BMJ Best Practice

Secondary hyperparathyroidism

Straight to the point of care

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Summary

Secondary hyperparathyroidism (SHPT) is elevation of parathyroid hormone (PTH) secondary to hypocalcemia.

PTH maintains calcium homeostasis by acting on the renal tubules, on calcium stores in the skeletal system, and indirectly on the gastrointestinal tract through activation of vitamin D and enteral absorption.

The disease most frequently associated with SHPT is chronic kidney disease. However, the most common reason for SHPT is vitamin D deficiency. Inadequate vitamin D stores are common in older people, those with malabsorption syndromes, or those with limited exposure to sunlight.

Management includes appropriate treatment of the underlying cause and vitamin D supplementation. Parathyroidectomy is infrequently required to remove irreversibly enlarged parathyroid glands in an effort to restore normal parathyroid physiology.

Untreated, it can result in significant skeletal and cardiovascular complications, which contribute to overall morbidity and mortality.

Definition

Any disorder that results in hypocalcemia will elevate PTH levels and can serve as a cause of SHPT. The most frequent causes are chronic kidney disease (CKD), malabsorption syndromes, and chronic inadequate sunlight exposure, acting via alterations in vitamin D, phosphorus, and calcium.

SHPT is a complication of CKD and is important in the pathogenesis of CKD-mineral bone disorder (MBD). CKD-MBD is defined as a systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following: abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism; abnormalities in bone turnover, mineralization, volume, linear growth, or strength; vascular or other soft-tissue calcification.[1]

Epidemiology

Secondary hyperparathyroidism (SHPT) is most commonly associated with chronic kidney disease (CKD) or vitamin D deficiency (which may arise from malabsorption syndromes or chronic lack of exposure to sunlight). Worldwide, severe vitamin D deficiency (<12 nanograms/mL) is seen in about 7% of the population.[3] National Health and Nutrition Examination Survey 2010 data estimate that the prevalence of 25-hydroxyvitamin D levels of <12 nanograms/mL are found in 6.7% of the US population.[4] The estimated global prevalence of all-stage CKD in 2017 was around 9%.[5] Over 80% of patients with CKD are at risk for the development of vitamin D deficiency, with an inverse correlation between decreasing 25-hydroxyvitamin D levels and elevated parathyroid hormone (PTH) levels across all stages of CKD.[6] Elevation of PTH levels begins about GFR 45 mL/minute/1.73 m^2 and increases in prevalence as glomerular filtration rate levels decline.[7] Estimates of the prevalence of SHPT in people on dialysis range from 30% to 49% in Australia, 54% in North America (US, Canada), 28% in India, and 11.5% in Japan.[8]

Etiology

Any disorder that results in hypocalcemia will elevate parathyroid hormone (PTH) levels and can serve as a cause of secondary hyperparathyroidism (SHPT).[9]

The three principal etiologies that may lead to this situation are chronic kidney disease (CKD), malabsorption syndromes, or chronic inadequate exposure to sunlight.

- With CKD there is loss of 1-alpha-hydroxylase in the kidney, which results in a decreased conversion of 25-hydroxyvitamin D to the active 1,25-dihydroxyvitamin D. The low level of 1,25-dihydroxyvitamin D, with or without hypocalcemia, is detected by receptors on the parathyroid glands and results in increased PTH secretion, which is commonly seen in late-stage CKD (stages 3 to 5D).
- In conditions such as Crohn disease, celiac disease, chronic pancreatitis, or Whipple disease, or following gastric bypass surgery, there is fat malabsorption that contributes to reduced absorption of vitamin D and dietary calcium (worsened if there is inadequate intake), ultimately leading to hypocalcemia and an increase in PTH.[2] [9]
- For most people, exposure to sunlight is the major source of vitamin D.[2] However, concerns of increased skin cancers due to ultraviolet radiation resulted in successful campaigns to minimize sun exposure during the precise times vitamin D can be synthesized in the skin.[10] Inadequate vitamin D exposure is common among older patients, particularly those who always use sunblock, are housebound, institutionalized, or hospitalized.[11] This may result in vitamin D deficiency, which can cause hypocalcemia and a consequent rise in PTH secretion.

Other causes include:

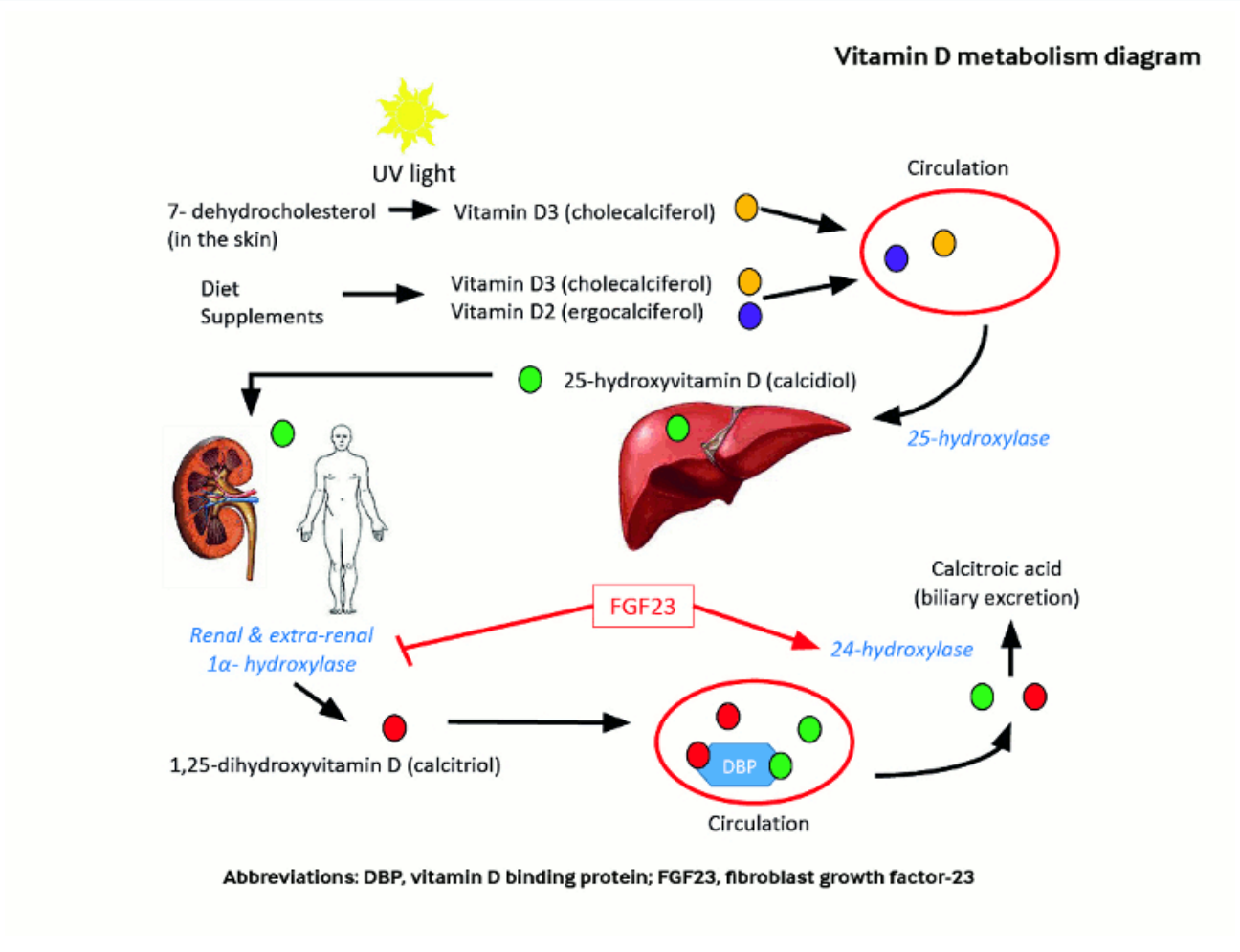
- Diminished dietary intake of calcium
- Increased calcium loss or increased metabolic requirement:
    - Bone growth in growing years
    - Pregnancy and breastfeeding
    - Bisphosphonate treatment
    - Idiopathic hypercalciuria
    - Loop diuretics

- Rhabdomyolysis
- Sepsis

- Diminished PTH effect:
  - CKD
  - Pseudohypoparathyroidism (G-protein deficiency)

Pathophysiology

The metabolism of vitamin D is central to understanding the pathophysiology of the main causes of SHPT. There are two main forms of vitamin D: cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2).



Vitamin D metabolism

Created by Dr Syazrah Salam; used with permission

Cholecalciferol (vitamin D3) is produced in the skin after sun exposure, and is found in a limited number of foods.[12] [13] Exposure to sunlight is the major source of vitamin D for most children and adults.[2] Cholecalciferol occurs naturally in relatively few foods: salmon, tuna, mackerel, and fish-liver oils are the best sources, with smaller amounts found in beef liver, cheese, and egg yolk. Ergocalciferol (vitamin D2) has a different side chain from cholecalciferol. It is also found naturally in small quantities in some mushrooms.[13]

Both vitamin D2 and D3 are used to fortify milk, bread, and multivitamins in the US. In Europe, vitamin D3 is almost exclusively used for multivitamins and food fortification.

Once vitamin D (D2 or D3) is made in the skin or ingested in the diet, it undergoes two hydroxylations, the first in the liver to form 25-hydroxyvitamin D. This compound then enters the circulation bound to vitamin D-binding protein (DBP) and travels to the kidney where the megalin receptor translocates the DBP-25-hydroxyvitamin D complex into the renal tubule. Here, the enzyme 25-hydroxyvitamin D-1-alpha-hydroxylase (CYP27B) introduces a hydroxyl function to form 1,25-dihydroxyvitamin D.[2]

Fibroblast growth factor-23 (FGF-23) is an important regulator of vitamin D metabolism. FGF-23 inhibits 1-alpha-hydroxylase activity in the kidneys and increases 24-hydroxylase activity, which removes cholecalciferol and 1,25-dihydroxyvitamin D from the circulation. The overall effect is a reduction in the level of 1,25-dihydroxyvitamin D.[14]

In the intestines 1,25-dihydroxyvitamin D induces expression of an epithelial calcium channel, calcium-binding protein (calbindin), and a number of other proteins that help increase transport of calcium from the diet into the circulation.[2] 1,25-dihydroxyvitamin D also interacts with nuclear vitamin D receptor in the osteoblast to stimulate the expression of receptor activator of nuclear factor kappa-B ligand (RANKL), which leads to osteoclast maturation and, thus, bone resorption. In this way 1,25-dihydroxyvitamin D helps maintain calcium homeostasis by increasing the efficiency of intestinal calcium absorption and mobilizing calcium stores from the skeleton.

