Calcium and Phosphate Hormones: Vitamin D, Parathyroid Hormone, and Fibroblast Growth Factor 23

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Education Gap

Disorders of vitamin D, parathyroid hormone, and fibroblast growth factor 23 encompass both very rare and fairly common patient presentations in the pediatric population, and so understanding the differential diagnosis is important.

Objectives

After completing this article, readers should be able to:

1. Understand the basic interplay among vitamin D, parathyroid hormone, and fibroblast growth factor 23 in the maintenance of optimal calcium and phosphorous levels and bone health.
2. Understand the differential diagnosis and basic evaluation of hormonal disorders resulting in low calcium and/or phosphorous levels.
3. Understand the basics of presentation, pathophysiology, and treatment of these hormone disorders.

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ABBREVIATIONS

1,25-D	1,25-dihydroxyvitamin D
25-D	25-hydroxyvitamin D
CaSR	calcium-sensing receptor
DMP1	dentin matrix acidic phosphoprotein 1
FDA	Food and Drug Administration
FGF23	fibroblast growth factor
PTH	parathyroid hormone
PTHrP	parathyroid hormone–related peptide

Plasma calcium and phosphorous concentrations are regulated by 3 major players: hormonal vitamin D, parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23). Understanding the interplay among them is essential for assessing calcium and phosphorous levels in children. This is especially important for pediatricians as they care for patients during the crucial times in bone formation and accrual as well as growth. This review focuses on the normal physiology as well as evaluation and treatment of the diseases associated with dysfunctions that result in too little calcium or phosphate in blood.

VITAMIN D

Physiology: Vitamin D Production and Action

Vitamin D is a precursor molecule to a critical hormone, calcitriol, involved in calcium and, to a lesser extent, phosphorus metabolism. It is not actually a vitamin because it can be produced in skin from 7-dehydrocholesterol by UV-B radiation. The product of this transformation is termed cholecalciferol or vitamin D_3. This

process is self-regulating, preventing vitamin D intoxication even in the setting of large amounts of sunlight exposure. A very similar compound, ergocalciferol (also called vitamin D_2) is derived from irradiation of certain plants and fungi and can also be converted to calcitriol. Dietary sources of either vitamin D are found naturally in shiitake mushrooms, cod liver oil, (1) and oily fish, and as an additive in foods such as milk and orange juice. (2)

Both ergocalciferol and cholecalciferol are 25-hydroxylated in the liver, producing 25-hydroxyvitamin D (25-D). This intermediate metabolite is inert (3) and functions mainly as a storage form of D. It has a relatively long serum half-life of 3 weeks and is, therefore, the level measured when assessing vitamin D sufficiency status in a patient. (3)(4) In multiple tissues, but especially in the proximal renal tubule, it can be further hydroxylated to form 1,25-dihydroxyvitamin D (1,25-D) (calcitriol), which is the active form. PTH (discussed later herein) is an important factor in this process. The kidney is the source of hormonal calcitriol, which has a serum half-life of only a few hours. (4) In its target tissues, calcitriol binds to its specific cytoplasmic vitamin D receptor but also requires a co-receptor, RXR. Together, this trio can attach to the vitamin D response elements on the DNA molecule to affect more than 300 genes in a tissue-specific manner. One target tissue of hormonal calcitriol is the intestine, where its net effect is to increase the absorption of calcium and phosphorous, thereby providing the building blocks for bone mineralization. (2)(4) Renal calcitriol production is increased by PTH and hypophosphatemia and is decreased by FGF23 and calcitriol. (4) Defects anywhere along this pathway can result in rickets.

Physiology: Vitamin D Reference Ranges

Severe vitamin D deficiency has been defined by the American Academy of Pediatrics as a 25-D level less than 5 ng/mL (<12.5 nmol/L), mild to moderate deficiency as 5 to 15 ng/mL (12.5–37.4 nmol/L), insufficiency as 16 to 20 ng/mL (39.9–49.9 nmol/L), and sufficiency as 21 to 100 ng/mL (52.4–249.6 nmol/L). (4) Infants should be provided with 400 IU of vitamin D, especially if they are breastfed, because human milk is vitamin D deficient. These levels are intended to prevent the development of rickets in children and do not address other possible vitamin D–related health outcomes that remain under study, such as its role in autoimmune disease prevention and infection control and as an antineoplastic agent. Sufficiency can be achieved either by the daily ingestion of 400 IU of vitamin D in food or supplement or by limited midday summer sunlight exposure of exposed sunscreen-free skin for approximately 20 to 30 minutes. (5)

