Complete Summary

GUIDELINE TITLE

Clinical practice guidelines for bone metabolism and disease in chronic kidney disease.

BIBLIOGRAPHIC SOURCE(S)

Eknoyan G, Levin A, Levin NW. Bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003 Oct;42(4 Suppl 3):1-201. [664 references] PubMed

COMPLETE SUMMARY CONTENT

SCOPE
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EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
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IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY

SCOPE

DISEASE/CONDITION(S)

- Mineral and bone metabolism and disease
- Chronic kidney disease

GUIDELINE CATEGORY

Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Nephrology

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To develop a set of clinical practice guidelines that would improve diagnoses and treatment of bone disease in chronic kidney disease and serve as a clinical action plan for the health care practitioner

TARGET POPULATION

Adults (18 years and older) with chronic kidney disease

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation

1. Measurement of serum levels of calcium, phosphorus, and intact plasma parathyroid hormone (PTH)
2. Assessment of bone disease, including:
    - Iliac crest bone biopsy with tetracycline labeling and bone histomorphometric analysis
    - Bone radiographs
    - Bone mineral density (BMD) by dual energy x-ray (DEXA)
3. Deferoxamine (DF0) testing
4. Measurement of serum 25-hydroxyvitamin D and serum levels for carbon dioxide

Treatment/Management

1. Maintain target plasma levels of intact PTH
2. Maintenance/monitoring of serum phosphorus levels
3. Dietary phosphorus restriction
4. Use of phosphate binders
    - Calcium-based binders, noncalcium-, nonaluminum-, and nonmagnesium-containing binders
    - Combination calcium-based and non-calcium based phosphate binders
5. Maintain corrected calcium levels within "normal" range
    - Calcium salts and/or oral vitamin D sterols
6. Vitamin D_2 therapy
7. Active vitamin D sterol therapy for patients on dialysis
    - Monitor serum levels of calcium and phosphorus and serum PTH
8. Maintain dialysate calcium at 2.5 mEq/L
9. Kidney transplant
10. High-flux dialyzers
11. Treatment of bone disease

- Therapeutic management based on specific type of bone disease (hyperparathyroid and mixed bone disease, osteomalacia, and adynamic bone disease) as outlined in the guideline

12. Parathyroidectomy in patients with chronic kidney disease
    - Supplemental alkali salts for metabolic acidosis
13. Immunosuppressive therapy for kidney transplant recipients

MAJOR OUTCOMES CONSIDERED

The Work Group Chair and Vice Chair initially formulated a working list of "key questions" that should be addressed in the evidence report and then converted into hypothetical guideline statements. Each key question typically had several outcomes of interest, from long-term, patient-oriented outcomes, such as quality of life and mortality, to short-term intermediate outcomes such as serum calcium and phosphate levels.

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The Work Group and Evidence Review Team agreed on a systematic process to review literature based on the key questions and hypothetical guideline statements. Based on these key questions, information specialists on the Evidence Review Team performed database literature searches to identify the relevant published medical literature. A list of terms pertaining to specific kidney and bone diseases was developed. Major databases searched included: Medline, Embase, PsychLit, Cochrane Library, and CINAHL. In total, 10 major data-bases were searched.

A priori criteria were established for determining whether an article identified by the literature searches should be retrieved before the searches were performed to reduce bias in selecting articles and establish minimum standards of relevance and quality of the retrieved articles. The cutoff date for all literature considered as evidence was January 1, 2001.

Abstracts of each article identified in the electronic searches were reviewed and articles were requested if they appeared to meet the criteria. The resulting articles were then evaluated to determine whether they met criteria for inclusion in this evidence report.

NUMBER OF SOURCE DOCUMENTS

467

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Strength of Evidence

Each rationale statement was graded according to the level of evidence on which it was based. The overall guideline was then graded according to the strength of evidence supporting the rationale statements.

Rationale Statements

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

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Evidence Tables

Five types of evidence tables were prepared included in the Evidence Reports prepared by the Evidence Review Team.

Detailed tables contain data from each field of the components of the data abstraction forms. These tables are contained in the Appendix of each Evidence Report.

In-text study detail tables summarized the most salient aspects of study design, in particular those aspects that were used to determine the methodology quality rating. In-text patient characteristics tables summarized the most salient aspects of the patients included in each study. In-text evidence tables were produced for each outcome measure within each key question. The evidence tables reported the evidence as it was used by the Evidence Review Team to perform quantitative analyses, not the evidence as it was reported by the authors of a study. Whenever possible, the results from each study were recalculated and standardized into a common, metric, Hedges´ d.

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

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

Quantitative Analysis of Studies

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

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Overview of Process

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

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

Development of Guideline Statements

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

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

Voting Procedures

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

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

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

In formulating the guidelines, the rationale and evidentiary basis of each recommendation was made explicit.