Any deficiency in vitamin D causes a decrease in the efficiency of intestinal absorption of dietary calcium (and phosphorus).[15] This results in a transient lowering of the ionized calcium, which promptly triggers increased production and secretion of PTH.[9] PTH acts to increase ionized calcium in the blood by interacting with its membrane receptor on mature osteoblasts, which induces expression of RANKL. The RANKL protein is recognized by a protein called receptor activator of nuclear factor kappa-B (RANK) present on the plasma membrane of preosteoclasts, and the RANKL-RANK interaction results in increased production and maturation of osteoclasts.[2] PTH also decreases the gene expression of osteoprotegerin (a decoy receptor for RANKL) in osteoblasts, which further enhances osteoclastogenesis. The osteoclasts release hydrochloric acid and collagenases to destroy bone, resulting in the mobilization of the calcium stores out of the skeleton. This vitamin D deficiency-induced SHPT results in the wasting of the skeleton, which can precipitate and exacerbate osteoporosis.[2]

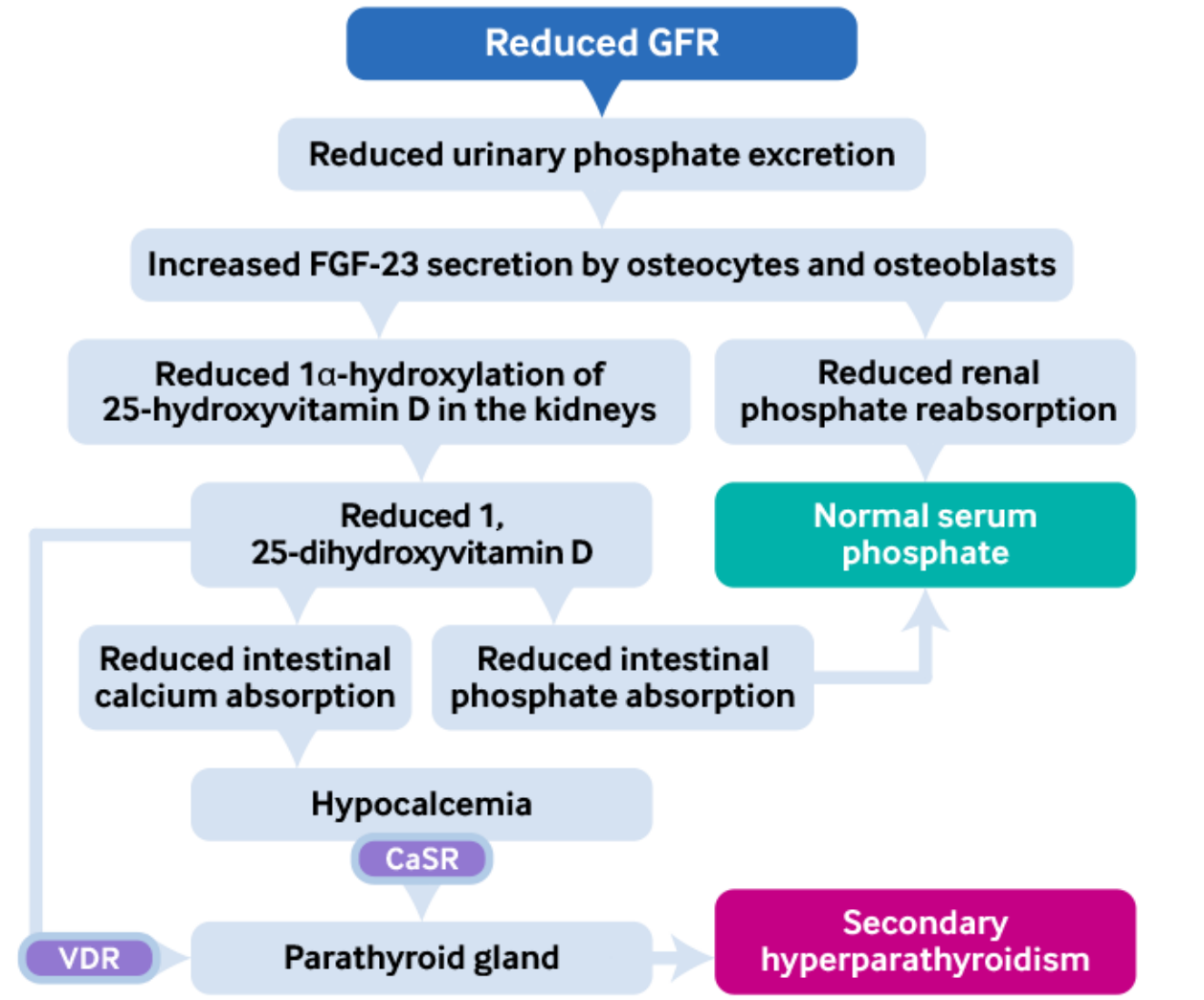
Another effect of vitamin D deficiency and SHPT is loss of phosphorus in the urine and a lowering of serum phosphorus levels.[15] The inadequate calcium-phosphorus product that results causes the bone matrix laid down by osteoblasts to be abnormally mineralized. In children, the weight of the body causes the abnormally mineralized skeleton to develop classic rachitic deformities such as bowed legs or knocked knees. However, in adults there is generally sufficient skeletal mineralization to prevent skeletal deformities, although in a vitamin D-deficient state, newly laid-down osteoid cannot be properly mineralized, leading to osteomalacia.[15] This is associated with throbbing bone pain often misdiagnosed as fibromyalgia, myositis, or chronic fatigue syndrome. A possible explanation of the pain in these patients is that the poorly mineralized osteoid becomes hydrated and cannot provide sufficient support for the sensory fibers in the periosteum.[16] The pain commonly affects the pelvis, hips, legs, lower back, and ribs.

Chronic kidney disease-mineral bone disorder

Chronic kidney disease-mineral bone disorder (CKD-MBD) is defined as a systemic disorder of bone and mineral metabolism due to CKD manifested by either one or a combination of the following:[1]

- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
- Vascular or other soft-tissue calcification.

The pathophysiology of CKD-MBD is complex. Principally there is a gradual decline in overall renal phosphate excretion, although paradoxically excretion per individual nephron rises sharply, which maintains serum phosphate in the normal range until CKD stage 4. There are also increased levels of PTH and FGF-23, two phosphaturic hormones that seem to accelerate the development of vascular disease particularly in the context of CKD.[17] Evidence for this comes from the Framingham Offspring study, which demonstrated that hyperphosphatemia was associated with increased risk of cardiovascular disease even in subjects free of CKD, and the Third National Health and Nutrition Examination Survey (NHANES).[18] [19] Although FGF-23 is implicated in the pathophysiology of CKD-MBD, its use in clinical practice as a biomarker of disease progression is yet to be tested prospectively. There are also unresolved questions pertaining to assays, and the ability to make a sustained major reduction in serum FGF-23 concentrations remains elusive.



Pathophysiology of secondary hyperparathyroidism in CKD-MBD

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There is a spectrum of histomorphometric abnormalities that can be seen in patients with CKD, and to date inadequate clinical data and the heterogeneous nature of the condition have made it difficult to create a reliable and accurate classification system based on serum biochemical abnormalities alone to aid its diagnosis and management.[20] Indeed, dysfunctional bone mineral homeostasis and soft-tissue calcification are not exclusive to CKD and are multifactorial processes that may have more than one underlying etiology. For example, bone fragility, increased risk of fracture, and vascular calcification with atherosclerotic disease are associated with normal aging processes, and may occur in patients with normal or only mildly reduced renal function, only to exist concomitantly with CKD-MBD when renal function has deteriorated. Traditionally, a bone biopsy might have been conducted if there were biochemical inconsistencies, inexplicable bone pain, or fractures that would not support the diagnosis of CKD-MBD.[1] However, bone biopsy is very rarely undertaken in current clinical practice owing to its invasive nature.

Case history

Case history #1

A 50-year-old obese woman with long-standing, poorly controlled diabetes mellitus presents with lethargy and fatigue. Screening labs report that she has a creatinine level of 2.5 mg/dL and a BUN level of 40 mg/dL. Additional labs are ordered, which reveal a calcium level of 7.4 mg/dL and a phosphorus level of 5.9 mg/dL. The parathyroid hormone level is 400 picograms/mL.

Case history #2

An 85-year-old female nursing-home patient is being seen for postmenopausal skeletal disease that has become a concern after she fell and broke her wrist. Her bone densitometry reveals osteoporosis (T-score: -3.5). Lab tests return with a calcium level of 8.8 mg/dL and a parathyroid hormone level of 120 picograms/mL. These results prompt vitamin D testing that returns a 25-hydroxyvitamin D level of 14 nanograms/mL.

Other presentations

The disease most frequently associated with secondary hyperparathyroidism (SHPT) is chronic kidney disease. However, the most common reason for SHPT is vitamin D deficiency, which is most often encountered among older patients, those with fat malabsorption syndromes, or those with limited exposure to sunlight.[2]

Approach

Secondary hyperparathyroidism (SHPT) is a diagnosis based on the clinical picture and metabolic derangements of low serum calcium and high parathyroid hormone (PTH). When phosphorus levels are also elevated, this points to chronic kidney disease (CKD) as the etiology. If phosphorus levels are normal or low, with low serum calcium and high PTH, vitamin D levels should be measured. If vitamin D levels are low, malabsorption syndromes, inadequate sunlight exposure, and other abnormalities of vitamin D metabolism should be considered.[9]

Clinical features

Clinical features will reflect the underlying metabolic derangement itself and the underlying disease causing the derangement.

Severe vitamin D deficiency and hypocalcemia classically presents with features of neuromuscular irritability.[32] This may manifest as numbness and paresthesia in the fingers, toes, or periorally; muscle cramps; laryngospasm; tetany; or seizures. Chvostek sign (tapping on the face just anterior to the ear produces twitching of muscles around the mouth) or Trousseau sign (inflating a blood pressure cuff above diastolic for about 3 minutes causes muscular flexion of the wrist, hyperextension of the fingers, and flexion of the thumb) may be elicited.

The inadequate calcium-phosphorus product that results from vitamin D deficiency causes the bone matrix laid down by osteoblasts to be abnormally mineralized. In children, this may lead to the development of rickets, with signs of growth retardation and skeletal deformities (e.g., bowed legs or knocked knees). In adults, inadequate bone mineralization may lead to osteomalacia, with symptoms such as muscle weakness and diffuse bone pain (commonly affecting the pelvis, hips, legs, lower back, or ribs).[15]

CKD is a frequent cause of SHPT and is often already diagnosed. Signs and symptoms of advanced CKD include skin discoloration and bruising, pruritus, lung rales, pericardial rub, edema, fatigue, nausea, poor concentration/memory, and myoclonus.[33] [34] Diagnostic tests for CKD-mineral bone disorder (CKD-MBD) are usually reserved for when the estimated GFR is <60 mL/minute/1.73 m². Initial investigations should include PTH, calcium, phosphorus, and 25-hydroxyvitamin D.[9] Imaging for vascular or cardiac valvular calcification should be considered because patients with CKD-MBD have the highest cardiovascular risk.[1]

Malabsorption (which may lead to vitamin D deficiency and poor calcium absorption) may arise from a number of conditions, such as Crohn disease, celiac disease, chronic pancreatitis, or Whipple disease, or following gastric bypass surgery.[15] Frequently these diagnoses have already been established. Patients often have a history of long-standing gastrointestinal symptoms such as abdominal pains, irregular bowel habit, and chronic diarrhea.

Inadequate exposure to sunlight may be particularly likely in older people (who may be housebound, hospitalized, or institutionalized), heavy/habitual users of sunblock, and those who routinely wear clothing that covers their entire body. The skin of older individuals also has a reduced capacity to synthesize vitamin D3 under the influence of ultraviolet light.[11] [23] Other factors that may lead to insufficient exposure to ultraviolet radiation include season, geographic latitude, time of day during sun exposure, degree of skin pigmentation, cloud cover, and smog.[3] [12] [15]

Vitamin D deficiency may also develop in individuals who strictly avoid dairy products in their diet or are users of drugs such as phenytoin, phenobarbital, rifampin, corticosteroids, isoniazid, and lithium.

