

Undiagnosed Vitamin D Deficiency in the Hospitalized Patient

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Vitamin D deficiency among hospitalized patients may be more widespread than realized. Vague musculoskeletal complaints in these chronically ill patients may be attributed to multiple underlying disease processes rather than a deficiency in vitamin D. However, the failure to diagnose an underlying deficiency places the patient at risk for continued pain, weakness, secondary hyperparathyroidism, osteomalacia, and fractures. The causes of hypocalcemia and hypophosphatemia in the chronically ill patient are many, and the patient may respond to simple replacement therapy. Elderly hospitalized patients with ionized hypocalcemia and hypophosphatemia, with or without an elevated parathyroid hormone level, are most likely deficient in vitamin D. Initiating treatment during hospitalization is reasonable once the diagnosis has been confirmed by finding a low 25-hydroxyvitamin D level. Treatment with high doses of vitamin D is safe. Unfortunately, some hospital formularies continue to provide multivitamin supplements that contain less vitamin D than currently is recommended. (*Am Fam Physician* 2005;71:299-304. Copyright© 2005 American Academy of Family Physicians.)

See page 225 for strength-of-recommendation labels.

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Vitamin D deficiency is diagnosed by finding a low 25-hydroxyvitamin D level.

Patients with severe vitamin D deficiency and hypocalcemia present with classic findings of neuromuscular irritability, including numbness, paresthesias, muscle cramps, laryngospasm, Chvostek's sign, Trousseau's phenomenon, tetany, and seizures.¹ By contrast, patients with mild vitamin D deficiency present with more subtle complaints such as muscle weakness or pain. Finding only a modest reduction in a patient's calcium or phosphate level should not reassure the physician that all is well. When vitamin D deficiency is the cause of hypocalcemia or hypophosphatemia, replacing calcium or phosphate alone does not restore the body to homeostasis.^{2,3}

Ionized hypocalcemia has been found in 15 to 50 percent of patients being treated in intensive care units (ICUs) and is associated with increased mortality and disease severity.^{4,5} However, chronically ill patients only rarely develop true tetany and hemodynamic instability.^{5,6}

Prolonged asymptomatic hypocalcemia from deficient vitamin D production or absorption stimulates the release of parathyroid hormone (PTH). If vitamin D is not provided, secondary hyperparathyroid-

ism develops with increased bone turnover and decreased bone mineralization.² The adult patient with severe vitamin D depletion develops osteomalacia and presents with localized bone pain, antigravity muscle weakness, difficulty rising from a chair or walking, and pseudofractures.^{3,7}

Illustrative Cases

Two hospitalized chronically ill patients with unrecognized vitamin D deficiency, hypocalcemia, and hypophosphatemia are presented below.

CASE 1

An elderly black woman was readmitted to the hospital from a nursing home because of progressive weakness. She had been discharged two weeks earlier following a four-month hospitalization for severe chronic obstructive pulmonary disease. During her previous hospital stay, she required prolonged mechanical ventilation through a tracheostomy tube and total, or central, parenteral nutrition (CPN). She was discharged to the nursing home on low-flow oxygen therapy. On readmission, she had a weak cough and required vigorous tracheal suctioning through her tracheostomy tube. Depressed levels of serum calcium and phosphate resistant to vigor-