- When all components of the rationale for a guideline were based on published evidence, the guidelines were labeled "Evidence."
- When no definite evidence existed or the evidence was considered inconclusive, and either the guideline or steps in its rationale were based on judgment they were labeled "Opinion."

As such, it is the available literature that determined the labeling of each guideline.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Prior to their publication, a final draft of the guidelines was subjected to a broad-based review by experts, organizations, and the public. Thus, the chain of

reasoning and recommendation of each opinion based guideline was exposed to open debate, with the final published product reflecting a wide consensus of healthcare professionals, providers, managers, organizations, associations, and patients.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Evidentiary Basis for Recommendations

- When all components of the rationale for a guideline were based on published evidence, the guidelines were labeled "Evidence."
- When no definite evidence existed or the evidence was considered inconclusive, and either the guideline or steps in its rationale were based on judgment they were labeled "Opinion."

Guideline 1. Evaluation of Calcium and Phosphorus Metabolism

1.1 Serum levels of calcium, phosphorus, and intact plasma parathyroid hormone (PTH) should be measured in all patients with chronic kidney disease (CKD) and glomerular filtration rate (GFR) <60 mL/min/1.73 m^2. (Evidence) The frequency of these measurements should be based on the stage of chronic kidney disease (see Table 14 in the original guideline document). (Opinion)

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

1.3 Measurement of plasma PTH levels may be done less frequently for those with levels within the low end of the target levels (see Table 15 in the original guideline document). (Opinion)

1.4 The target range of plasma levels of intact PTH in the various stages of CKD are denoted in Table 15 in the original guideline document

Guideline 2. Assessment of Bone Disease Associated with CKD

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

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

> 2.2a Fractures with minimal or no trauma (pathological fractures) (Opinion)

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

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

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

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

Guideline 3. Evaluation of Serum Phosphorus Levels

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

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

Guideline 4. Restriction of Dietary Phosphorus in Patients with CKD

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

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

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

Guideline 5. Use of Phosphate Binders in CKD

In CKD Patients (Stages 3 and 4):

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

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

In CKD Patients with Kidney Failure (Stage 5):

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

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

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

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

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

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

Guideline 6. Serum Calcium and Calcium-Phosphorus Product

In CKD Patients (Stages 3 and 4):

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

In CKD Patients With Kidney Failure (Stage 5):

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

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

> 6.3a In patients taking calcium-based phosphate binders, the dose should be reduced or therapy switched to a noncalcium-,

nonaluminum-, nonmagnesium-containing phosphate binder. (Opinion) See Guideline 5.

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

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

In CKD Patients (Stages 3 to 5):

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

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

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

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

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

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

Guideline 7. Prevention and Treatment of Vitamin D Insufficiency and Vitamin D Deficiency in CKD Patients (Algorithm 1)

In CKD Patients (Stages 3 and 4):

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

7.2 If the serum level of 25-hydroxyvitamin D is <30 ng/mL, supplementation with vitamin D_2 (ergocalciferol) should be initiated (see Table 26 in the original guideline document). (Opinion)

7.3 Following initiation of vitamin D therapy:

7.3a The use of ergocalciferol therapy should be integrated with the serum calcium and phosphorus (see Algorithm 1 in the original guideline document).

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

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

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

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

In CKD Patients With Kidney Failure (Stage 5):

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

Guideline 8. Vitamin D Therapy in CKD Patients

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

Guideline 8A. Active Vitamin D Therapy in Patients with Stages 3 and 4 CKD (Algorithm 2)

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

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

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

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

be measured at least every 3 months for 6 months, and every 3 months thereafter. (Opinion)

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

> 8A.3a If plasma levels of intact PTH fall below the target range for the CKD stage (see Table 15 in the original guideline document, Guideline 1), hold active vitamin D sterol therapy until plasma levels of intact PTH rise to above the target range, then resume treatment with the dose of active vitamin D sterol reduced by half. If the lowest daily dose of the active vitamin D sterol is being used, reduce to alternate-day dosing. (Opinion)
>
> 8A.3b If serum levels of corrected total calcium exceed 9.5 mg/dL (2.37 mmol/L), hold active vitamin D sterol therapy until serum calcium returns to <9.5 mg/dL (2.37 mmol/L), then resume treatment at half the previous dose. If the lowest daily dose of the active vitamin D sterol is being used, reduce to alternate-day dosing. (Opinion)
>
> 8A.3c If serum levels of phosphorus rise to >4.6 mg/dL (1.49 mmol/L), hold active vitamin D therapy, initiate or increase dose of phosphate binder until the levels of serum phosphorus fall to $\leq$4.6 mg/dL (1.49 mmol/L); then resume the prior dose of active vitamin D sterol. (Opinion)