Laboratory testing

Laboratory investigations are required to confirm the metabolic derangement of elevated PTH and hypocalcemia, and to help establish the underlying cause. Initial investigations should include PTH, calcium, phosphorus, 25-hydroxyvitamin D, and assessment of renal function.[9]

Intact parathyroid hormone (iPTH)

- Elevation of iPTH is the definitive test to establish hyperparathyroidism. iPTH should always be ordered with a paired calcium level so that the iPTH level can be properly interpreted. PTH levels vary over the course of a day, peaking at about 2 a.m.[35]

Calcium level

- The relationship between the calcium level and the iPTH level is what distinguishes primary from SHPT. In SHPT, the calcium level is low, which results in a loss of negative feedback on the parathyroid glands. This causes an increase in the production of PTH in an attempt to increase calcium levels back into the normal range. Total or ionized calcium can be measured, but it is important to use the same test on every occasion in order to allow accurate comparisons and trend analysis.

25-hydroxyvitamin D

- Evaluation for possible vitamin D deficiency should form part of the workup of a patient with suspected SHPT, as it is the most common reason for PTH elevation.[11] [25][36]
- The level of 25-hydroxyvitamin D is the most accurate measure of the amount of vitamin D in the body. Other metabolites may be measured, but these do not reflect the total body stores of this fat-soluble vitamin as accurately as 25-hydroxyvitamin D. Thresholds for the definition of vitamin D deficiency for the general population differ between advisory bodies.[37] The normal range may vary between laboratories, but is usually 16 to 74 nanograms/mL. Many experts hold that any value 30 nanograms/mL or less demonstrates vitamin D insufficiency.[3] If the PTH is elevated and the 25-hydroxyvitamin D level is low, the latter should be corrected before considering aggressive drug therapy or surgery.
- In some cases, measurement of 1,25-dihydroxyvitamin D may appear normal despite significant vitamin D deficiency. Elevated PTH drives the conversion of 25-hydroxyvitamin D, thus creating the appearance that the 1,25-dihydroxy form is normal when 25-hydroxyvitamin D reserves are depleted.[21]

Renal function and phosphorus levels

- Serum creatinine, BUN, and calculated GFR are used to assess renal function. These laboratory tests form part of routine serum multianalysis panels and, if elevated, suggest kidney disease, the most serious cause of SHPT.[38]
- Biochemical changes of CKD-MBD increase when estimated GFR falls below 60 mL/minute/1.73 m^2.[9]
- Measuring phosphorus levels allows an appreciation of the severity of kidney disease and may indicate the need for phosphorus reduction therapy. When phosphorus levels are elevated in

addition to elevated serum creatinine and BUN, this points to CKD as the etiology of SHPT. If phosphorus levels are low, other anomalies such as vitamin D deficiency are more likely.[9]

Magnesium level

- Hypomagnesemia and hypermagnesemia can cause tissue resistance to PTH or reduce PTH production, which in turn causes hypocalcemia.[39] Therefore, PTH can be low, normal, or mildly elevated. CKD may result in either hypomagnesemia or hypermagnesemia.[40]

Imaging

Once the diagnosis is established and if surgical treatment is considered, ultrasound, high-resolution contrast computed tomography (CT), magnetic resonance imaging, and 99Tc-sestamibi (MIBI) nuclear medicine scans may be used to confirm parathyroid hyperplasia, and to estimate the size and location of the glands.[41] [42] One meta-analysis has, however, found that planar parathyroid scintigraphy using 99Tc-MIBI did not provide adequate diagnostic accuracy in patients with SHPT and diffuse or nodular hyperplasia, and therefore should not be used as a first-line diagnostic imaging method in the presurgical detection of parathyroid gland hyperplasia.[43] 99mTc-MIBI single-photon emission computed tomography (SPECT)/CT has shown better sensitivity than 99mTc-MIBI planar scintigraphy in identifying parathyroid lesion in SHPT. 99mTc-MIBI SPECT/CT sensitivity is further improved when used in combination with ultrasound.[44]

History and exam

Key diagnostic factors

features of chronic kidney disease (uncommon)

- Includes discolored skin, bruising, pruritus, evidence of fluid overload (lung rales, pericardial rub, and peripheral edema), elevated blood pressure, fatigue, nausea, poor concentration/memory, and myoclonus.[33] [34]

features of underlying malabsorption syndrome (uncommon)

- Malabsorption (which may lead to vitamin D deficiency and poor calcium absorption) may arise from a number of conditions, such as Crohn disease, celiac disease, chronic pancreatitis or Whipple disease, or following gastric bypass surgery.[15] Frequently these diagnoses have already been established. Patients often have a history of long-standing gastrointestinal symptoms such as abdominal pains, irregular bowel habit, and chronic diarrhea.

Other diagnostic factors

muscle cramps and bone pain (common)

- These are common symptoms of SHPT and/or osteomalacia.
- A possible explanation of the pain in patients with vitamin D deficiency is that the poorly mineralized osteoid becomes hydrated and cannot provide sufficient support for the sensory fibers in the periosteum.[16] The pain commonly affects the pelvis, hips, legs, lower back, and ribs.

perioral tingling or paresthesia in fingers or toes (uncommon)

- Indicative of hypocalcemic states.

Chvostek sign (uncommon)

- Tapping on the face just anterior to the ear and seeing a twitching of muscles around the mouth. Seen in most hypocalcemic states. Demonstrates neuromuscular excitability.

Trousseau sign (uncommon)

- Inflating blood pressure cuff above diastolic for about 3 minutes causes muscular flexion of the wrist, hyperextension of the fingers, and flexion of the thumb. Seen in most hypocalcemic states. Demonstrates neuromuscular excitability.

bowed legs or knock knees (uncommon)

- Characteristic features of rickets in children. The weight of the body causes the abnormally mineralized skeleton to develop these classic rachitic deformities.

fractures (uncommon)

- Feature of osteomalacia arising from SHPT. Fractures occur with even mild trauma or movement. Any bone may be affected, but long bone fractures are the most common.

Risk factors

Strong

aging

- Serum parathyroid hormone (PTH) levels increase as a function of age. Factors that may explain this include loss of renal capacity, calcium malabsorption, peripheral resistance to PTH calcemic effects, endemic vitamin D deficiency, and chronic metabolic acidosis.[21] Calcium intake in older patients is frequently insufficient precisely when their demand for this mineral is increased. This raises PTH levels, which has the undesirable consequence of skeletal resorption.[22] This is reversible with dietary supplementation.
- The skin of older individuals also has a reduced capacity to synthesize vitamin D3 under the influence of ultraviolet light.[11] [23]

chronic kidney disease

- With decreased renal function, calcium and vitamin D are lost and result in a compensatory rise in parathyroid hormone (PTH). The presence of hypocalcemia and elevated PTH is classic for SHPT.[24] When phosphorus levels are also elevated, this points to chronic kidney disease (CKD) as the etiology.
- Patients with CKD commonly develop renal osteodystrophy. If phosphorus levels are low, other anomalies such as vitamin D deficiency should be considered.[9]

vitamin D deficiency: inadequate sunlight exposure

- Vitamin D deficiency is a global issue.[2] Inadequate direct sunlight exposure (or heavy/habitual sunscreen use) and inadequate vitamin D intake usually occur simultaneously to result in clinical vitamin D deficiency.

- Casual sun exposure provides most people's vitamin D requirement.[2] Sunscreen with a SPF of 30, if used properly, can reduce the capacity of the skin to produce cholecalciferol by over 95%.[2] Consequently, those who always wear a sunscreen before going outside are at higher risk for vitamin D deficiency. Likewise, melanin in the skin of darkly pigmented individuals also acts to hinder vitamin D synthesis. A person with a skin type VI (dark brown, black) requires at least 5 to 10 times longer sun exposure than white people to produce adequate cholecalciferol in their skin.[2]
- Particularly susceptible groups include older people (who may not be exposed to enough sunlight or are housebound, hospitalized, or institutionalized) and individuals who are confined to the home or who wear clothing that covers the entire body and face.[11] Other factors include season, geographic latitude, time of day during sun exposure, degree of skin pigmentation, cloud cover, and smog.[3] [12] [15] Ultraviolet-B radiation does not penetrate glass, so exposure to sunshine indoors through a window does not produce vitamin D.[2]

nutritional deficiency (especially absence of dairy products and fish)

- Dairy products and fish are important sources of vitamin D and calcium. Diets deficient in these can contribute to poor intake of calcium and vitamin D deficiency.

vitamin D deficiency: malabsorption

- Malabsorption is a common problem among older patients. One feature is reduced absorption of fats and, as vitamin D is a fat-soluble vitamin, this can contribute to hypovitaminosis D. This can be further aggravated by the fact that only small amounts of 25-hydroxyvitamin D are recirculated enterohepatically.[11] [25] A history of celiac disease, Crohn disease, chronic pancreatitis, Whipple disease, or lactose intolerance can be a significant contributory factor to the development of vitamin D deficiency and poor calcium absorption.[15]

Weak

vitamin D deficiency: hepatic dysfunction

- Hepatic dysfunction, concurrent with chronic kidney disease (CKD), or that develops as a result of CKD (hepatorenal syndrome), can also interfere with production of active vitamin D metabolites (25 hydroxylation).[11] [25]

vitamin D deficiency: genetic disorder

- Type 1 hereditary vitamin D-dependent rickets is an autosomal recessive disorder characterized by absent or defective conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D in the kidneys.
- Type 2 hereditary vitamin D-dependent rickets has several forms and is due to mutations in the 1,25-dihydroxyvitamin D receptor. This receptor affects the metabolism of gut, kidney, bone, and other cells. In this disorder, 1,25-dihydroxyvitamin D is abundant but ineffective because the receptor is not functional.[11] [25]
- X-linked familial hypophosphatemia is a genetic disease that causes high fibroblast growth factor-23 (FGF-23) levels, which in turn reduces vitamin D synthesis in the kidneys and increases the breakdown of vitamin D.[14]

vitamin D deficiency: obesity

- Class III obesity (BMI 40 or above) has been associated with vitamin D deficiency and SHPT. In a case-control study, 90% of 41 prebariatric surgery patients had 25-hydroxyvitamin D levels <75 nanomol/L (versus 32% in controls), and 61% had 25-hydroxyvitamin D levels <50 nanomol/L (versus

12% in controls). Additionally, 49% of the prebariatric surgery patients had SHPT versus 2% of controls.[26]

- Although vitamin D is fat soluble and is partially sequestered in the body fat to be used during the winter (when there is less sunlight exposure), in obese children and adults cholecalciferol is sequestered deep in the body fat, which reduces its bioavailability. Lower vitamin D levels likely reflect a volumetric dilution.[2] [27] Consequently, obese individuals require larger than usual doses to correct vitamin D deficiency.[28]

medication use

- Many anticonvulsants (phenytoin, phenobarbital) and glucocorticoids increase the need for vitamin D supplementation above basal requirements.[15]

Investigations

1st test to order

Test	Result
serum calcium • First-line test for diagnosis. Highly sensitive and specific. Normal limits can vary between laboratories. Blood sample should be taken at same time as sample for intact parathyroid hormone (iPTH) is taken. Either total or ionized calcium levels may be used, but the same test should be used consistently over time to allow proper comparison and trend analysis. • Total serum calcium levels should be corrected for serum albumin. An ionized calcium level is preferred.	**<8.4 mg/dL**
serum intact parathyroid hormone (iPTH) • First-line and definitive test for diagnosis of hyperparathyroidism. Older assays using parathyroid hormone (PTH) fragments are less reliable and have been abandoned for the intact assay. iPTH should always be ordered with a paired calcium level so that the PTH level can be properly interpreted. Value varies with reference laboratory used.	**>88 picograms/mL**
serum creatinine • Used to establish renal function, in combination with BUN. Estimated GFR values are calculated using the isotope dilution mass spectrometry (IDMS)-traceable modification of diet in renal disease (MDRD) equation.[38] • GFR values of up to 59 mL/minute/1.73 m^2 may be associated with chronic kidney disease (CKD).	**>1.2 mg/dL in CKD**
serum BUN • In combination with serum creatinine, it establishes renal function. Estimated GFR values are calculated using the isotope dilution mass spectrometry (IDMS)-traceable modification of diet in renal disease (MDRD) equation.[38]	**>20 mg/dL in chronic kidney disease**