Strength of Recommendations

Key clinical recommendation	Label	References
Daily vitamin D supplementation of 800 to 1,000 IU is a reasonable dose for adults.	C	2, 9, 10
Levels of 25-hydroxyvitamin D should be maintained above 32 ng per mL (80 nmol per L) to maximize bone health.	C	11
In patients with severe vitamin D deficiency (serum levels of below 8 ng per mL with hypocalcemia), 50,000 IU of vitamin D should be given daily for one to three weeks, followed by weekly doses of 50,000 IU.	C	2, 7
After repletion of body stores, 800 IU of vitamin D daily or 50,000 IU of vitamin D once or twice monthly is adequate maintenance therapy.	C	2, 10
Patients with no sun exposure, malabsorption, or those taking antiepileptic drugs may require larger maintenance doses of vitamin D (i.e., up to 50,000 IU one to three times weekly).	C	2, 7
In critically ill patients, albumin-adjusted calcium levels underestimate true or ionized hypocalcemia. Therefore, measured ionized calcium levels are recommended, particularly in patients who are being treated in an intensive care unit.	B	12
If calcium supplementation alone fails to maintain normal serum levels, the patient is vitamin D deficient or resistant and may benefit from a trial of calcitriol (Rocatalol).	C	5
If the vitamin D deficiency is severe, the patient will require 90 mmol per L in the first 24 hours: 6 mL of K ₂ PO ₄ added to each liter of fluid and given at 200 mL per hour (1 mL of K ₂ PO ₄ is equal to 4 mEq of potassium and 3.0 mmol per L or 93 mg of phosphate).	C	14

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, opinion, or case series. See page 225 for more information.

ous oral and intravenous replacement were noted on both hospital admissions. Before she was to return to the nursing home, her 25-hydroxyvitamin D level was 7 ng per mL (17 nmol per L; normal: 8 to 38 ng per mL [20 to 95 nmol per L]), and her PTH level was 161 pg per mL (17 pmol per L; normal: 9.5 to 49.4 pg per mL [1.0 to 5.2 pmol per L]). Vitamin D and calcium supplementation was to begin in the nursing home.

CASE 2

An elderly black man was transferred to the hospital from an extended-care facility because of progressive weakness, hypokalemia, and congestive heart failure. On admission, his potassium level was 2.2 mEq per L (2.2 mmol per L), digoxin was 1.6 ng per mL (2.0 nmol per L), magnesium was 1.1 mEq per L (0.55 mmol per L; normal: 1.3 to 2.0 mEq per L [0.65 to 1.00 mmol per L]), phosphorus was 2.3 mg per dL (0.74 mmol per L;

normal: 2.5 to 4.5 mg per dL [0.81 to 1.45 mmol per L]), and calcium was 6.9 mg per dL (1.72 mmol per L; normal: 8.4 to 10.2 mg per dL [2.10 to 2.55 mmol per L]). He was in chronic atrial fibrillation with an ejection fraction of 12 percent and a therapeutic prothrombin time.

At the time of admission, he was diuresed and given potassium, magnesium, and calcium. Before discharge, the on-call physician noted that the patient's serum calcium and phosphorus levels were still low, and that his ionized calcium level was 3.9 mg per dL (0.97 mmol per L; normal: 4.5 to 5.3 mg per dL [1.12 to 1.32 mmol per L]). The patient was thin, dyspneic, and had a positive Chvostek's sign. The clinical diagnosis of vitamin D deficiency was made. Oral vitamin D supplementation was initiated in a dosage of 50,000 IU three times weekly.

One week after the patient was discharged from the hospital, the reference laboratory reported that his 25-hydroxyvitamin D level was 6 ng per mL (15 nmol per L). PTH levels were not obtained.

Unrecognized vitamin D deficiency can cause secondary hyperparathyroidism with increased bone turnover and decreased bone mineralization.

Risk Factors for Developing Vitamin D Deficiency

Vitamin D deficiency is common. The results of a 1998 study⁸ reported a 57 percent prevalence of vitamin D deficiency in 290 patients admitted to a hospital in Massachusetts. The investigators found that assessment of common clinical risk factors through a multivariate model failed to identify many patients with vitamin D deficiency.⁸

The vitamin D–deficient patients presented in the two illustrative cases in this article were elderly, chronically ill, and malnourished with a poor vitamin D intake. Furthermore, these patients had no exposure to the sun. To produce a similar amount of vitamin D as persons with lightly pigmented skin, persons with darkly pigmented skin require three to six times more sun exposure.⁷

For the patient in case 1, the daily multivitamin supplement infused into the CPN provided only 200 IU of vitamin D (an amount thought to be adequate until recently). In 1997, based on the assumption that young and middle-aged adults were exposed to more sunlight than older adults, new dietary intakes of vitamin D were recommended as follows: 200 IU daily for children and adults 50 years and younger, 400 IU daily for adults 51 to 70 years of age, and 600 IU daily for adults older than 70 years. However, vitamin D supplementation was thought to have such a large margin of safety that 800 to 1,000 IU daily is not an unreasonable dose for all adults.^{2,9,10}