Guideline 8B. Vitamin D Therapy in Patients on Dialysis (CKD Stage 5)

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

> 8B.1a The intermittent, intravenous administration of calcitriol is more effective than daily oral calcitriol in lowering serum PTH levels. (Evidence)
>
> 8B.1b In patients with corrected serum calcium and/or phosphorus levels above the target range (see Guidelines 3 and 6, respectively), a trial of alternative vitamin D analogs, such as paricalcitol or doxercalciferol may be warranted. (Opinion)

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

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

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

Guideline 9. Dialysate Calcium Concentrations

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

9.2 Higher or lower dialysate calcium levels are indicated in selected patients. (See Clinical Applications section in the original guideline document) (Opinion)

Guideline 10. Beta$_2$-Microglobulin Amyloidosis

10.1 Screening for beta$_2$-microglobulin amyloidosis, including measurement of serum levels of beta$_2$-microglobulin, is not recommended. (Opinion)

> 10.1a No currently available therapy (except kidney transplantation) can stop disease progression of beta$_2$-microglobulin amyloidosis or provide symptomatic relief. (Evidence)
>
> 10.1b Kidney transplant should be considered to stop disease progression or provide symptomatic relief in patients with beta$_2$-microglobulin amyloidosis. (Evidence)
>
> 10.1c In patients with evidence of, or at risk for, beta$_2$-microglobulin amyloidosis noncuprophane (Evidence), high-flux dialyzers (Opinion) should be used.

Guideline 11. Aluminum Overload and toxicity in CKD

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

> 11.1a CKD patients ingesting aluminum should not receive citrate salts simultaneously. (Evidence)

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

> 11.2a Baseline levels of serum aluminum should be <20 micrograms/L. (Opinion)

11.3 A deferoxamine (DFO) test should be performed if there are elevated serum aluminum levels (60 to 200 micrograms/L); clinical signs and symptoms of aluminum toxicity (see Table 31 in the original guideline document); or prior to

parathyroid surgery if the patient has had aluminum exposure. (Evidence) (see Algorithms 6 and 7 in the original guideline document).

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

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

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

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

Guideline 12. Treatment of Aluminum Toxicity (See Algorithm 8 and Algorithm 9 in the original guideline document)

12.1 In all patients with baseline serum aluminum levels >60 micrograms/L, a positive DFO test, or clinical symptoms consistent with aluminum toxicity (Guideline 11, see Table 31 in the original guideline document), the source of aluminum should be identified and eliminated. (Opinion)

12.2 In symptomatic patients with serum aluminum levels >60 micrograms/L but <200 micrograms /L or a rise in aluminum after DFO >50 micrograms /L, DFO should be given to treat the aluminum overload. (See Algorithm 8 and Algorithm 9 in the original guideline document). (Opinion)

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

Guideline 13. Treatment of Bone Disease in CKD

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

Guideline 13A. Hyperparathyroid (High-Turnover) and Mixed (High-Turnover with Mineralization Defect) Bone Disease

13A.1 In CKD patients (Stages 3 and 4) who have plasma levels of intact PTH >70 pg/mL (7.7 pmol/L) (Stage 3) or >110 pg/mL (12.1 pmol/L) (Stage 4) on more

than 2 consecutive measurements, dietary phosphate intake should be restricted. If this is ineffective in lowering plasma PTH levels, calcitriol (Evidence) or one of its analogs [alfacalcidol (Evidence) or doxercalciferol (Opinion)] should be given to prevent or ameliorate bone disease. (See Guideline 8A.)

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

Guideline 13B. Osteomalacia

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

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

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

> 13B.3a If osteomalacia due to vitamin D deficiency fails to respond to ergocalciferol or cholecalciferol, particularly in patients with kidney failure (Stage 5), treatment with an active vitamin D sterol may be given. (Opinion) (See Guideline 8B.)
>
> 13B.3b Doses of phosphate supplementation should be adjusted upwards until normal serum levels of phosphorus are achieved. (Opinion)

Guideline 13C. Adynamic Bone Disease

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

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

Guideline 14. Parathyroidectomy in Patients with CKD

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

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

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

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

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

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

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

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

14.4 Imaging of parathyroid glands with ^{99}Tc-Sestamibi scan, ultrasound, computed tomography (CT) scan, or magnetic resonance imaging (MRI) should be done prior to re-exploration parathyroid surgery. (Opinion)

Guideline 15. Metabolic Acidosis

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

15.1a The frequency of these measurements should be based on the stage of CKD as shown in Table 32 in the original guideline document. (Opinion)

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

Guideline 16. Bone Disease in the Kidney Transplant Recipient

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

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

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

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

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

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

16.4b If bone mineral density t-score is equal to or less than –2 at the time of the transplant, or at subsequent evaluations, therapy with parenteral amino-bisphosphonates should be considered. (Opinion)

