Am J Nephrol* 4:369-374, 1984
488. Milne FJ, Sharf B, Bell P, Meyers AM: The effect of low aluminum water and desferrioxamine on the outcome of dialysis encephalopathy. *Clin Nephrol* 20:202-207, 1983
489. Sprague SM, Corwin HL, Wilson RS, Mayor GH, Tanner CM: Encephalopathy in chronic renal failure responsive to deferoxamine therapy. Another manifestation of aluminum neurotoxicity. *Arch Intern Med* 146:2063-2064, 1986
490. Ackrill P, Ralston AJ, Day JP: Role of desferrioxamine in the treatment of dialysis encephalopathy. *Kidney Int Suppl* 18:S104-S107, 1986
491. Altmann P, Plowman D, Marsh F, Cunningham J: Aluminium chelation therapy in dialysis patients: evidence for inhibition of haemoglobin synthesis by low levels of aluminium. *Lancet* 1:1012-1015, 1988
492. von Bonsdorff M, Sipila R, Pitkanen E: Correction of haemodialysis-associated anaemia by deferoxamine. Effects on serum aluminium and iron overload. *Scand J Urol Nephrol Suppl* 131:49-54, 1990
493. Van Cutsem J, Boelaert JR: Effects of deferoxamine, ferroxamine and iron on experimental mucormycosis (zygomycosis). *Kidney Int* 36:1061-1068, 1989
494. Boelaert JR, de Locht M, Van Cutsem J, Kerrels V, Cantinieaux B, Verdonck A, Van Landuyt HW, Schneider YJ: Mucormycosis during deferoxamine therapy is a siderophore-mediated infection. In vitro and in vivo animal studies. *J Clin Invest* 91:1979-1986, 1993
495. Windus DW, Stokes TJ, Julian BA, Fenves AZ: Fatal *Rhizopus* infections in hemodialysis patients receiving deferoxamine. *Ann Intern Med* 107:678-680, 1987
496. Boelaert JR, Vergauwe PL, Vandepitte JM: Mucormycosis infection in dialysis patients. *Ann Intern Med* 107:782-783, 1987
497. De Broe ME, Druke TB, Ritz E: Consensus Conference: Diagnosis and treatment of aluminum overload in end-stage renal failure patients. *Nephrol Dial Transplant* 8:1-4, 1993 (suppl 1)
498. Hercz G, Andress DL, Nebeker HG, Shinaberger JH, Sherrard DJ, Coburn JW: Reversal of aluminum-related bone disease after substituting calcium carbonate for aluminum hydroxide. *Am J Kidney Dis* 11:70-75, 1988
499. Hercz G, Andress DL, Norris KC, Shinaberger JH, Slatopolsky EA, Sherrard DJ, Coburn JW: Improved bone formation in dialysis patients after substitution of calcium carbonate for aluminum gels. *Trans Assoc Am Physicians* 100:139-146, 1987
500. Adhemar JP, Laederich J, Jaudon MC, Masselot JP, Galli A, Kleinknecht D: Removal of aluminium from patients with dialysis encephalopathy. *Lancet* 2:1311, 1980
501. Arze RS, Parkinson IS, Carlidge NE, Britton P, Ward MK: Reversal of aluminium dialysis encephalopathy after desferrioxamine treatment. *Lancet* 2:1116, 1981
502. Poggilitsch H, Petek W, Wawschinek O, Holzer W: Treatment of early stages of dialysis encephalopathy by aluminium depletion. *Lancet* 2:1344-1345, 1981
503. Molitoris BA, Alfrey AC, Alfrey PS, Miller NL: Rapid removal of DFO-chelated aluminum during hemodialysis using polysulfone dialyzers. *Kidney Int* 34:98-101, 1988
504. Delmez J, Weerts C, Lewis-Finch J, Windus D, Slatopolsky E: Accelerated removal of deferoxamine mesylate-chelated aluminum by charcoal hemoperfusion in hemodialysis patients. *Am J Kidney Dis* 13:308-311, 1989
505. Vasilakakis DM, D'Haese PC, Lamberts LV, Lemoniatiou E, Digenis PN, De Broe ME: Removal of aluminum and ferrioxamine by charcoal hemoperfusion and hemodialysis. *Kidney Int* 41:1400-1407, 1992
506. Hercz G, Salusky IB, Norris KC, Fine RN, Coburn JW: Aluminum removal by peritoneal dialysis: intravenous vs. intraperitoneal deferoxamine. *Kidney Int* 30:944-948, 1986
507. Molitoris BA, Alfrey PS, Miller NL, Hasbargen JA, Kaehney WD, Alfrey AC, Smith BJ: Efficacy of intramuscular and intraperitoneal deferoxamine for aluminum chelation. *Kidney Int* 31:986-991, 1987
508. Barata JD, D'Haese PC, Pires C, Lamberts LV, Simoes J, De Broe ME: Low-dose (5 mg/kg) desferrioxamine treatment in acutely aluminium-intoxicated haemodialysis patients using two drug administration schedules. *Nephrol Dial Transplant* 11:125-132, 1996
509. Widmer B, Gerhardt RE, Harrington JT, Cohen JJ: Serum electrolyte and acid base composition. The influence of graded degrees of chronic renal failure. *Arch Intern Med* 139:1099-1102, 1979
510. Eiser AR, Slifkin RF, Neff MS: Intestinal mucormycosis in hemodialysis patients following deferoxamine. *Am J Kidney Dis* 10:71-73, 1987
511. Veis JH, Contiguglia R, Klein M, Mishell J, Alfrey AC, Shapiro JI: Mucormycosis in deferoxamine-treated patients on dialysis. *Ann Intern Med* 107:258, 1987
512. Boelaert JR, Van Cutsem J, de Locht M, Schneider YJ, Crichton RR: Deferoxamine augments growth and pathogenicity of *Rhizopus*, while hydroxypyridinone chelators have no effect. *Kidney Int* 45:667-671, 1994
513. Coburn JW, Maung HM: Mucormycosis in dialysis patients, in Sweny P, Rubin RH, Tolkoff-Rubin N (eds), London, Oxford University Press, 2002
514. Salusky IB, Goodman WG: Adynamic renal osteodystrophy: is there a problem? *J Am Soc Nephrol* 12:1978-1985, 2001
515. Malluche HH, Monier-Faugere MC: Risk of adynamic bone disease in dialyzed patients. *Kidney Int Suppl* 38:S62-S67, 1992
516. Atsumi K, Kushida K, Yamazaki K, Shimizu S, Ohmura A, Inoue T: Risk factors for vertebral fractures in renal osteodystrophy. *Am J Kidney Dis* 33:287-293, 1999