Pathology: Rickets

Rickets. Rickets is defined as inadequate mineralization in a growing bone, thereby impacting the growth plate/metaphyseal region. (4) A lack of adequate mineralization is termed osteomalacia; hence, adults can develop osteomalacia but not rickets. (3) 25-D levels less than 10 ng/mL (<25.0 nmol/L) are often seen in the setting of nutritional rickets. (1) Estimates of the prevalence of rickets vary from 5 to 9 cases per 1 million children in the United States, and most will be due to nutritional deficiencies of vitamin D and/or calcium intake and absorption. (5)(6)

Symptoms related to vitamin D disorders include delayed motor milestones, weakness, delayed tooth eruption, abnormal-appearing teeth due to enamel hypoplasia, bone pain, infections (especially pulmonary ones), and short stature. Hypocalcemia may occur, resulting in additional symptoms, including muscle cramps, paresthesia, numbness, tetany, seizures, and laryngospasm. (2)

Multiple skeletal findings may be found on physical examination, including cranial bone softening (craniotabes), delayed fontanelle closure, frontal bossing, deformities of the long bones typically leading to bowleggedness or knock-knee appearance in the lower extremities, widened wrists and ankles with the medial malleoli containing a double bump (a mid-malleolus groove that runs parallel with the plane of the foot), and rib deformities such as a rachitic rosary (which describes palpable enlargements at the costochondral junctions), (4) pectus carinatum, pectus excavatum, and, in severe cases, a horizontal indentation of the lower ribs at the insertion points of the diaphragm called the Harrison groove.

Assessment includes dietary intake of minerals and vitamin D, sunlight exposure, family history of short stature, poor dentition, consanguinity, alopecia, and other orthopedic abnormalities. (4) Nutritional rickets can also be due to poor intake of calcium and not related to vitamin D intake, (5) and these patients will have 25-D levels within the reference range.

Risk Factors for Vitamin D–Deficient Rickets. Vitamin D deficiency is the most common cause of rickets and continues to be seen worldwide, even in developed countries. Less common are disorders of vitamin D metabolism. These can arise from inherited mutations of critical genes, leading to calcitriol production or activity or secondary to other diseases that interfere with absorption, conversion, or retention of vitamin D and its metabolites. Risk factors include having darker skin, living in northern latitudes, maternal vitamin D deficiency, decreased sun exposure, winter season, malnutrition, being breastfed beyond 3 months (hence

the recommendation that breastfed infants and those receiving <1 liter of formula daily should be supplemented with vitamin D), malabsorption, liver failure, biliary atresia, renal insufficiency, obesity, cystic fibrosis, inflammatory bowel disease, asthma, and sickle cell anemia. (4) In renal insufficiency there is decreased formation of calcitriol. (6) Anticonvulsants can also cause low 25-D levels by affecting liver metabolism. (6)

Laboratory Findings. To assess vitamin D disorders, testing may include measurement of levels of serum total and ionized calcium, phosphorous, alkaline phosphatase, magnesium, PTH, blood urea nitrogen, creatinine, 25-D, and 1,25-D. A spot urine sample for calcium and creatinine measurement and urinalysis should be obtained. Urine phosphorous may also be assessed if hypophosphatemic rickets is suspected. (5) Expected findings will be an abnormal vitamin D metabolite level, ie, low 25-D; low or normal serum calcium, phosphate, and bicarbonate; and elevated alkaline phosphatase (due to increased bone turnover) and PTH levels. (6) Of note, because 25-D is the storage form, assessment for sufficiency is best evaluated by measuring this level. In the initial stages, a secondary hyperparathyroidism is able to maintain normal calcium levels. As the disease progresses the patient is unable to maintain normal calcium levels even in the setting of an elevated PTH level. In the presence of low 25-D levels, 1,25-D levels are not interpretable. (5)

Knee or wrist radiographs may be performed, which may demonstrate fraying and widening of the metaphysis and widening of the physis. (5)

Treatment for Nutritional Rickets. Previously, stoss therapy has been used consisting of giving 200,000 to 600,000 IU of vitamin D as a single dose, but this is not available in the United States. (7) Guidelines vary. The Endocrine Society has endorsed both vitamin D 50,000 IU weekly for 6 weeks and lower-dose daily supplementation, eg, 5,000 IU daily. (7)

