

## Protocol for the Prevention and Management of Renal Osteodystrophy in Adult Dialysis Patients

**Background:** Progressive renal failure leads to decreased phosphorus excretion in the urine, diminished production of endogenous calcitriol by the kidneys, and reduced dietary calcium absorption. These abnormalities lead to an increased production of parathyroid hormone, a condition known as secondary hyperparathyroidism. Left untreated, secondary hyperparathyroidism can lead to many adverse clinical outcomes, one of which is a form of bone disease, often referred to as renal osteodystrophy.<sup>1</sup>

**Purpose:** This protocol provides a uniform approach to the prevention and management of renal osteodystrophy that will have two positive outcomes.

1. Screening of all patients upon initiation of dialysis will permit early intervention.
2. Appropriate monitoring of key laboratory parameters and initiation of dietary and drug therapy will improve bone health.

**Note:** The PTH assay referred to in this document is intact, 2<sup>nd</sup> generation assay, as described in the 2003 K/DOQI Clinical Practice Guidelines. The target values identified here should not be applied to the 3<sup>rd</sup> generation BioIntact assay.

### Procedures

#### A. Patient Screening

All patients to be initiated on dialysis and all patients currently receiving chronic dialysis who have not yet been evaluated should undergo the following evaluation:

1. Measure serum iPTH, calcium, phosphorus, albumin, aluminum, alkaline phosphatase, and magnesium concentrations
2. Determine “corrected” serum calcium concentration:

Step 1: Normal serum albumin (4.0 gm/dL) minus the most recent serum albumin measurement = X  
Step 2: X times 0.8 = Y  
Step 3: Measured serum calcium concentration + Y = “corrected” serum calcium

Example calculation: (In this example, the patient’s serum calcium and albumin are 9.9 mg/dL and 3.2 gm/dL respectively.)

Step 1:  $4.0 - 3.2 = 0.8$   
Step 2:  $0.8 \times 0.8 = 0.64$   
Step 3:  $9.9 + 0.64 = 10.54$  (10.5 is the corrected serum calcium)

3. Determine corrected calcium x phosphorus product (Ca x P)  
Multiply the corrected calcium times the phosphorus concentration  
For example: Corrected calcium (10.5 mg/dL) times phosphorus (5.3 mg/dL) = 55.65

*Note: Corrected serum calcium and Ca x P results should be used in evaluating patients and in making decisions regarding drug therapy.*

## **B. Management of Hyperphosphatemia**

### 1. Dietary<sup>2</sup>

Patients should be seen by a dietitian to obtain a baseline dietary history and evaluation of phosphorus intake. Patients should be instructed in a renal diet that includes restriction of dietary phosphorus to 800-1000 mg/day.

Patient adherence to dietary restrictions should be monitored frequently. A dietician should evaluate patients quarterly. Dietary phosphorus may require further restriction based on an increase in serum phosphorus concentrations.

### 2. Drug therapy

*Decisions to use calcium-based phosphate binders and vitamin D therapy should be based on corrected serum calcium results.*

Pharmacologic treatment of hyperphosphatemia is initiated with a calcium-based phosphate binder, using either calcium carbonate (Oscal®, Tums® and many others) or calcium acetate (Phos-Lo®). Alternatively, sevelamer (Renagel®) may be considered for use in place of calcium-based products. The usual starting dose of calcium carbonate is approximately 1250 mg (500 mg elemental calcium) with each meal. The usual starting dose of calcium acetate is 1334 mg or two tablets (338 mg elemental calcium) with each meal.<sup>3</sup> The usual starting dose of sevelamer is 2 to 4 tablets (800-1600 mg) three times daily with meals.<sup>4</sup> Phosphate binding drugs should be adjusted to maintain the serum phosphorus between 3.5-5.5 mg/dL.

Calcium-based binders have the advantage of supplying needed calcium that a *priori* has been limited in a low-phosphorus diet due to restriction of dairy products. Care should be taken to ensure daily ingestion of adequate amounts of elemental calcium. Conversely, patients taking calcium-based phosphate binders must also be monitored frequently for hypercalcemia, especially if vitamin D products are prescribed concurrently (see below).