517. Coco M, Rush H: Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. *Am J Kidney Dis* 36:1115-1121, 2000
518. D'Amour P, Huet PM: Ca²⁺ concentration influences the hepatic extraction of bioactive human PTH-(1-34) in rats. *Am J Physiol* 256:E87-E92, 1989
519. Chou FF, Chan HM, Huang TJ, Lee CH, Hsu KT: Autotransplantation of parathyroid glands into subcutaneous forearm tissue for renal hyperparathyroidism. *Surgery* 124: 1-5, 1998
520. Kostakis A, Vaiopoulos G, Kostantopoulos K, Zavos G, Bocos I, Sgouromalis S: Parathyroidectomy in the treatment of secondary hyperparathyroidism in chronic renal failure. *Int Surg* 82:85-86, 1997
521. Gasparri G, Camandona M, Jeantet A, Nano M, Desimone M, Bronda M, Deipoli M: Results after 223 parathyroidectomies for secondary hyperparathyroidism. *Acta Chir Austriaca* 28:32-34, 1996 (suppl 124)
522. Neonakis E, Wheeler MH, Krishnan H, Coles GA, Davies F, Woodhead JS: Results of surgical treatment of renal hyperparathyroidism. *Arch Surg* 130:643-648, 1995
523. Gagne ER, Urena P, Leite-Silva S, Zingraff J, Chevalier A, Sarfati E, Dubost C, Druke TB: Short- and long-term efficacy of total parathyroidectomy with immediate autografting compared with subtotal parathyroidectomy in hemodialysis patients. *J Am Soc Nephrol* 3:1008-1017, 1992
524. Takagi H, Tominaga Y, Uchida K, Yamada N, Kawai M, Kano T, Morimoto T: Subtotal versus total parathyroidectomy with forearm autograft for secondary hyperparathyroidism in chronic renal failure. *Ann Surg* 200:18-23, 1984
525. Esselstyn CB Jr, Popowniak KL: Parathyroid surgery in the treatment of renal osteodystrophy and tertiary hyperparathyroidism. *Surg Clin North Am* 51:1211-1217, 1971
526. Olaizola I, Zingraff J, Heuguerot C, Fajardo L, Leger A, Lopez J, Acuna G, Petraglia A, Alvarez A, Caorsi H, Druke T, Ambrosioni P: [(99m)Tc]-sestamibi parathyroid scintigraphy in chronic haemodialysis patients: static and dynamic explorations. *Nephrol Dial Transplant* 15:1201-1206, 2000
527. Neumann DR, Esselstyn CB, Jr., Madera A, Wong CO, Lieber M: Parathyroid detection in secondary hyperparathyroidism with 123I/99mTc-sestamibi subtraction single photon emission computed tomography. *J Clin Endocrinol Metab* 83:3867-3871, 1998
528. Blocklet D, Martin P, Schoutens A, Verhas M, Hooghe L, Kinnaert P: Presurgical localization of abnormal parathyroid glands using a single injection of technetium-99m methoxyisobutylisonitrile: comparison of different techniques including factor analysis of dynamic structures. *Eur J Nucl Med* 24:46-51, 1997
529. Tanaka Y, Tominaga Y, Funahashi H, Sato K, Numano M, Takagi H: Preoperative localization studies in secondary hyperplasia. *Acta Chir Austriaca* 28:14-16, 1996 (suppl 124)
530. Hindie E, Urena P, Jeanguillaume C, Mellièrè D, Berthelot JM, Menoyo-Calonge V, Chiappini-Briffa D, Janin A, Galle P: Preoperative imaging of parathyroid glands with technetium-99m-labelled sestamibi and iodine-123 subtraction scanning in secondary hyperparathyroidism. *Lancet* 353:2200-2204, 1999