Other tests to consider

Test	Result
serum phosphorus • Allows appreciation of the severity of kidney disease. May indicate the need for phosphorus reduction therapy. • When phosphorus level is elevated in addition to elevated serum creatinine and BUN, this points to chronic kidney disease (CKD) as the etiology of SHPT. If phosphorus levels are low, other anomalies such as vitamin D deficiency are more likely.[9] • High calcium and phosphorus levels may be a risk for calciphylaxis, a lethal, small-, and mid-size arteriolar vasculopathy.	**variable; >4.5 mg/dL in CKD**
serum 25-hydroxyvitamin D • Deficiency may be the principal cause of SHPT or the consequence of another underlying condition, and will need correction by replenishment.	**<16 to 30 nanograms/mL (varies on reference lab) if inadequate vitamin D**
serum magnesium • Hypomagnesemia and hypermagnesemia can cause tissue resistance to parathyroid hormone (PTH) or reduce PTH production, which in turn causes hypocalcemia.[39] • Chronic kidney disease may result in either hypomagnesemia or hypermagnesemia.[40]	**may be normal, low, or mildly elevated**
ultrasound neck • Used to confirm parathyroid gland disease. Provides an estimate of parathyroid gland size and location, and might be used as a surgical road map for resection.	**parathyroid gland hyperplasia**
99Tc-sestamibi (MIBI) scan • Used to confirm parathyroid gland disease. Provides an estimate of parathyroid gland size and location, and might be used as a surgical road map for resection (can allow for intraoperative radioguided parathyroid gland surgery).[41] • One meta-analysis has, however, found that planar parathyroid scintigraphy using 99Tc-MIBI did not provide adequate diagnostic accuracy in patients with SHPT and diffuse or nodular hyperplasia, and therefore should not be used as a first-line diagnostic imaging method in the presurgical detection of parathyroid gland hyperplasia.[43] • 99mTc-MIBI single-photon emission computed tomography (SPECT)/CT has shown better sensitivity than 99mTc-MIBI planar scintigraphy in identifying parathyroid lesion in SHPT. 99mTc-MIBI SPECT/CT sensitivity is further improved when used in combination with ultrasound.[44]	**parathyroid gland hyperplasia**
high-resolution contrast CT scan neck and upper chest • Allows for visualization of parathyroid tissue based on the pattern of tissue enhancement, following the administration of iodinated intravenous contrast medium. The upper chest is included in the imaging to look for possible ectopic or supernumerary parathyroid glands.	**parathyroid gland hyperplasia**
MRI neck and upper chest • May be used to confirm parathyroid gland disease. Provides an estimate of parathyroid gland size and location, and might be used	**parathyroid gland hyperplasia**

Test	Result
as a surgical road map for resection. The upper chest is included in the imaging to look for possible ectopic or supernumerary parathyroid glands.	

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Primary hyperparathyroidism	• Difficult to distinguish clinically from SHPT. Both types cause constitutional symptoms and skeletal disease. Kidney stones are a hallmark of primary hyperparathyroidism, but may be absent. Blood tests are used to differentiate between the two forms.	• Low serum calcium in the presence of elevated parathyroid hormone distinguishes secondary from primary hyperparathyroidism (high calcium).

Screening

Routine screening laboratory tests that include blood calcium are advised for people at risk of secondary hyperparathyroidism (SHPT), such as those with known kidney disease or at high-risk of vitamin D deficiency.

There is no rationale to screen the general population for SHPT.

Approach

Secondary hyperparathyroidism (SHPT) is a significant disorder and is often found in patients with kidney disease, malabsorption syndromes, or inadequate exposure to sunlight. SHPT may improve with optimum medical management of the underlying condition, but if left untreated can result in significant skeletal and cardiovascular complications that contribute to overall morbidity and mortality.

Lack of sunlight-related SHPT

If inadequate exposure to sunlight is identified as a factor in vitamin D insufficiency and SHPT, advice on safe sun exposure should be given and the reasons explained. Exposure to sunlight depends on physical factors (e.g., geographic latitude, season, weather, time of day) and personal factors (e.g., skin pigmentation, body surface area exposed, sunscreen use).[3] [12] [15] For a white person, exposure to sunlight at most latitudes for no more than 10 to 15 minutes/day between 10 a.m. and 3 p.m., on arms and legs or hands, face, and arms, during the spring, summer, and fall, provides adequate vitamin D. Ultraviolet-B radiation does not penetrate glass, so exposure to sunshine indoors through a window does not produce vitamin D.[2] Limited exposure of bare skin to sunlight should be followed by the application of a sunscreen with an SPF of at least 15 to prevent damaging effects due to excessive exposure to sunlight and to prevent sun burning.

If there is concern that it may be difficult for the patient to receive sufficient ultraviolet radiation exposure, vitamin D-containing dietary supplements may be given. There are various multivitamin supplements that contain vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol). The recommended daily adequate intake of vitamin D may vary between countries and guidelines; consult local guidance.

In the US, a number of dairy products, juice and juice drinks, and cereals are fortified with vitamin D, and their consumption should be encouraged as part of a balanced diet in individuals at risk of vitamin D deficiency. Similarly, if there is evidence of (or a risk of) poor dietary intake of calcium, then calcium supplements may also be appropriate in conjunction with vitamin D.

Malabsorption-related SHPT

Patients with intestinal malabsorption syndromes (e.g., Crohn disease, Whipple disease, cystic fibrosis, chronic pancreatitis, celiac disease, lactose intolerance) are often vitamin D and calcium deficient. This is because they are unable to efficiently absorb the fat-soluble vitamin into the chylomicrons. This negatively impacts absorption of calcium. As the metabolic pathways in the liver and the kidneys are not compromised in these patients, the best method to correct vitamin D deficiency is to encourage sensible exposure to sunlight or ultraviolet-B-emitting light source/tanning bed.[2] This can be augmented with oral supplements of vitamin D and calcium.

Treatment of the underlying disease should also be optimized to help improve absorption. Depending on the cause, this may involve a gluten-free diet for celiac disease, a lactose-free diet for lactose intolerance, protease and lipase supplements for pancreatic insufficiency, or corticosteroids and anti-inflammatory agents for inflammatory bowel disease.

Estimates are that the body uses an average of 3000 to 5000 international units of cholecalciferol per day.[45] In the absence of adequate sun exposure, it is estimated that 1000 international units of cholecalciferol are needed to maintain a healthy 25-hydroxyvitamin D level of at least 30 nanograms/mL. One meta-analysis comparing ergocalciferol and cholecalciferol has shown cholecalciferol to be more

effective in maintaining serum concentrations of 25-hydroxyvitamin D.[13] Dosage requirements vary for each individual, depending on the capacity of vitamin D absorption and of liver hydroxylation.[13]

Vitamin D or its analogs serve to help increase gastrointestinal calcium absorption, thereby reducing parathyroid hormone (PTH) levels. Intramuscular administration is sometimes used, as these patients have malabsorption from the gastrointestinal tract; however, this formulation is not available in the US and some other countries.

Chronic kidney disease (CKD)-related SHPT

The vast majority of patients with CKD develop SHPT at some point in the course of their disease, with the prevalence of an elevated PTH level increasing as the glomerular filtration rate (GFR) declines.[1][7] Various stages of CKD have been defined as follows:[46]

- Stage 1: Kidney damage with normal or increased GFR (greater than or equal to 90 mL/minute/1.73 m^2)
- Stage 2: Kidney damage with mild decrease in GFR (60-89 mL/minute/1.73 m^2)
- Stage 3a: Mild to moderate decrease in GFR (45-59 mL/minute/1.73 m^2)
- Stage 3b: Moderate to severe decrease in GFR (30-44 mL/minute/1.73 m^2)
- Stage 4: Severe decrease in GFR (15-29 mL/minute/1.73 m^2)
- Stage 5: Kidney failure (GFR <15 mL/minute/1.73 m^2 or on dialysis [stage 5D]).

In mild renal impairment, homeostatic mechanisms are recruited to maintain normal phosphorus levels, but these become increasingly inadequate in moderate to late-stage CKD. It follows, therefore, that early therapeutic intervention in this group of patients to control hyperphosphatemia and SHPT would help avert clinical (skeletal and cardiovascular) consequences of CKD-MBD.[17] However, there is a lack of data from randomized controlled trials.

The international organization Kidney Disease: Improving Global Outcomes (KDIGO) has produced extensive guidelines for the management of bone metabolism and disease in both adults and children at various stages of CKD.[1][46] The management of SHPT in patients with CKD is complex because all the variables involved (levels of calcium, phosphorus, vitamin D, PTH) affect one another. One significant unknown is in recognizing the optimal time to initiate therapy and thereafter maintaining biochemical homeostasis.

Serum PTH concentrations are widely used as indicators for CKD-related SHPT and initiating therapy, but may be technically unreliable for many reasons.[47] Although the optimum PTH concentration in moderate to severe CKD is unknown, it is thought that fluctuations in PTH are clinically relevant and useful in guiding treatment. KDIGO recommends that patients with serum PTH levels that are progressively rising or persistently above the upper limit of normal, for the assay used, be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency. Treatment should not be based on a single elevated PTH value.[1]

KDIGO guidelines recommend lowering elevated serum calcium and phosphate concentrations toward the normal range. There is an absence of evidence supporting efforts to maintain phosphate in the normal range in nondialysis CKD; therefore, treatment should specifically aim at lowering hyperphosphatemia and avoiding hypercalcemia in all patients with CKD.[1]

The approach to managing SHPT is to optimize serum phosphorus and calcium levels through a combination of a low phosphorus diet, phosphate binders, vitamin D derivatives, and calcimimetic medications.[48]