In the setting of vitamin D deficiency and elevated PTH and alkaline phosphatase levels, higher intakes of calcium than the recommended daily allowance for age are needed to counteract hungry bone syndrome in which calcium is taken up in large amounts by the bone for healing. (3)

Monitoring includes measurement of serum calcium, PTH, and phosphorous levels. Urine calcium to creatinine ratios should be monitored and should be less than 0.25 because hypercalciuria can increase the risk of nephrocalcinosis. (3) Repeated radiography may also be obtained, but biochemical improvements are generally sufficient to indicate healing. Improvement in physical examination findings takes months. (5)

Nonnutritional Rickets Due to Vitamin D Problems. The most common forms of rickets are nutritional, but some rare causes can be genetic. (3) Liver disease may impair vitamin D to 25-D conversion; some drugs may stimulate alternate catabolic pathways, resulting in destruction of vitamin D rather than its conversion to 25-D. Vitamin D–dependent rickets type 1 is a consequence of mutations in the 1α-hydroxylase gene preventing formation of calcitriol; 25-D levels are normal, with low 1,25-D levels and secondary hyperparathyroidism. It is inherited in an autosomal recessive manner. Vitamin D–resistant rickets (vitamin D–dependent rickets type 2) is the result of an impaired or absent vitamin D receptor (4) or postreceptor issues. Because the defect is at the receptor level, 25-D levels (the storage form) are normal and calcitriol levels (the active form) are markedly elevated. (6) The latter is sometimes associated with alopecia. (5)

Treatment of vitamin D–dependent rickets type 1 is with replacement doses of calcitriol. The dose is 0.25 to 2 μg daily (10–40 ng/kg per day). In the most severe forms of vitamin D–resistant rickets, continuous intravenous calcium infusions may be required. In lesser forms, large doses of calcitriol may be sufficient. (5)

PARATHYROID HORMONE

Physiology

PTH serves as the primary regulator of serum calcium. PTH acts directly through its target tissues, bone, and kidney to increase release of calcium from bony stores and decrease calcium excretion, and through vitamin D activation acts indirectly to increase intestinal calcium absorption. PTH also causes the release of phosphorus from bone, but because of direct effects in the kidney to increase phosphorus excretion, the net effect of PTH is to lower serum phosphorus levels.

Physiological Effects

PTH is a peptide hormone produced in the parathyroid gland. The PTH receptor is a protein-coupled receptor that is cell membrane bound. This is in contrast to calcitriol, whose receptor is in the cell, thus requiring cell entry for activity. The PTH signals primarily through activation of the G protein Gs-alpha, which, in turn, activates adenylate cyclase and increases intracellular cyclic adenosine monophosphate. The PTH receptor can also signal through coupling to the G protein Gq and stimulate the inositol-trisphosphate system. (8) The action of PTH in the kidney is to increase calcium absorption by increasing sodium-calcium cotransport in the distal convoluted tubule. It also increases the

activity of the enzyme 1α-hydroxylase, which converts 25-D to its active form, calcitriol, which ultimately increases intestinal calcium (and phosphorus) absorption. PTH also sequesters phosphate transporters NaPi-2 from the proximal renal apical membrane, which increases phosphate excretion. The net result is increases in body calcium and decreases in body phosphate amounts.

The action of PTH in the bone is complex. PTH/PTH-related peptide (PTHrP) receptors are found on osteoblasts, which stimulate bone formation. This activation also increases expression of receptor activator of nuclear factor-κB and macrophage colony-stimulating factor by the osteoblasts, which induces osteoclast precursor cells to form active osteoclasts and increase bone removal. The net effect is to increase bone turnover and, with continuous exposures, to increase bone reabsorption.

Pathology: Hypoparathyroidism

Causes. Hypoparathyroidism can result from primary dysfunction of the parathyroid glands or from secondary suppression of PTH production. Primary glandular dysfunction is usually the result of either an inherited disorder or thyroid or parathyroid surgery. Secondary suppression is most typically seen as a physiological response to hypercalcemia or with defects in calcium sensing. Last, there are disorders of PTH resistance, called pseudohypoparathyroidism, in which PTH levels are elevated but the target tissues are not responsive.