Other disease states and characteristics not present in the illustrative cases but associated with the development of vitamin D deficiency include significant renal or hepatic disease, history of gastric resection or bypass, malabsorption, and use of certain medications such as anticonvulsants.⁷ To remain normocalcemic, patients treated with phenytoin (Dilantin) or phenobarbital require two to five times the recommended daily amount of vitamin D.³

Vitamin D Metabolism and Physiology

Vitamin D is absorbed from the small intestine and is produced in the skin. Dietary

vitamin D₂ comes from yeasts and plants; fish and cod-liver oil are good sources of vitamin D₃, which also is made in the skin.³ In the skin, 7-dehydrocholesterol is converted to 3-cholecalciferol (or vitamin D₃) after exposure to ultraviolet B radiation.^{2,9} Vitamins D₂ and D₃ are equipotent in humans, and together are called “vitamin D.”³ Vitamins D₂ and D₃ are bound to the vitamin D–binding protein and transported to the liver, where 25-hydroxylation of vitamin D produces 25-hydroxyvitamin D, or calcidiol.

Calcidiol is the major circulating form of vitamin D. Although biologically inert, the 25-hydroxyvitamin D level most accurately reflects body stores.^{2,3,9} Under the influence of PTH, 25-hydroxyvitamin D is further hydroxylated in the kidneys to 1,25-dihydroxyvitamin D or calcitriol, the hormonally active form of vitamin D. Calcitriol facilitates calcium absorption in the intestines and is required for the efficient utilization of dietary calcium.^{3,10} 1,25-dihydroxyvitamin D also is thought to inhibit cellular growth, stimulate insulin secretion, and activate the immune system.¹⁰

The ICU patient with multiorgan failure has decreased hepatic production of 25-hydroxyvitamin D and reduced renal synthesis of 1,25-dihydroxyvitamin D.^{3,4} PTH levels increase in response to decreasing 1,25-hydroxyvitamin D levels and impaired dietary calcium absorption. In the kidneys, PTH induces phosphaturia and increases tubular reabsorption of calcium.^{2,7} High levels of PTH also activate osteoclasts in bone to provide essential calcium, resulting in osteopenia and osteoporosis. As both hypocalcemia and hypophosphatemia worsen, the calcium-phosphate product is no longer adequate to mineralize bone properly. Osteoblasts deposit a poorly mineralized collagen, a rubbery matrix that provides inadequate skeletal support. Painful osteomalacia (rickets, in children) is caused by the activation of periosteal sensory pain fibers deformed by weakened and poorly calcified bones.¹⁰

Inadequate sunlight exposure and chronic sunscreen use can cause vitamin D deficiency.

Adults older than 70 years need at least 600 IU of vitamin D daily.

TABLE 1
Causes and Management of Vitamin D Deficiency

Causes	Management
Lack of adequate sunlight or chronic sunscreen use*	Ultraviolet lamp or increased sun exposure†
Total (central) parenteral nutrition	400 to 800 IU of vitamin D orally per day, or 20 to 25 IU of vitamin D per kg intravenously per day
Vitamin D–deficient diet	Usually 1,500 to 5,000 IU of vitamin D ₂ orally per day, or 50,000 IU of vitamin D ₂ orally per week or 10,000 to 50,000 IU of vitamin D ₂ intramuscularly per month
Fat malabsorption	25-hydroxyvitamin D, 20 to 30 mcg per day
Cirrhosis, nephrotic syndrome, renal failure, gastric or small bowel resection, rifampin, chronic corticosteroids, anticonvulsants	1,25-dihydroxyvitamin D, 0.15 to 0.5 mcg daily‡

*— Whole body exposure to a minimal erythral dose of sunlight is equal to 10,000 to 75,000 IU of oral vitamin D.