531. Ishibashi M, Nishida H, Okuda S, Suekane S, Hayabuchi N: Localization of parathyroid glands in hemodialysis patients using Tc-99m sestamibi imaging. *Nephron* 78:48-53, 1998
532. Jeanguillaume C, Urena P, Hindie E, Prieur P, Petrover M, Menoyo-Calonge V, Janin A, Chiappini-Briffa D, Mellièrè D, Boulahdour H, Galle P: Secondary hyperparathyroidism: detection with I-123-Tc-99m-Sestamibi subtraction scintigraphy versus US. *Radiology* 207:207-213, 1998
533. Chesser AM, Carroll MC, Lightowler C, Macdougall IC, Britton KE, Baker LR: Technetium-99m methoxy isobutyl isonitrile (MIBI) imaging of the parathyroid glands in patients with renal failure. *Nephrol Dial Transplant* 12:97-100, 1997
534. Pons F, Torregrosa JV, Vidal-Sicart S, Sabater L, Fuster D, Fernandez-Cruz L, Herranz R: Preoperative parathyroid gland localization with technetium-99m sestamibi in secondary hyperparathyroidism. *Eur J Nucl Med* 24:1494-1498, 1997
535. Takebayashi S, Matsui K, Onohara Y, Hidai H: Sonography for early diagnosis of enlarged parathyroid glands in patients with secondary hyperparathyroidism. *AJR Am J Roentgenol* 148:911-914, 1987
536. Fabretti F, Calabrese V, Fornasari V, Poletti I: Subtotal parathyroidectomy for secondary hyperparathyroidism in chronic renal failure. *J Laryngol Otol* 105:562-567, 1991
537. Tomic Brzac H, Pavlovic D, Halbauer M, Pasini J: Parathyroid sonography in secondary hyperparathyroidism: correlation with clinical findings. *Nephrol Dial Transplant* 4:45-50, 1989
538. Takagi H, Tominaga Y, Uchida K, Yamada N, Ishii T, Morimoto T, Yasue M: Preoperative diagnosis of secondary hyperparathyroidism using computed tomography. *J Comput Assist Tomogr* 6:527-528, 1982
539. Fukagawa M, Kitaoka M, Tominaga Y, Akizawa T, Kurokawa K: Selective percutaneous ethanol injection therapy (PEIT) of the parathyroid in chronic dialysis patients—the Japanese strategy. Japanese Working Group on PEIT of Parathyroid, Tokyo, Japan. *Nephrol Dial Transplant* 14:2574-2577, 1999
540. Domrongkitchaiporn S, Pongsakul C, Stitchantrakul W, Sirikulchayanonta V, Ongphiphadhanakul B, Radinahamed P, Karnsombut P, Kunkitti N, Ruang-raksa C, Rajatanavin R: Bone mineral density and histology in distal renal tubular acidosis. *Kidney Int* 59:1086-1093, 2001
541. McSherry E, Morris RC Jr: Attainment and maintenance of normal stature with alkali therapy in infants and children with classic renal tubular acidosis. *J Clin Invest* 61:509-527, 1978
542. Coen G, Mazzaferro S, Ballanti P, Sardella D, Chicca S, Manni M, Bonucci E, Taggi F: Renal bone disease in 76 patients with varying degrees of predialysis chronic renal failure: a cross-sectional study. *Nephrol Dial Transplant* 11:813-819, 1996
543. Parfitt AM, Kleerekoper M, Cruz C: Reduced phosphate reabsorption unrelated to parathyroid hormone after renal transplantation: implications for the pathogenesis of hyperparathyroidism in chronic renal failure. *Miner Electrolyte Metab* 12:356-362, 1986
544. Ambuhl PM, Meier D, Wolf B, Dydak U, Boesiger P, Binswanger U: Metabolic aspects of phosphate replacement