Primary hypoparathyroidism can be seen with several inherited disorders. 22q11.2 deletion syndrome (DiGeorge syndrome), or velocardiofacial syndrome, is a well-known disorder of absent thymus and failure of the parathyroid glands to develop. It is caused by a deletion on chromosome 22. The hypoparathyroidism that results can be variable, with some patients having transient hypocalcemia after birth and during infancy or with stress, but normal serum calcium levels at other times. Defects in the *GCMB* gene, which are either autosomal recessive or dominant negative, can lead to failure of the parathyroid glands to develop. Hypoparathyroidism from autoimmune destruction of the parathyroid gland can be seen as part of autoimmune polyglandular syndrome type 1, associated with defects in the *AIRE* gene. Regarding acquired disorders that can cause hypoparathyroidism, the most common is postsurgical. The parathyroid glands may be removed intentionally as a treatment for hyperparathyroidism or unintentionally during thyroidectomy. Thyroid surgery will often result in transient hypoparathyroidism because the glands can become temporarily inflamed from manipulation from the procedure.

Extracellular calcium concentrations are perceived by a transmembrane-bound calcium-sensing receptor (CaSR). Gain-of-function mutations of the *CASR* gene can mimic hypercalcemia, resulting in reduced PTH release, thus causing hypocalcemia. Because these same CaSRs are also located in the renal tubules, they also respond as if the extracellular calcium concentration is elevated although it is actually low, and this results in inappropriate increased calcium excretion. The increased calcium excretion can lead to nephrocalcinosis and eventual kidney failure. This combination of low PTH, low serum calcium, and high urine calcium levels is unique to this disorder, leading to the name familial hypercalciuric hypocalcemia. One allele of the CaSR is sufficient to cause this syndrome, thus the inheritance is autosomal dominant. (9)

Pseudohypoparathyroidism is a syndrome of resistance to PTH. The PTH levels are elevated, but because of the lack of tissue responses, calcium levels are low. Most hormone resistance syndromes are caused by a defect in the receptor. However, in the case of PTH, the receptor is shared with the paracrine factor PTHrP. Defects in the PTH/PTHrP receptor result in hypocalcemia and elevated PTH levels; however, the most prominent phenotype is the deranged growth plates from impaired PTHrP signaling. As a result, the long bones do not grow, and the syndrome, Bloomstrand chondrodystrophy, is lethal in the neonatal period. (10)

In traditional pseudohypoparathyroidism, the defect is not in the PTH/PTHrP receptor but rather in the downstream signaling G protein Gs-alpha. In pseudohypoparathyrodism type 1A, there is a coding defect in *GNAS1,* which encodes Gs-alpha. Although *GNAS1* is located on an autosome (chromosome 20), the inheritance of this syndrome is neither dominant nor recessive. *GNAS1* is expressed only from the maternally inherited allele in the kidney (termed paternal imprinting); thus, hormone resistance occurs only if the defect is inherited from the mother. In the bone, *GNAS1* is expressed from both alleles equally. There is a mild growth plate defect that leads to short stature, bone spurs, and round face, which is termed Albright hereditary osteodystrophy, which occurs regardless of which parent transmitted the defect. In pseudohypoparathyroidism type 1B, there is no coding defect in *GNAS1,* but the DNA methylation tags that distinguish the maternal and paternal chromosomes are disrupted. Because these tags are placed before the gametes form a zygote, the hormone resistance is again seen only if the defect is inherited from the mother. Defects inherited from the father show no phenotype; there is no associated Albright hereditary osteodystrophy in pseudohypoparathyroidism type 1B. Hormone resistance can also

occur if both copies of chromosome 20 are inherited from the father, a genetic defect termed paternal isodisomy. (11)

Signs and Symptoms. Hypoparathyroidism causes hypocalcemia, which results in most of the signs and symptoms. Hypocalcemia often presents as seizures. There are signs of muscle hyperactivity (Chvostek and Trousseau signs), cramping, tetany, and paresthesia, but hypocalcemia is often asymptomatic before becoming severe enough to cause a seizure. Interestingly, hypoparathyroidism is not harmful to the bones; in fact, patients with hypoparathyroidism have slower bone turnover and increased bone mineral density.

Diagnosis. Hypoparathyroidism can be confirmed by measuring PTH levels at the time of hypocalcemia. There will be an absence of expected PTH response to the hypocalcemia, resulting in either low or inappropriately normal PTH levels. Pseudohypoparathyroidism can be much more difficult to diagnose. The PTH resistance develops over time; in genetically at-risk individuals, changes can be seen after the first year of life, but in sporadic cases the disorder often presents with a hypocalcemic seizure at 8 to 10 years of age. The degree and time to develop PTH resistance can vary within a family. Familial hypercalciuric hypocalcemia can be diagnosed based on the finding of elevated urine calcium and low PTH levels at the time of hypocalcemia.