Management of phosphate levels in CKD

- It could be argued that phosphate binders should be initiated when PTH and fibroblast growth factor-23 (FGF-23) levels rise, as this is clearly indicative of total body phosphate retention. However, reserving treatment for hyperphosphatemia may neglect the fact that there are likely ongoing subclinical changes to bone metabolism with changes in serum phosphorus minimized by phosphaturia, keeping the serum phosphate concentration within the accepted normal range.[49]
- Elevated serum levels of phosphorus should be lowered toward the normal target ranges. Dietary phosphorus should be restricted to 800 to 1000 mg/day in adults or to Dietary Reference Intake (DRI) for age when serum phosphate and plasma levels of PTH are progressively or persistently elevated above the normal reference range.[1]
- Foods that contain high levels of phosphorus include dairy foods (e.g., milk, cheese, yogurts, eggs, ice cream), some meats (e.g., liver, kidney, pate, game), fish (e.g., shellfish, kippers, whitebait, roe), some breakfast cereals (e.g., containing bran, nuts, or chocolate), biscuits/cakes (e.g., oatcakes, scones, flapjacks, rye crispbread), and miscellaneous other foods (e.g., milk chocolate, nuts, baking powder, cocoa, marzipan). Although there is evidence that SHPT can be managed with dietary phosphate and protein control, only a few studies have investigated the impact on bone disease and shown an improvement in bone and vascular health.[50] [51] [52] [53] The impracticality with this approach is that phosphate is ubiquitous in food, it can be organic or inorganic in origin, and its content is difficult to quantify accurately. Dietary restriction also risks protein malnutrition and is particularly troublesome as patients with kidney disease are likely to have additional restrictions on salt and carbohydrate intake.[54] [55] [56]
- Serum phosphorus levels should be monitored monthly in stage 5 CKD and every 3 months in stages 3 or 4 following initiation of dietary phosphorus restriction. Hypophosphatemia should be corrected via dietary modification or enteral supplementation, or by reducing the use of phosphate binders.
- If phosphorus or PTH levels cannot be controlled within the target range despite dietary phosphorus restriction, phosphate binders should be prescribed.[48] Either calcium-based phosphate binders, iron-based phosphate binders (e.g., iron sucrose, sucroferric oxyhydroxide), or others (e.g., sevelamer, lanthanum) are effective.[57] Calcium may not be sufficiently excreted in the context of CKD, and the use of inexpensive calcium salts as phosphate binders may render patients hypercalcemic or in a positive calcium balance and may contribute to soft-tissue calcification.[58] Either type of binder may be used as the primary therapy in most cases. Combination of different types may be required under specialist supervision.
- Aluminum-based phosphate binders (e.g., aluminum hydroxide) are an alternative, but may increase the risk of adynamic bone disease due to the toxic effects of aluminum on bone.[1] They may be used in adolescents and adults for a single course of short-term therapy (4 weeks) if serum phosphorus levels remain severely elevated despite the use of other phosphate binders. Use of citrate-based products must be avoided in patients taking aluminum binders, as this has been shown to lead to enhanced absorption and cases of neurologic toxicity.[59] After initial treatment, the aluminum-based phosphate binder should be replaced by a different phosphate binder. In patients receiving dialysis (with persistent, severely elevated phosphorus levels), the dialysis prescription should also be modified to increase dialytic phosphate removal.[59]

- In infants and young children, calcium-based phosphate binders should be used as primary therapy; other types of phosphate binders may be used in older children.
- In patients receiving dialysis who have severe vascular and/or other soft-tissue calcification, noncalcium-based phosphate binders are preferred.[58] Calcium-based phosphate binders should not be used in patients on dialysis who are hypercalcemic or whose plasma PTH levels are persistently low.[1] The total dose of elemental calcium provided by calcium-based phosphate binders should not exceed twice the DRI for calcium based on age, and the total intake of elemental calcium (including dietary calcium) should not exceed 2500 mg/day.
- There is little evidence to suggest that non-calcium-based phosphate binders are superior to their calcium-containing counterparts. Indeed, the lower cost of calcium-based phosphate binders has encouraged their use for a generation. UK guidelines from the National Institute for Health and Care Excellence also recommend that adults with CKD should be offered calcium acetate as the first-line phosphate binder, and to consider a non-calcium-based binder only if they are not tolerated, hypercalcemia develops, or PTH levels are low in those with stage 4 or 5 CKD.[60]
- One Cochrane systematic review that assessed adults with CKD of any stage, including patients receiving dialysis, concluded that sevelamer may lower death (all causes) compared with calcium-based binders, and may induce less treatment-related hypercalcemia in patients on dialysis. The effect of treatment with lanthanum on death and cardiovascular events, compared with calcium-based binders, remains uncertain in patients on dialysis. In CKD stages 2 to 5, sevelamer, lanthanum, iron-based, and calcium-based phosphate binders have uncertain effects on death and cardiovascular outcomes compared with placebo or usual care.[61] Further studies are required to evaluate the effects of these different phosphate binders in CKD, and to answer the question of whether phosphate binders can decrease mortality in patients with CKD compared with no treatment.
- The OPTIMA study was an open-label, randomized study using cinacalcet to improve achievement of the Kidney Disease Outcomes Quality Initiative (KDOQI) targets (PTH 150 to 300 picograms/mL) in patients with end-stage renal disease. One post-hoc analysis of the study found that serum phosphorus levels in patients on dialysis with SHPT were better controlled when serum PTH levels were lowered effectively, regardless of the treatment received.[62]

Management of vitamin D deficiency in CKD

- If plasma PTH is above the normal reference range, serum 25-hydroxyvitamin D should be measured.[1] Vitamin D deficiency in CKD is corrected using treatment strategies recommended for the general population.[1][37]
- If the serum level of 25-hydroxyvitamin D is <30 nanograms/mL, vitamin D supplementation with ergocalciferol or cholecalciferol should be initiated.[6] [13] [37] [63] Vitamin D therapy should be adjusted in light of serum calcium and phosphorus levels (which should be measured at least every 3 months).[1] Once the patient is replete of 25-hydroxyvitamin D, continue supplementation with a vitamin D-containing multivitamin preparation or a low dose of vitamin D, and check serum levels of 25-hydroxyvitamin D annually.[15]
- Calcifediol, a prohormone of calcitriol, is a more potent vitamin D3 supplement.[64] It is approved in the US for the management of SHPT in patients with CKD stages 3 to 4 and serum total 25-hydroxyvitamin D levels <30 nanograms/mL.[65]

Management of calcium levels in CKD

- Serum levels of corrected total calcium should be maintained within the normal range for the laboratory used.[1]

- Hypocalcemia is a classical feature of untreated CKD and contributes to the pathogenesis of SHPT. It may also develop in the context of calcimimetic treatment. Patients with hypocalcemia should receive therapy to increase serum calcium levels if significant or symptomatic.[1] Therapy for hypocalcemia should be individualized and include calcium salts such as calcium carbonate or calcium acetate orally, or calcium gluconate or calcium chloride parenterally, and/or an oral vitamin D sterol/analog.
- If the corrected total serum calcium level exceeds the normal range, therapies that cause serum calcium to rise should be adjusted as follows:[1]
    - The use of calcium-based phosphate binders should be restricted and therapy switched to a noncalcium-based phosphate binder (e.g., sevelamer, lanthanum, or an iron-based phosphate binder)
    - The dose of vitamin D therapy should be reduced or therapy discontinued until the serum levels of corrected total calcium return to the target range.

Management of PTH levels in CKD stages 3 to 5

- The target range for PTH in patients on dialysis is 2 to 9 times the upper limit of normal for the PTH assay.[1] The target range for CKD stages 3 to 5, predialysis, is undefined, but severe and progressive SHPT in this group can be treated following the same principles.
- Therapy with an active oral vitamin D sterol (calcitriol) or a synthetic vitamin D analog (e.g., doxercalciferol, paricalcitol) is indicated when modifiable factors (hyperphosphatemia, hypocalcemia, vitamin D deficiency) have been addressed and plasma levels of PTH continue to rise toward the upper limit of the target range.[1][37] It is suggested that the use of calcitriol and vitamin D analogs be reserved for patients with CKD stage 4 to 5, and on dialysis, with severe and progressive hyperparathyroidism.[1] In one multicenter, randomized trial, calcitriol and paricalcitol had equal efficacy in suppressing PTH with very few hypercalcemic events.[66] During therapy with a vitamin D sterol/analog, serum levels of calcium and phosphorus should be monitored at least every month after initiation of therapy for the first 3 months, then at least every 3 months thereafter. Plasma PTH levels should be measured at least every 3 months for 6 months, and every 3 months thereafter. Dose adjustments for patients receiving vitamin D sterol/analog therapy could be made as follows:
    - If serum levels of PTH decrease to values below the target range, vitamin D sterol/analog therapy should be stopped until serum PTH is within the target range; treatment may then be resumed at one half of the previous dose of vitamin D sterol/analog. If the lowest daily dose of the vitamin D sterol/analog is being used, dosing should be reduced to alternate days.
    - If there is hypercalcemia, vitamin D sterol/analog therapy should be stopped until serum calcium returns to normal, and then resumed at one half of the previous dose. If the lowest daily dose of the vitamin D sterol/analog is being used, dosing should be reduced to alternate days.
    - If there is hyperphosphatemia, vitamin D therapy should be stopped and a phosphate binder initiated, or the phosphate binder dose increased, until the level of serum phosphorus is normal, at which point the prior dose of vitamin D sterol/analog should be resumed.
    - If serum levels of PTH fail to decrease by at least 30% after the initial 3 months of therapy, and serum levels of calcium and phosphorus are within the normal range, the dose of vitamin

D sterol/analog should be increased by 50%. Serum levels of PTH, calcium, and phosphorus must be measured monthly for 3 months thereafter.

Management of persistently high PTH levels in CKD stage 5

Calcimimetic therapy

- Calcimimetic medications, such as cinacalcet, bind to calcium-sensing receptors (CaSR) and increase their sensitivity to extracellular ionized calcium.[67] This results in decreases in PTH, and thus calcium and phosphate levels.[63] The effect on PTH levels can be seen as quickly as 2 to 4 hours after administration.[68] Essentially, use of calcimimetics serve to reset the set point of calcium or produce a shift of the PTH-calcium curve to the right, thus loosening control over this axis.[63]
- Calcimimetics are reserved for CKD stage 5D where a vitamin D sterol/analog has inadequately suppressed PTHto within the target range, with or without hypercalcemia.[69] [70] [71] Calcimimetics can be used in combination with a vitamin D sterol/analog.[1][72]
- There is anecdotal evidence of a reduction in fractures after starting cinacalcet therapy, but this has not been supported by bone densitometry results. A prespecified secondary analysis in the EVOLVE trial (evaluation of cinacalcet hydrochloride therapy to lower cardiovascular events) looked at the effect of cinacalcet on fracture events in patients receiving hemodialysis. The unadjusted data showed no significant benefit; when adjusted for baseline characteristics, multiple fractures, and/or events prompting discontinuation of the study drug, cinacalcet reduced the rate of clinical fracture by 16% to 29%.[73] There are no randomized, prospective data that demonstrate improved quality of life, improvement in anemia, reduction in phosphate binders, reduction in use of vitamin D analogs, or reduction in mortality.
- The EVOLVE trial found that cinacalcet did not significantly reduce the risk of death or major cardiovascular events in people with moderate-to-severe SHPT undergoing dialysis.[74] A meta-analysis, including the EVOLVE trial, showed no benefit with cinacalcet on all-cause or cardiovascular mortality.[75] It should be noted, however, that cinacalcet is a cytochrome P-450 inhibitor and thus can affect the metabolism of other medications. Hypocalcemia from cinacalcet was infrequent, transient, asymptomatic, and correctable through a dose reduction.[68] [76] Literature supports cinacalcet therapy to improve patient outcomes, especially with regard to vascular calcifications and presumably the very lethal condition of calciphylaxis.[77] [78] [79] [80] [81] [82] [83] [84] Analysis of adverse events in the EVOLVE trial showed the risk of calciphylaxis was lower in the patients who received cinacalcet versus placebo.[85]
- Etelcalcetide is a second-generation, type II calcimimetic. It is a novel D-amino acid-containing peptide agonist of CaSR and is approved for the treatment of SHPT in adult patients with CKD on hemodialysis, where treatment with a calcimimetic is indicated but cinacalcet is not tolerable or there is poor compliance.[86] [87] Patients treated with etelcalcetide (administered intravenously at the end of hemodialysis) were significantly more likely to achieve the primary efficacy end point of a greater than 30% reduction in mean PTH compared with placebo.[88] [89] In an active-comparator randomized controlled trial, etelcalcetide achieved its noninferiority end point compared with cinacalcet.[90] Importantly, a higher rate of hypocalcemia was observed for etelcalcetide compared with cinacalcet (68.9% vs. 59.8%).