therapy for hypophosphatemia after renal transplantation: impact on muscular phosphate content, mineral metabolism, and acid/base homeostasis. *Am J Kidney Dis* 34:875-83, 1999

545. Giannini S, D'Angelo A, Carraro G, Antonello A, Di Landro D, Marchini F, Plebani M, Zaninotto M, Rigotti P, Sartori L, Crepaldi G: Persistently increased bone turnover and low bone density in long-term survivors to kidney transplantation. *Clin Nephrol* 56:353-363, 2001

546. Cayco AV, Wysolmerski J, Simpson C, Mitnick MA, Gundberg C, Klinger A, Lorber M, Silver D, Basadonna G, Friedman A, Insogna K, Cruz D, Bia M: Posttransplant bone disease: evidence for a high bone resorption state. *Transplantation* 70:1722-1728, 2000

547. Lane NE, Lukert B: The science and therapy of glucocorticoid-induced bone loss. *Endocrinol Metab Clin North Am* 27:465-483, 1998

548. Erben RG, Bante U, Birner H, Stangassinger M: 1 α -hydroxyvitamin D2 partially dissociates between preservation of cancellous bone mass and effects on calcium homeostasis in ovariectomized rats. *Calcif Tissue Int* 60:449-456, 1997

549. Feber J, Braillon P, David L, Cochat P: Body composition in children after renal transplantation. *Am J Kidney Dis* 38:366-370, 2001

550. Feber J, Cochat P, Braillon P: Bone mineral density in children after renal transplantation. *Pediatr Nephrol* 14:654-657, 2000

551. Ellis EN, Floyd-Gimon DM, Berry PL, Wells TG, Seibert J, Belsha C: Risk factors for bone mineral density loss in pediatric renal transplant patients. *Pediatr Transplant* 4:146-150, 2000

552. Chesney RW, Rose PG, Mazess RB: Persistence of diminished bone mineral content following renal transplantation in childhood. *Pediatrics* 73:459-466, 1984

553. Zimakas PJ, Sharma AK, Rodd CJ: Osteopenia and fractures in cystinotic children post renal transplantation. *Pediatr Nephrol* 18:384-390, 2003

554. Sambrook P, Birmingham J, Kelly P, Kempler S, Nguyen T, Pocock N, Eisman J: Prevention of corticosteroid osteoporosis. A comparison of calcium, calcitriol, and calcitonin. *N Engl J Med* 328:1747-1752, 1993

555. Adachi JD, Bensen WG, Bianchi F, Cividino A, Pillersdorf S, Sebaldt RJ, Tugwell P, Gordon M, Steele M, Webber C, Goldsmith CH: Vitamin D and calcium in the prevention of corticosteroid induced osteoporosis: a 3 year followup. *J Rheumatol* 23:995-1000, 1996

556. De Sevaux RG, Hoitsma AJ, Corstens FH, Wetzels JF: Treatment with vitamin D and calcium reduces bone loss after renal transplantation: a randomized study. *J Am Soc Nephrol* 13:1608-1614, 2002

557. Harris AF, Cotty VF: The effect of lanthanum chloride and related compounds on calcification. *Arch Int Pharmacodyn Ther* 186:269-278, 1970