†—In a Boston study, exposure of hands, face, and arms to sunlight for five to 15 minutes daily between 11 a.m. to 2 p.m. provided adequate vitamin D.

‡—In cases of liver failure or nephrotic proteinuria, levels of 25-hydroxyvitamin D may be low; replacement may suffice. In cases of renal failure with normal or elevated 25-hydroxyvitamin D levels and ionized hypocalcemia, 1,25-dihydroxyvitamin D replacement is required. The dose should be carefully adjusted to normalize calcium, phosphate, and 25-hydroxyvitamin D levels.

Information from references 3, 8, and 10.

Diagnosis and Treatment

VITAMIN D DEFICIENCY

The findings of muscle weakness and pain on physical examination are nonspecific, and often are misdiagnosed as fibromyalgia.¹⁰ The most sensitive test to diagnose vitamin D deficiency is the serum 25-hydroxyvitamin D level.^{2,3,7} PTH levels are normal in early or mild vitamin D deficiency.² Only later do the findings of prolonged secondary hyperparathyroidism present (i.e., osteomalacia, osteoporosis).

If the vitamin D deficiency is mild (8 to 15 ng per mL [20 to 37 nmol per L]), patients should be given 800 IU of vitamin D with 1,500 mg of elemental calcium daily.² Alternatively, serum 25-hydroxyvitamin D levels

should increase from less than 15 ng per mL to 25 to 40 ng per mL (62 to 100 nmol per L) after eight weekly doses of 50,000 IU of vitamin D. With no additional vitamin D, adequate levels will be sustained for only two to four months.³ Current recommendations are that patient levels be maintained above 32 ng per mL (80 nmol per L) to maximize bone health.¹¹

In patients with severe vitamin D deficiency (serum levels of below 8 ng per mL with hypocalcemia), 50,000 IU of vitamin D should be given daily for one to three weeks, followed by weekly doses of 50,000 IU.^{2,7} After repletion of body stores, 800 IU of vitamin D daily or 50,000 IU of vitamin D once or twice monthly is adequate maintenance therapy.^{2,10} However, patients with no sun exposure or malabsorption, and those taking antiepileptic drugs may require larger maintenance doses of vitamin D (i.e., up to 50,000 IU one to three times weekly).^{2,7} Table 1^{3,8,10} lists other treatment options.

HYPOCALCEMIA

In critically ill patients, albumin-adjusted calcium levels underestimate true or ionized hypocalcemia. Therefore, measured ionized

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Classification and Causes of Ionized Hypocalcemia

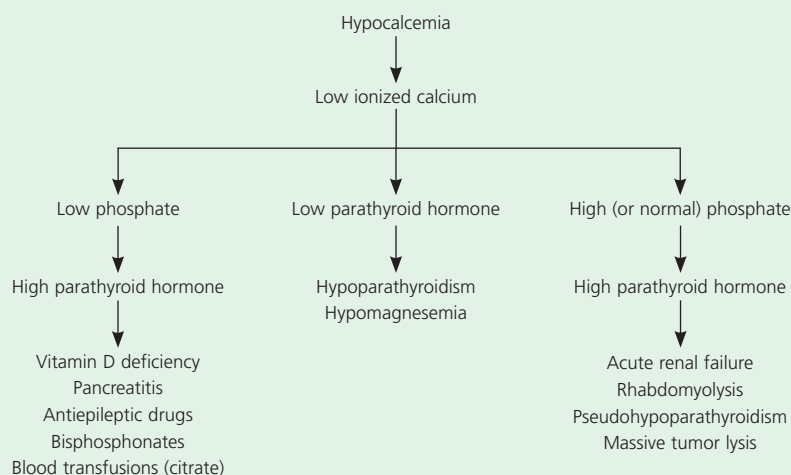


Figure 1. Classification and causes of ionized hypocalcemia.

Information from references 1 through 14.

calcium levels are recommended, particularly in patients who are being treated in an ICU.¹² Serum phosphate levels are elevated in most cases of hypocalcemia. However, patients deficient in vitamin D usually have low phosphate levels. Many disease processes can cause ionized hypocalcemia; *Figure 1*¹⁻¹⁴ may help focus the evaluation.