- In the US, pharmacologic therapy with calcimimetics is commonly used for SHPT in patients on dialysis.[91] Increased risk of adverse effects, including hypocalcemia, vomiting and diarrhea, patient compliance, and availability influence usage.[92]

Parathyroidectomy

- It is unusual for surgery to be considered except in refractory SHPT in late-stage CKD.[41] [92] The indications for surgical intervention in SHPT are not as clear as those for primary hyperparathyroidism. Compelling reasons for surgery in this patient group include a desire to avoid cardiovascular complications (a common cause of death in patients with CKD) and severe skeletal complications.[91]
- Parathyroidectomy is recommended in patients with severe hyperparathyroidism (above 9 times the upper limit of normal for the assay) associated with hypercalcemia and/or hyperphosphatemia that are refractory to medical therapy.[1][92] After kidney transplantation, subtotal parathyroidectomy is the treatment of choice for patients with severe hypercalcemia caused by persistently elevated parathyroid levels.[93] One study concluded that subtotal parathyroidectomy was superior to medical management with cinacalcet in achieving normocalcemia (66% vs. 100%) in patients >6 months from time of transplantation.[94]
- Parathyroidectomy for SHPT is used less frequently in the US than in the rest of the world.[95] Historically, parathyroidectomy rates initially fell with the introduction of new medical therapies for SHPT, particularly cinacalcet, but they now remain stable.[96]
- Effective surgical therapy of severe hyperparathyroidism can be accomplished by subtotal parathyroidectomy or total parathyroidectomy with parathyroid tissue auto-transplantation.[1][92] In subtotal parathyroidectomy, approximately half of the most normal-appearing gland is left behind in its anatomic position.[92] For total parathyroidectomy, all 4 glands are excised and 1 of the glands auto-transplanted in the sternocleidomastoid muscle in the neck, or in the brachioradialis muscle, or subcutaneous abdominal adipose.[91] Both methods can effectively reduce PTH levels and the ramifications of hyperparathyroidism.[92]
- The 30-day postoperative mortality ranges from 0.8% to 3%.[92] Despite short-term risk, patients undergoing surgery actually have a reduction of long-term death with a 28% decrease in all-cause mortality and a 37% decrease in cardiovascular mortality (mean follow-up ranging from 1 to 8 years).[92] Benefits of surgery include improvements in anemia and quality of life.
- The main drawback of surgery is hypoparathyroidism and the severe hypocalcemia that may follow the acute drop in PTH level.[91] The risk of this appears to be greater in total parathyroidectomy with auto-transplantation compared with subtotal parathyroidectomy.[92]
- In patients who undergo parathyroidectomy, in the 72 hours prior to parathyroidectomy consideration should be given to administration of a vitamin D sterol/analog to lessen postoperative hypocalcemia.[92] [97] Preoperative levels of PTH, corrected total calcium, and total alkaline phosphatase can predict the incidence of postoperative hypocalcemia, but careful monitoring is still required.[98] 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. If the blood levels of ionized or corrected total calcium fall below normal (i.e., <3.6mg/dL ionized calcium corresponding to corrected total calcium of 7.2 mg/dL), a calcium gluconate infusion should be initiated according to local protocols. The calcium infusion should be gradually reduced when the level of ionized calcium reaches the

normal range and remains stable. When oral intake is possible, the patient should receive calcium carbonate as well as calcitriol, and these therapies should be adjusted as necessary to maintain the level of ionized calcium in the normal range. 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.

- There is debate around the use of methylene blue as an intraoperative adjunct for the localization of enlarged parathyroid glands; there are adverse effects associated with methylene blue, and other preoperative and intraoperative localization methods are available. Observational evidence has suggested, however, that methylene blue was effective in identifying enlarged parathyroid glands, and its toxicity profile appeared to be mild in the absence of concomitant use of serotonin reuptake inhibitors.[99]
- Nonsurgical options for parathyroid gland obliteration include thermal (e.g., microwave, radiofrequency, laser) and chemical (e.g., ethanol) ablation.[92] [100] [101] This treatment option is considered in patients who are not candidates for general anesthesia.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
lack of sunlight		
	1st	ultraviolet radiation exposure
	adjunct	vitamin D supplementation
	adjunct	calcium supplementation
malabsorption-related		
	1st	optimized management of underlying disease
	adjunct	ultraviolet radiation exposure
	adjunct	vitamin D supplementation
	adjunct	calcium supplementation
CKD stages 3 to 5D		
	1st	dietary phosphate restriction
	adjunct	phosphate binder
with low vitamin D	plus	vitamin D supplementation
with normal serum 25-hydroxyvitamin D	plus	vitamin D sterol/analog
with hypercalcemia	plus	reduction of calcium load
with hypocalcemia	plus	calcium salt and/or vitamin D sterol
with persistently elevated PTH	plus	parathyroidectomy or calcimimetic

MANAGEMENT

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

lack of sunlight

1st **ultraviolet radiation exposure**

» Exposure to sunlight depends on physical factors (e.g., geographic latitude, season, weather, time of day) and personal factors (e.g., skin pigmentation, body surface area exposed, sunscreen use).[3] [12] [15]

» For a white person, exposure to sunlight at most latitudes for no more than 10 to 15 minutes/day between 10 a.m. and 3 p.m., on arms and legs or hands, face, and arms, during the spring, summer, and fall, provides adequate vitamin D. Ultraviolet-B radiation does not penetrate glass, so exposure to sunshine indoors through a window does not produce vitamin D.[2] Limited exposure of bare skin to sunlight should be followed by the application of a sunscreen with an SPF of at least 15 to prevent damaging effects due to excessive exposure to sunlight and to prevent sun burning.

adjunct **vitamin D supplementation**

Treatment recommended for SOME patients in selected patient group

Primary options

» ergocalciferol (vitamin D2): children and adults: dose depends on serum 25-hydroxyvitamin D levels; consult specialist for guidance on dose

OR

» cholecalciferol (vitamin D3): children and adults: dose depends on serum 25-hydroxyvitamin D levels; consult specialist for guidance on dose

» If there is concern that it may be difficult for the patient to receive sufficient ultraviolet radiation exposure, vitamin D-containing dietary supplements may be given.

» There are various multivitamin supplements that contain either ergocalciferol or cholecalciferol.

Acute

» In the US, a number of dairy products, juice and juice drinks, and cereals are fortified with vitamin D, and consumption of these should be encouraged as part of a balanced diet in individuals at risk of vitamin D deficiency.

adjunct **calcium supplementation**

Treatment recommended for SOME patients in selected patient group

Primary options

» calcium carbonate: children: 210-1300 mg/day orally given in 3-4 divided doses; adults: 1000-1500 mg/day orally given in 3-4 divided doses
Dose expressed as elemental calcium.

» If there is evidence of, or a risk of, poor dietary intake of calcium, then calcium supplements may also be appropriate.

malabsorption-related

1st **optimized management of underlying disease**

» Treatment of the underlying disease should also be optimized to help improve absorption. Depending on the cause, this may involve a gluten-free diet for celiac disease, a lactose-free diet for lactose intolerance, protease and lipase supplements for pancreatic insufficiency, or corticosteroids and anti-inflammatory agents for inflammatory bowel disease.

adjunct **ultraviolet radiation exposure**

Treatment recommended for SOME patients in selected patient group

» Patients with intestinal malabsorption syndromes are often vitamin D deficient.

» As the metabolic pathways in the liver and the kidneys are not compromised in these patients, the best method to correct vitamin D deficiency is to encourage sensible exposure to sunlight or ultraviolet-B-emitting light source/tanning bed.[2]

adjunct **vitamin D supplementation**

Treatment recommended for SOME patients in selected patient group

Primary options

» ergocalciferol (vitamin D2): children and adults: dose depends on serum 25-hydroxyvitamin D levels; consult specialist for guidance on dose

Acute

OR

» cholecalciferol (vitamin D3): children and adults: dose depends on serum 25-hydroxyvitamin D levels; consult specialist for guidance on dose

» Augmentation with oral supplements of vitamin D may be required.

» Estimates are that the body uses an average of 3000 to 5000 international units of cholecalciferol per day.[45]

» In the absence of adequate sun exposure, it is estimated 1000 international units of cholecalciferol is needed to maintain a healthy 25-hydroxyvitamin D level of at least 30 nanograms/mL.

» One meta-analysis comparing ergocalciferol and cholecalciferol has shown cholecalciferol to be more effective in maintaining serum concentrations of 25-hydroxyvitamin D.[13]

» Vitamin D or its analogs serve to help increase gastrointestinal calcium absorption, thereby reducing parathyroid hormone levels. Intramuscular administration is sometimes used, as these patients have malabsorption from the gastrointestinal tract; however, this formulation is not available in the US and some other countries.

adjunct **calcium supplementation**

Treatment recommended for SOME patients in selected patient group

Primary options

» calcium carbonate: children: 45-65 mg/kg/day orally given in 4 divided doses; adults: 2-4 g/day orally given in 3-4 divided doses Dose expressed as elemental calcium.

» Patients with intestinal malabsorption syndromes are often calcium deficient.

CKD stages 3 to 5D

1st **dietary phosphate restriction**

» In patients with chronic kidney disease (CKD), dietary phosphorus should be restricted to 800 to 1000 mg/day in adults or to Dietary Reference Intake (DRI) for age when serum phosphate and plasma levels of parathyroid

Acute

hormone are elevated above the the normal reference range.[1]

» Serum phosphorus levels should be monitored monthly in stage 5 CKD and every 3 months in stages 3 or 4 following initiation of dietary phosphorus restriction.

adjunct **phosphate binder**

Treatment recommended for SOME patients in selected patient group

Primary options

» calcium acetate: children: consult specialist for guidance on dose; adults: 1334 mg orally with each meal, adjust dose according to serum phosphorus level, maximum 2868 mg/dose

OR

» sevelamer hydrochloride: children and adults: consult specialist for guidance on dose

OR

» lanthanum: children and adults: consult specialist for guidance on dose

OR

» iron sucrose: children and adults: consult specialist for guidance on dose

OR

» sucroferric oxyhydroxide: children and adults: consult specialist for guidance on dose

Secondary options

» aluminum hydroxide: children and adults: consult specialist for guidance on dose

» If phosphorus or parathyroid hormone levels cannot be controlled within the target range despite dietary phosphorus restriction, phosphate binders should be prescribed.[48]

» Either calcium-based phosphate binders, iron-based phosphate binders (e.g., iron sucrose, sucroferric oxyhydroxide), or others (e.g., sevelamer, lanthanum) are effective.[57]

Acute

Combination of different types may be required under specialist supervision.

» Aluminum-based phosphate binders (e.g., aluminum hydroxide) are an alternative, but may increase the risk of adynamic bone disease due to the toxic effects of aluminum on bone.[1] They may be used in adolescents and adults for a single course of short-term therapy (4 weeks) if serum phosphorus levels remain severely elevated despite the use of other phosphate binders. Use of citrate-based products must be avoided in patients taking aluminum binders, as this has been shown to lead to enhanced absorption and cases of neurologic toxicity.[59]

» After initial treatment, the aluminum-based phosphate binder should be replaced by a different phosphate binder. In patients receiving dialysis (with persistent, severely elevated phosphorus levels), the dialysis prescription should also be modified to increase dialytic phosphate removal.[59]

» In infants and young children, calcium-based phosphate binders should be used as primary therapy; other types of phosphate binders may be used in older children.