Target values:<sup>5</sup>

Table No. 1

| Parameter  | Target Range  |
|------------|---------------|
| Calcium*   | 8.4-9.5 mg/dL |
| Phosphorus | 3.5-5.5 mg/dL |
| Ca x P*    | <55           |
| iPTH**     | 150-300 pg/ml |

\*Corrected value

\*\* Normal range: 10-65

Note: Upper limit values of Ca and P are modified for patients on Vitamin D therapy. Upper limit for Ca is 10.2 and P is 6.0. See page 3, Section C.1 and page 4 Section C.4.

### C. Suppression of Elevated Parathyroid Hormone Concentration

#### 1. Criteria for the initiation of vitamin D therapy<sup>6</sup>

All of the following criteria should be met before initiating vitamin D therapy:

- a. iPTH >300 pg/mL (>4 times the upper limit of normal)  
Recommended assay: Immunoradiometric assay for intact parathyroid hormone (iPTH). Normal range: 10-65 pg/mL  
Treatment decisions for initiating vitamin D therapy should be based upon iPTH values measured at least six weeks after initiation of dialysis.
- b. Corrected serum calcium <10.2 mg/dL (normal range 8.4 to 10.2 mg/dL)
- c. Serum phosphorus <5.5 or 6.0 mg/dL (normal range 3.0 to 4.5 mg/dL)
- d. Corrected calcium x phosphorus product <55
- e. Serum aluminum <60 mcg/L

Other considerations prior to initiating vitamin D therapy<sup>6</sup>

- a. Assess patient adherence to prescribed dietary modifications and phosphate-binding medications. Reinforce patient education.
- b. Consider low dialysate calcium concentration (< 2.5 meq/L) if patient has a history of hypercalcemia.
- c. Possible aluminum toxicity if serum aluminum >60 mcg/L. Consider deferoxamine challenge and/or bone biopsy for diagnosis.

#### 2. Initiating vitamin D therapy

Vitamin D therapy should be initiated with one of the following products: calcitriol intravenous (Calcijex®), paricalcitol (Zemplar®), calcitriol oral (Rocaltrol®), doxercalciferol intravenous (Hectorol®), or doxercalciferol oral (Hectorol®). Patients receiving peritoneal dialysis usually should be treated with Rocaltrol® or oral Hectorol® due to lack of intravenous access. Patients with a history of hypercalcemia should be considered for treatment with paricalcitol or doxercalciferol.<sup>7,8</sup>

Usual starting doses are the following:

- Calcijex®-0.5 to 1.5 mcg intravenously every hemodialysis treatment\*
- Zemplar®- 0.03 to 0.8 mcg/kg (2.5 to 5.0 mcg) intravenously every hemodialysis treatment\*
- Hectorol®- 2 mcg intravenously every hemodialysis treatment\*
- Hectorol®-2.5-10 mcg orally three times a week\*
- Rocaltrol®- 0.25-1.5mcg/daily orally for peritoneal dialysis, 0.5 to 1.5 mcg/daily for hemodialysis.\* Alternatively, Rocaltrol® can be given as pulse oral dosing 0.5 to 2.0 mcg with each dialysis (or three times per week), or Doxercalciferol 2.5-5.0 mcg 3 times per week.

*\*Initial dose should be based on the severity of iPTH elevation.*

### 3. Monitoring vitamin D therapy

- a. Monitor corrected serum calcium, phosphorus, and Ca x P at least two times per month upon initiating therapy and during titration.
- b. Monitor iPTH within one month of initiation of treatment and during titration. Monitor iPTH every three months when dose is stable.
- c. Evaluate patient dietary and phosphate binder consumption monthly or more often based upon the above laboratory parameters.

### 4. Evaluation of vitamin D therapy

a. **Hypercalcemia:** Vitamin D therapy is withheld if corrected serum calcium concentration is >10.2 mg/dL. Serum calcium is monitored at least weekly until patient becomes normocalcemic. Vitamin D therapy can then be re-started at a reduced dose. Other measures to manage hypercalcemia include:

- Withdraw or decrease calcium-based phosphate binders.
- Withdraw or decrease calcium supplements.
- Consider a change to sevelamer if hypercalcemia persists.
- Institute a low calcium diet.
- Instruct patient on dietary and phosphate binder changes and importance of adherence to the prescription.
- Consider low dialysate calcium concentration.

b. **Hyperphosphatemia:** Vitamin D therapy is withheld if serum phosphorus >6.0 mg/dL.

c. **Elevated Ca x P:** Vitamin D therapy is withheld if corrected serum Ca x P >55. Serum calcium and phosphorus is monitored weekly until Ca x P returns to <55. Vitamin D therapy can be re-started at a reduced dose level. Other measures include:

- Evaluate patient adherence with diet and phosphate binder prescription.
- Increase phosphate binder dosage.