Asymptomatic patients with ionized calcium levels higher than 3.2 mg per dL (0.8 mmol per L) can be closely monitored without therapy. Treatment can be considered if symptoms develop or the ionized calcium level falls below 3.2 mg per dL.⁵ This cautious approach to calcium replacement is supported by a few case reports and animal studies that suggest mortality is increased when hypocalcemia is corrected in the setting of sepsis.^{4,5,13}

There are no prospective studies on humans that support the use of calcium supplementation in asymptomatic ICU patients with hypocalcemia.⁴ However, hypocalcemia should be aggressively corrected if the patient develops tetany, seizures, QT prolongation, bradycardia, or hypotension refractory to pressors, or in the mechanically ventilated patient where hypocalcemia is associated with decreased diaphragmatic function.^{4,5}

Patients with severe or symptomatic hypocalcemia should be treated with intravenous calcium gluconate, which has 90 mg of elemental calcium in each 10-mL ampule and is less irritating to the veins than calcium chloride.⁵ A bolus of 100 to 180 mg of elemental calcium given over five to 10 minutes will raise the calcium level for one to two hours. An infusion of 15 mg per kg of elemental calcium over four to six hours will increase the serum levels by 2 to 3 mg per dL (0.50 to 0.75 mmol per L).⁵ Calcium levels should be checked every two to four hours, and serum calcium levels should be maintained in the low normal range. When calcium levels stabilize, oral supplementation should begin at a dosage of 1 to 4 g of elemental calcium daily. If calcium supplementation alone fails to maintain normal serum levels, the patient is vitamin D deficient or resistant and may benefit from a trial of calcitriol (Rocatriol).⁵

HYPOPHOSPHATEMIA

The patient described in case 1 required prolonged intubation and ventilatory support during her previous one-month hospitalization. Mechanical ventilation, theophylline, corticosteroids, and beta₂ agonists can cause

hypophosphatemia.¹⁴ Other causes of hypophosphatemia in the hospitalized patient include protein malnutrition, malabsorption, diabetic ketoacidosis, respiratory alkalosis, sepsis, antacid phosphate binders, and vitamin D deficiency.⁶ Because hypophosphatemia and hypocalcemia decrease diaphragmatic function, serum calcium and phosphorous levels must be closely monitored in all patients who require mechanical ventilation.^{13,14}

Symptoms of hypophosphatemia may range from fatigue and irritability to seizures and acute respiratory failure.¹⁴ Mild hypophosphatemia (phosphate level higher than 1 mg per dL [0.50 mmol per L]) may be treated orally with sodium or potassium phosphate (e.g., Neutra-Phos-K, one packet twice daily).⁶ In non-life-threatening situations (e.g., when using CPN) the patient may require 30 mmol per L or less per day of sodium or potassium phosphate for homeostasis. This is achieved by adding 2 mL of phosphate solution (K₂PO₄) to each liter of fluid given at 200 mL per hour.¹⁴

Severe hypophosphatemia (phosphate level below 0.5 mg per dL [0.15 mmol per L]) requires intravenous treatment with sodium or potassium phosphate.⁶ In the critically ill patient, phosphorous is infused slowly to prevent tetany, hypotension, and hypocalcemia.^{6,14} If the deficiency is severe, the patient will require 90 mmol per L in the first 24 hours: 6 mL of K₂PO₄ is added to each liter of fluid and given at 200 mL per hour (1 mL of K₂PO₄ is equal to 4 mEq of potassium and 3.0 mmol per L or 93 mg of phosphate).¹⁴

The safety of faster infusion rates (i.e., 15 to 45 mmol per L over one to three hours) has recently been demonstrated and may be preferred.⁶ However, the vitamin D-depleted patient may present with refractory hypophosphatemia. In the absence of hyper-

calcemia or hypercalciuria, and after 25-hydroxyvitamin D levels have been drawn, the patient may benefit from a trial of calcitriol (0.25 to 0.50 mcg orally or via feeding tube) to decrease renal phosphate losses.⁶

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