» In patients receiving dialysis who have severe vascular and/or other soft-tissue calcification, noncalcium-based phosphate binders are preferred.[58]

with low vitamin D **plus** **vitamin D supplementation**

Treatment recommended for ALL patients in selected patient group

Primary options

» ergocalciferol (vitamin D2): children and adults: dose depends on serum 25-hydroxyvitamin D levels; consult specialist for guidance on dose

OR

» cholecalciferol (vitamin D3): children and adults: dose depends on serum 25-hydroxyvitamin D levels; consult specialist for guidance on dose

OR

» calcifediol: adults: 30 micrograms orally once daily at bedtime initially, may increase to 60 micrograms once daily after 3 months if

Acute

serum intact PTH level is above the treatment goal

» Vitamin D deficiency in chronic kidney disease is corrected using treatment strategies recommended for the general population.[1][37]

» If the serum level of 25-hydroxyvitamin D is <30 nanograms/mL, vitamin D supplementation with ergocalciferol or cholecalciferol should be initiated.[6] [13] [37] [63]

» Following initiation of vitamin D therapy, dose adjustments should be made in light of serum calcium and phosphorus levels. Serum levels of corrected total calcium and phosphorus should be measured at least every 3 months.

» Once the patient is replete of 25-hydroxyvitamin D, continue supplementation with a vitamin D-containing multivitamin preparation or a low dose of vitamin D, and check serum levels of 25-hydroxyvitamin D annually.[15]

» Calcifediol, a prohormone of calcitriol, is a more potent vitamin D3 supplementation.[64] It is approved in the US for the management of SHPT in patients with CKD stages 3 to 4 and serum total 25-hydroxyvitamin D levels <30 nanograms/mL.[65]

with normal serum 25-hydroxyvitamin D **plus** **vitamin D sterol/analog**

Treatment recommended for ALL patients in selected patient group

Primary options

» calcitriol: children: consult specialist for guidance on dose; adults: 0.25 micrograms orally once daily initially, adjust dose according to serum PTH, calcium, and phosphorus levels

Secondary options

» doxercalciferol: children and adults: dose based on serum PTH level; consult specialist for guidance on dose

OR

» paricalcitol: children and adults: dose based on serum PTH level; consult specialist for guidance on dose

» The target range for parathyroid hormone (PTH) in patients on dialysis is 2 to 9 times the upper limit of normal for the PTH assay.[1] The

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target range for chronic kidney disease stages 3 to 5, predialysis, is undefined, but severe and progressive SHPT in this group can be treated following the same principles.

» Therapy with an active oral vitamin D sterol (calcitriol) or a synthetic vitamin D analog (e.g., doxercalciferol, paricalcitol) is indicated when modifiable factors (hyperphosphatemia, hypocalcemia, vitamin D deficiency) have been addressed and plasma levels of PTH continue to rise toward the upper limit of the target range.[1] [37]

» Treatment with a vitamin D sterol/analog should be undertaken only in patients with serum levels of 25-hydroxyvitamin D, corrected total calcium, and phosphorus within the normal range.

» During therapy with a vitamin D sterol/analog, serum levels of calcium and phosphorus should be monitored at least every month after initiation of therapy for the first 3 months, then at least every 3 months thereafter. Plasma PTH levels should be measured at least every 3 months for 6 months, and every 3 months thereafter.

» If serum levels of PTH decrease to values below the target range, vitamin D sterol/analog therapy should be stopped until serum PTH is within the target range; treatment may then be resumed at one half of the previous dose of vitamin D sterol/analog. If the lowest daily dose of the vitamin D sterol/analog is being used, dosing should be reduced to alternate days.

» If there is hypercalcemia, vitamin D sterol/analog therapy should be stopped until serum calcium returns to normal, and then resumed at one half of the previous dose. If the lowest daily dose of the vitamin D sterol/analog is being used, dosing should be reduced to alternate days.

» If there is hyperphosphatemia, vitamin D therapy should be stopped and a phosphate binder initiated, or the phosphate binder dose increased, until the level of serum phosphorus is normal, at which point the prior dose of vitamin D sterol/analog should be resumed.

» If serum levels of PTH fail to decrease by at least 30% after the initial 3 months of therapy, and serum levels of calcium and phosphorus are within the normal range, the dose of vitamin D sterol/analog should be increased by 50%. Serum levels of PTH, calcium, and phosphorus

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must be measured monthly for 3 months thereafter.

with hypercalcemia **plus** **reduction of calcium load**

Treatment recommended for ALL patients in selected patient group

Primary options

» sevelamer hydrochloride: children and adults: consult specialist for guidance on dose

OR

» lanthanum: children and adults: consult specialist for guidance on dose

OR

» iron sucrose: children and adults: consult specialist for guidance on dose

OR

» sucroferric oxyhydroxide: children and adults: consult specialist for guidance on dose

» Serum levels of corrected total calcium should be maintained within the normal range for the laboratory used.[1]

» If there is hypercalcemia, the use of calcium-based phosphate binders should be restricted and therapy switched to a noncalcium-based phosphate binder (e.g., sevelamer, lanthanum, or an iron-based phosphate binder).[1]

» The dose of vitamin D therapy should be reduced or therapy discontinued until the serum levels of corrected total calcium return to the target range.[1]

» In patients treated with dialysis, the dialysate calcium concentration should be targeted to 2.5 to 3.0 mEq/L (1.25 to 1.50 mmol/L).

with hypocalcemia **plus** **calcium salt and/or vitamin D sterol**

Treatment recommended for ALL patients in selected patient group

Primary options

» calcium carbonate: children: 45-65 mg/kg/day orally given in 4 divided doses; adults: 2-4 g/day orally given in 3-4 divided doses

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Dose expressed as elemental calcium.

-or-

» calcium gluconate: children: 200-500 mg/kg/day intravenously by infusion or given in 4 divided doses; adults: 2-15 g/day intravenously by infusion or given in 4 divided doses

Dose expressed as calcium gluconate salt.

--AND/OR--

» calcitriol: children: consult specialist for guidance on dose; adults: 0.25 micrograms orally once daily initially, adjust dose according to serum PTH, calcium, and phosphorus levels

-or-

» doxercalciferol: children and adults: dose based on serum PTH level; consult specialist for guidance on dose

-or-

» paricalcitol: children and adults: dose based on serum PTH level; consult specialist for guidance on dose

» Hypocalcemia is a classical feature of untreated chronic kidney disease and contributes to the pathogenesis of SHPT. It may also develop in the context of calcimimetic treatment. Patients with hypocalcemia should receive therapy to increase serum calcium levels if significant or symptomatic.[1]

» Therapy for hypocalcemia should be individualized and include calcium salts such as calcium carbonate or calcium acetate orally, or calcium gluconate or calcium chloride parenterally, and/or an oral vitamin D sterol/analog.

» Adjust dose of calcium salt according to serum calcium levels.

with persistently elevated PTH **plus** **parathyroidectomy or calcimimetic**

Treatment recommended for ALL patients in selected patient group

Primary options

» cinacalcet: children: consult specialist for guidance on dose; adults: 30 mg orally once daily initially, increase dose according to serum PTH level, maximum 180 mg/day

Secondary options

» etelcalcetide: adults: 5 mg intravenously three times weekly at the end of hemodialysis

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treatment, adjust dose according to PTH level and corrected serum calcium response, maintenance dose ranges from 2.5 to 15 mg three times weekly

» If the parathyroid hormone (PTH) level is above 9 times the upper limit of normal in patients on dialysis, and there is hypercalcemia and/or hyperphosphatemia, despite optimization of medical therapy (to control serum phosphorus, calcium, and vitamin D), parathyroidectomy or calcimimetic therapy is indicated.[1]

» Effective surgical therapy can be accomplished by subtotal parathyroidectomy or total parathyroidectomy with parathyroid tissue auto-transplantation.[1][92]

» If surgical parathyroidectomy is considered to have a high risk of complications, calcimimetic medications can be used. Calcimimetics can also be used as a bridging therapy to parathyroidectomy.

» In patients who undergo parathyroidectomy, 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.

» If the blood levels of ionized or corrected total calcium fall below normal (<3.6 mg/dL corresponding to corrected total calcium of 7.2 mg/dL), a calcium gluconate infusion should be initiated at a rate of 1 to 2 mg elemental calcium/kg body weight/hour and adjusted to maintain an ionized calcium in the normal range (4.6 to 5.4 mg/dL). A 10 mL ampule of 10% calcium gluconate contains 90 mg of elemental calcium. The calcium infusion should be gradually reduced when the level of ionized calcium reaches the normal range and remains stable. When oral intake is possible, the patient should receive calcium carbonate 1 to 2 grams, 3 times a day, and 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.

» 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.

» Calcimimetic medications, such as cinacalcet, bind to calcium-sensing receptors (CaSR) and increase their sensitivity to extracellular ionized

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calcium.[67] This results in decreases in PTH, and thus calcium and phosphate levels.[63]

» The effect on PTH levels can be seen as quickly as 2 to 4 hours after administration.[68]

» Etelcalcetide is a second-generation calcimimetic and CaSR agonist, which may be used where treatment with a calcimimetic is indicated but cinacalcet is not tolerable or there is poor compliance.[86] [87] It is given intravenously (rather than orally like cinacalcet) and has a longer half-life than cinacalcet.

Emerging

Evocalcet

Evocalcet is an oral calcimimetic agent that aims to address the gastrointestinal issues related to oral cinacalcet. A head-to-head comparison of evocalcet with cinacalcet in hemodialysis patients with secondary hyperparathyroidism showed that evocalcet is noninferior to cinacalcet and there were fewer gastrointestinal-related adverse events.[102] Evocalcet is currently only approved in Japan.

Primary prevention

Management of hypertension can help avoid chronic kidney disease (CKD) and the secondary hyperparathyroidism (SHPT) that frequently result. Likewise, diabetes mellitus requires aggressive, optimal management to reduce complications. Weight management and improved nutrition could help prevent the huge burden of type 2 diabetes mellitus and the resulting kidney damage and SHPT.

Prevention of hyperparathyroidism in CKD requires aggressive phosphorus management early in the disease course and adequate replacement of the active form of vitamin D (1,25-dihydroxyvitamin D).[1] Calcium levels can be managed in the dialysis fluid of the patients requiring dialysis. Low-phosphorus diets and the use of phosphorus-binding drugs that prevent enteral absorption can help limit hyperphosphatemia. Phosphorus binders containing aluminum are avoided as they can be toxic to the skeleton.[11] [25][29] [30]

To prevent vitamin D deficiency, it is recommended that individuals are exposed to direct sunlight on their arms or legs at least twice a week.[31] However, season, geographic latitude, time of day during sun exposure, degree of skin pigmentation, cloud cover, and smog are all factors that dictate how much vitamin D is produced, such that there is no consensus on what constitutes safe and effective exposure to sunlight.[3] [12] [15] A combination of sensible sun exposure along with adequate vitamin D supplementation for all children and adults is suggested to prevent vitamin D deficiency in the general population.[2] [15]

Secondary prevention

The patient should maintain adequate nutrition (including calcium) and either appropriate intake of vitamin D or adequate sunlight exposure to induce normal vitamin D levels, along with an adequate level of physical activity.

Patient discussions

Individual advice depends upon the underlying medical condition; all factors affecting the disease process should be addressed. This often includes adherence to special medical or physical therapies or diets. In patients with kidney disease, close adherence to medication regimens to control hypertension and diabetes mellitus is especially important. Dietician involvement is crucial for appropriate advice on a low phosphate diet that does not inadvertently lead to malnutrition. Risk factors for vascular disease such as smoking should be strongly discouraged.

Monitoring

Monitoring

Electrolytes, such as calcium, magnesium, and phosphorus, parathyroid hormone (PTH), and 25-hydroxyvitamin D levels should be monitored at a frequency appropriate for the underlying disease. For example, in patients with chronic kidney disease, electrolytes, PTH, and 25-hydroxyvitamin D levels are typically measured every 3 months (more regularly if the patient is receiving dialysis).[1]

Bone densitometry should only be measured if the results will impact treatment decisions. In rare situations, bone biopsy may also be required for clinical monitoring.