- Initiate sevelamer therapy or short-term treatment with an aluminum-based phosphate binder (e.g. aluminum hydroxide) if corrected Ca x P >55.

#### 5. Titration of vitamin D doses

The initial vitamin D dose may be adjusted after 2 to 8 weeks of treatment based on patient response.

**Table No. 2**

| iPTH response    | iPTH decreased but above target range                    | iPTH decreased and in target range | iPTH unchanged and above target range | iPTH increased from baseline | iPTH below 150 pg/mL  |
|------------------|--|------------------------------------|---------------------------------------|------------------------------|---|
| Vitamin D dosing | Maintain or increase after two to eight weeks of therapy | Maintain dose                      | Increase dose                         | Increase dose                | Withhold dose, restart at reduced dose when iPTH >200 pg/mL |

*\*Incremental doses must be individualized, refer to product labeling for maximum dosage.*

#### 6. Over-suppression of iPTH

If the iPTH <150 pg/mL, vitamin D therapy should be withheld until the iPTH >200 pg/mL, and then restarted at a reduced dose. Patients should be observed for symptoms of hypercalcemia, as this is often associated with over-suppression of iPTH.

Serum calcium and phosphorus (Ca x P product) should be monitored at least two times per month, and serum iPTH should be monitored monthly during dosing adjustment or titration.

#### 7. Maintenance therapy

The optimal range for iPTH is 150-300 pg/mL.

Once iPTH concentrations are within this range and the vitamin D dose has been stable for 8 weeks, iPTH is monitored at least quarterly.

Once the iPTH concentration and vitamin D dose are stable, serum calcium, phosphorus, albumin, alkaline phosphatase, and magnesium are monitored at least monthly if within normal limits.

#### 8. Non-response to vitamin D therapy

Potential causes of hyporesponsiveness to vitamin D therapy include inadequate dietary phosphorus restriction and lack of adherence to the prescribed vitamin D prescription. After evaluating these factors, increase the dose of the vitamin D product up to the maximal recommended dose or consider an alternate vitamin D

product. Non-responsive patients with severe hyperparathyroidism should be evaluated for parathyroidectomy.

#### **D. Drug Interactions**

**Aluminum toxicity:** Chronic use of aluminum-based antacids should be avoided. Serum aluminum concentrations are monitored quarterly in patients in whom aluminum-based antacids must be used. If the serum aluminum concentration is greater than 60 mcg/L, possible aluminum toxicity should be considered. Consider deferoxamine challenge and/or bone biopsy for diagnosis. Patients should be advised to avoid citrate-containing products such as calcium citrate, as citrate enhances absorption and bone deposition of aluminum.

**Magnesium toxicity:** Magnesium-based antacids and laxatives should be avoided to minimize the risk of hypermagnesemia.

Calcium-, aluminum-, and magnesium-based phosphate binders may decrease the absorption of oral iron products, digoxin, oral quinolones, and tetracycline. If these products must be used in combination, doses should be spaced 1 to 2 hours apart.

**Cholestyramine:** Cholestyramine and mineral oil may reduce the intestinal absorption of oral vitamin D preparations.

Vitamin D preparations should be used with precaution in patients receiving thiazides and digitalis preparations due to the increased potential for hypercalcemia.

**Sevelamer (Renagel®):** There is a possibility that sevelamer may bind co-administered drugs and reduce their gastrointestinal absorption.

#### **E. Patient Education**

Patients (or spouse/guardians) should be informed about the importance of dosing and diet adherence as well as use of calcium supplementation and phosphate binder usage. Patients should understand that phosphate binders should be taken with meals and snacks. Patients should be informed about the symptoms of hypercalcemia (or hypermagnesemia in patients receiving magnesium-containing phosphate binders). Patients should also be informed to consult with their health care provider before using both over-the-counter and prescription medications. Patients should be informed to avoid drugs that may have a potential for interaction with vitamin D therapy, unless otherwise advised.

#### **F. References**

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**Note:** The 2003 revisions of this protocol and subsequent drug protocols based on:

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).