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

CLINICAL ALGORITHM(S)

The following algorithms are provided in the original guideline document:

- Algorithm 1: Vitamin D supplementation in chronic kidney disease (CKD) (Stages 3 and 4)
- Algorithm 2: Management of chronic kidney disease (CKD) patients (Stages 3 and 4) with active Vitamin D sterols
- Algorithm 3: Managing Vitamin D sterols based on serum calcium levels
- Algorithm 4: Managing Vitamin D sterols based on serum phosphorus levels
- Algorithm 5: Managing Vitamin D sterols based on intact parathyroid hormone (PTH) levels
- Algorithm 6: Evaluation of aluminum neurotoxicity
- Algorithm 7: Evaluation of aluminum-related disorders: considerations for deferoxamine (DFO) test and subsequent DFO treatment
- Algorithm 8: DFO treatment after P_{Al} rise $\geq$300 micrograms/L
- Algorithm 9: DFO treatment after P_{Al} rise between 50 and 300 micrograms/L
- Algorithm 10: CKD Stages 3 and 4
- Algorithm 11: CKD Stage 5 (on dialysis)

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

In formulating the guidelines, the rationale and evidentiary basis of each recommendation was made explicit. When all components of the rationale for a guideline were based on published evidence, the guidelines were labeled "Evidence." When no definite evidence existed or the evidence was considered inconclusive, and either the guideline or steps in its rationale were based on judgment they were labeled "Opinion." As such, it is the available literature that determined the labeling of each guideline.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Prevention of the disturbances in mineral and bone metabolism and their management early in the course of chronic kidney disease are extremely important in improving patients´ quality of life and longevity.
- Although much remains to be learned about these conditions, the recommendations made in these guidelines are intended to aid clinicians in developing an integrated approach to their diagnosis and management of this complicated area, based on the best available evidence.

POTENTIAL HARMS

A deferoxamine (DFO) test should not be performed if the serum levels of aluminum are greater than 200 micrograms/L to avoid deferoxamine-induced neurotoxicity.

Subgroups Most Likely to Experience Harms

- Calcium-based phosphate binders should not be used in dialysis patients who are hypercalcemic or whose plasma parathyroid hormone (PTH) levels are <150 pg/mL on 2 consecutive measurements.
- Vitamin D sterols should not be prescribed for patients with rapidly worsening kidney function or those who are noncompliant with medications or follow-up.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

No clinical practice guidelines, irrespective of the rigor of their development, can accomplish the intended improvement in outcomes without an implementation plan. Since the majority of the recommendations made in this set of guidelines are based on opinion, it is imperative that evaluation of their clinical outcomes be made a component of their implementation. In addition, the paucity of evidence-based information in this field requires that a more integrated approach to research efforts be planned and conducted to provide answers to the many issues that remain to be elucidated.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Eknoyan G, Levin A, Levin NW. Bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003 Oct;42(4 Suppl 3):1-201. [664 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Oct

GUIDELINE DEVELOPER(S)

National Kidney Foundation - Disease Specific Society

SOURCE(S) OF FUNDING

National Kidney Foundation (NKF)

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NKF-K/DOQI (National Kidney Foundation-Kidney Disease Outcomes Quality Initiative) Chronic Kidney Disease Work Group

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Jack W. Coburn, MD, FACP, is on the Medical Advisory Boards of Bone Care International, R & D Laboratories, and Amgen, Inc., and has also consulted with Genzyme Corporation.

Glenn M. Chertow, MD, MPH, has received research support from and has served as an advisor to Amgen, Inc., Genzyme, Inc., and GelTex Pharmaceuticals, Inc.

Keith A. Hruska, MD, is on the Medical Advisory Board of Bone Care International and has received funding or compensation from it as well as Allo-Source, Creative BioMolecules, Inc., and Monsanto/Pharmacia.

Craig B. Langman, MD, is on the Academic Advisory Board of Total Renal Care, Inc, and has been a consultant for many pharmaceutical laboratories, health-care companies, and health-care-related foundations, including Merck USA, Roche Pharmaceuticals, Abbott Laboratories, and the Oxalosis and Hyperoxaluria Foundation.

Hartmut Malluche, MD, has received several grants from the NIH and other organizations including the Veterans Administration.

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Donald J. Sherrard, MD, has received funding from and consulted with Amgen, Inc., Abbott Laboratories, and Geltex Pharmaceuticals.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the National Kidney Foundation (NKF) Web site.

Print copies: Available from the National Kidney Foundation (NKF), 30 East 33rd St., New York, NY 10016. These guidelines are also available on CD-ROM.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on April 8, 2004.

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Date Modified: 11/15/2004