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
renal osteodystrophy	**long term**	**high**
Renal osteodystrophy is characterized by abnormal bone turnover and/or mineralization. Extremely low and extremely high parathyroid hormone (PTH) levels predict low and high bone turnover status respectively. There is a U-shaped association between fracture risk and PTH level, where extremely low and extremely high PTH levels are associated with an increased risk of fracture compared with PTH levels within the target range for patients on dialysis with SHPT.[104] However, PTH is a poor marker for bone turnover status when the level is within the target range aimed for controlling SHPT.[105] If there is still suspicion of high bone turnover disease or a mineralization defect, despite achieving acceptable PTH levels (e.g., unexplained hypercalcemia, bone pain, or fractures), bone biopsy may be required to confirm the diagnosis and guide further management.[1] Osteoporosis can also coexist with renal osteodystrophy in chronic kidney disease (CKD). Bone densitometry can be used to detect reduced bone density and monitor its response to treatment. However, bone densitometry is a poor tool to predict fracture risk in CKD stages 4 to 5. There is also a lack of evidence that any intervention (including medical treatment to control SHPT) can prevent renal osteodystrophy or reduce fracture risk in severe CKD.		
osteoporosis	**long term**	**high**
Osteoporosis is the loss of bone mass due to the dysregulation of bone formation to bone resorption. During the cycle of the development and course of SHPT (and in many cases exacerbated by the underlying disease) either too much bone is removed and/or too little bone is reconstructed, leading to skeletal fragility and fractures. Osteoporosis can also coexist with renal osteodystrophy in chronic kidney disease (CKD). Bone densitometry can be used to detect reduced bone density and monitor its response to treatment. However, bone densitometry is a poor tool to predict fracture risk in CKD stages 4 to 5.		
calciphylaxis	**long term**	**low**
This is a vascular and tissue manifestation of chronic hypercalcemia. This primarily occurs in patients with SHPT and chronic kidney disease.[106] Other more specific names used for this condition are calcific uremic arteriolopathy, uremic small-vessel disease, uremic gangrene syndrome, and uremic small-artery disease with medial calcification and intimal hyperplasia. As these terms imply, calciphylaxis is characterized by systemic calcification of the tunica media of small vessels. This leads to the clinical manifestation of tissue ischemia and necrosis. Affected areas initially manifest as painful, purpuritic, nodular plaques and typically progress to necrotic ulcers with eschar. Mortality remains between 60% and 87%, usually as a result of overwhelming infection and sepsis.[107] Uremic small-artery disease has been found to occur in 4% of patients on dialysis. Females are more commonly affected. A superimposed event such as local tissue trauma from injection of medications can lead to the development of wounds in these sensitized patients. A calcium-phosphate product of 70 or more increases the likelihood of developing calciphylaxis. Other factors that might contribute to calciphylaxis are type 1 diabetes mellitus, protein C or protein S deficiency, calcium carbonate usage, prednisone, and administration of warfarin.[107]		

Prognosis

The outlook for patients with secondary hyperparathyroidism mirrors the underlying disease. In patients with chronic kidney disease, aggressive electrolyte management optimizes the condition; many patients require calcimimetics, a treatment that has reduced the frequency of surgery for this condition. Ultimately, surgery can be performed, which often reduces the level of parathyroid hormone, but is rarely curative. Renal transplantation may be curative, but hyperparathyroidism can persist after the transplant (as tertiary hyperparathyroidism) and cause damage to the new kidney.

Diagnostic guidelines

International

ACR appropriateness criteria: parathyroid adenoma (https://www.acr.org/Clinical-Resources/ACR-Appropriateness-Criteria) [42]

Published by: American College of Radiology **Last published:** 2021

Evaluation, treatment, and prevention of vitamin D deficiency (https://www.endocrine.org/clinical-practice-guidelines/guidelines-by-year) [15]

Published by: The Endocrine Society **Last published:** 2011

KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD) (https://kdigo.org/guidelines) [1]

Published by: Kidney Disease: Improving Global Outcomes (KDIGO) **Last published:** 2017

Treatment guidelines

International

Evaluation, treatment, and prevention of vitamin D deficiency (https://www.endocrine.org/clinical-practice-guidelines/guidelines-by-year) [15]

Published by: The Endocrine Society **Last published:** 2011

Dietary reference intakes for calcium and vitamin D (https://www.ncbi.nlm.nih.gov/books/NBK56070) [103]

Published by: National Academy of Medicine (Institute of Medicine) **Last published:** 2011

KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD) (https://kdigo.org/guidelines) [1]

Published by: Kidney Disease: Improving Global Outcomes (KDIGO) **Last published:** 2017

Key articles

- Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl (2011). 2017 Jul;7(1):1-59. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6340919) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30675420?tool=bestpractice.bmj.com)
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Images

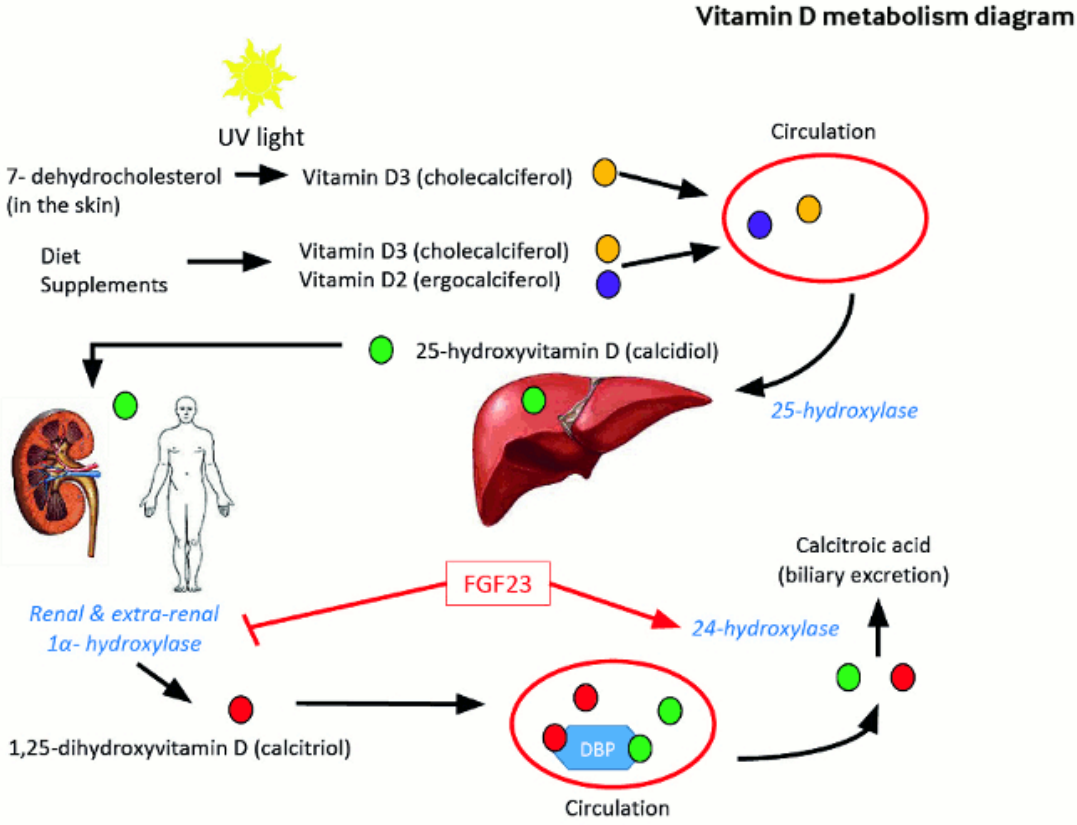

Figure 1: Vitamin D metabolism

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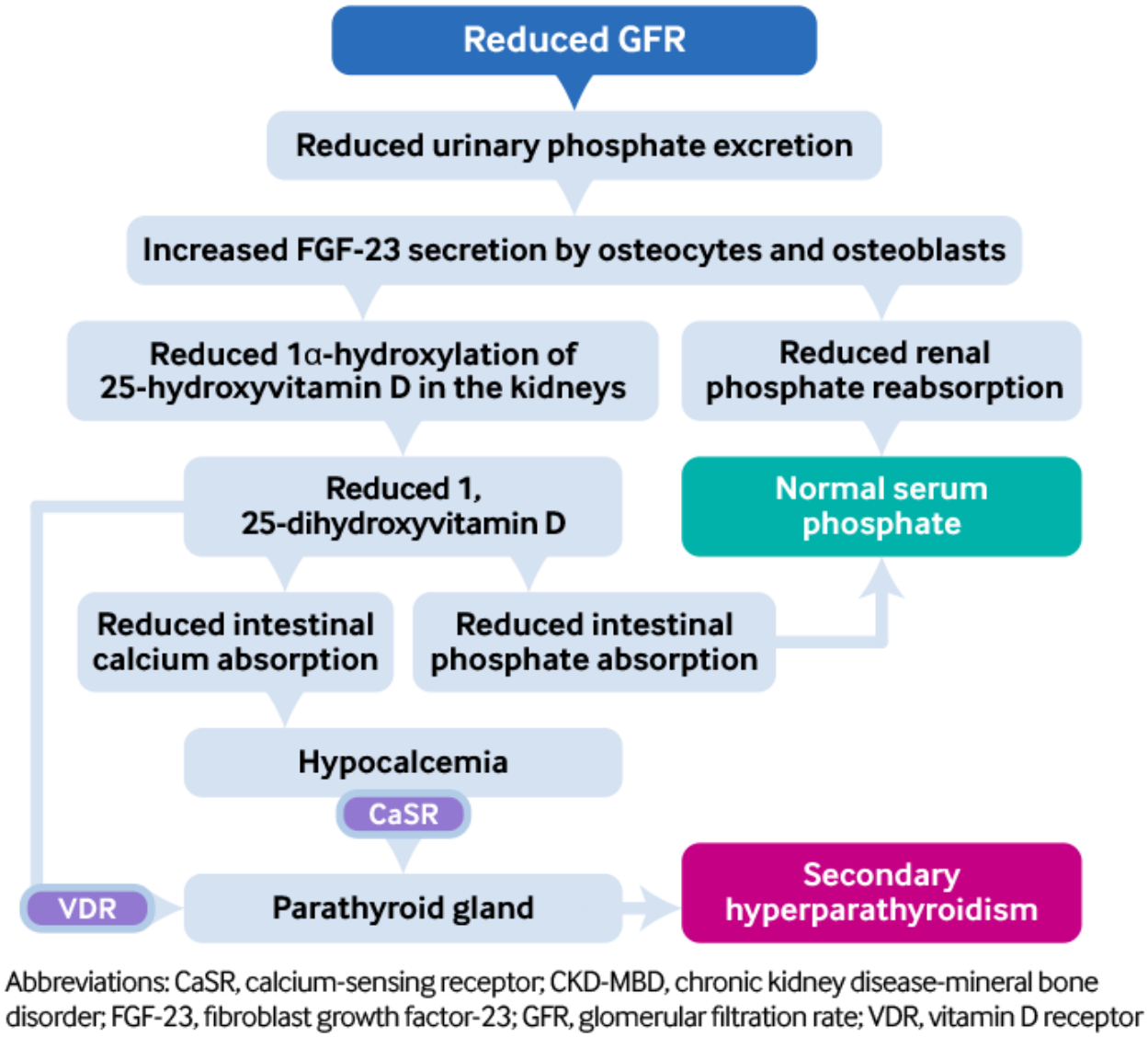

Figure 2: Pathophysiology of secondary hyperparathyroidism in CKD-MBD

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BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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