Therapy. Although PTH analogues are available as treatment for severe osteoporosis, they are rarely used and are not Food and Drug Administration (FDA) approved for the treatment of hypoparathyroidism. PTH analogues have a very short half-life in the serum; maintaining serum calcium would require multiple daily injections. Instead, hypoparathyroidism is generally treated with a combination of oral calcium supplements and activated calcitriol, thus bypassing the lack of PTH stimulation of calcitriol production. With activating mutations of the CaSR, there is additional concern that treating hypocalcemia will result in further increases in calcium excretion, worsening nephrocalcinosis. Thus, patients with this disorder are treated the same way, although the goal for serum calcium level is much lower, just above the level for preventing hypocalcemic seizures.

FGF23 AND PHOSPHATE METABOLISM

Physiology

Three hormones largely regulate inorganic phosphate (Pi) homeostasis in humans: PTH, FGF23, and calcitriol (Table 1). The first 2 downregulate the amount of Pi in the body by increasing urinary Pi excretion, and the latter enhances intestinal Pi absorption and urinary conservation.

FGF23 is believed to act on the proximal renal tubule cell. For activity it requires the co-receptor klotho. Activation results eventually in the removal of the phosphate-capturing molecules, the NaPi cotransporters IIa and IIc from the luminal (apical) side of the cell. FGF23 also inhibits the production of calcitriol, preventing an increase in intestinal Pi absorption. Simultaneously, FGF23 increases the production of the enzyme that diverts 25-D toward 24-hydroxylation, resulting in inactive 24,25-dihydroxyvitamin D production. Through these mechanisms, FGF23 decreases body levels of Pi.

FGF23 is produced in osteocytes/osteoblasts. Its production, stimulation, and degradation are controlled by an ever-increasing list of factors, including the enzyme GALNT3 (polypeptide N-acetylgalactosaminyltransferase 3) and kinase FAM20C (family with sequence similarity 20, member C).

Pathology

The pediatric bone disease that develops as a result of chronic hypophosphatemia is termed hypophosphatemic rickets. Excess FGF23 activity has multiple causes, but the skeletal findings are those common to other etiologies of rickets (as described earlier in the "Vitamin D" section). Anecdotally, it seems that the lower extremities are more profoundly deformed than in the vitamin D disorders, although this may reflect the greater difficulty in treating hypophosphatemic disorders and, thus, the longer duration of active bone disease in these weightbearing long bones.

FGF23 as the cause of hypophosphatemic osteomalacia was first discovered in a patient with the autosomal dominant form. The *FGF23* gene mutation made FGF23

TABLE 1. **Fibroblast Growth Factor 23 Regulators**

UPREGULATORS	DOWNREGULATORS
Phosphate	Dentin matrix acidic phosphoprotein 1
Calcitriol	Ectonucleotide pyrophosphatase/ phosphodiesterase 1
Parathyroid hormone	Phosphate-regulating endopeptidase homolog on the X chromosome
Leptin	Iron

resistant to degradation, allowing for its accumulation and persistence. Although this partially explains high levels once produced, it does not account for the initial stimulus to production in the face of hypophosphatemia. In addition, given its congenital nature, the typical appearance of FGF23 in adolescence and adulthood also implies that other factors are important. One such factor seems to be iron status. Iron deficiency anemia is a stimulus for FGF23 production. Because the mutant product is resistant to degradation, levels rise. Because iron deficiency is corrected, hormone levels decline. In people with normal *FGF23* genes, iron deficiency also results in increased FGF23 production, but only inactive fragments are found in the circulation.

The most common form of genetic hypophosphatemic rickets is due to an X-linked mutation in the phosphate-regulating neutral endopeptidase gene *(PHEX)*. The product of this gene is a transmembrane-bound enzyme receptor. The substrate for the external portion of the receptor is 1 of several members of a family of molecules called the SIBLINGs (small integrin-binding ligand, N-linked glycoprotein molecules). All the SIBLINGS contain a region rich in serine and aspartate termed an ASARM (acidic serine aspartate-rich MEPE-associated motif) that are capable of preventing mineralization. *PHEX* works together with another receptor to bind several members of the SIBLING family. One of particular importance is dentin matrix acidic phosphoprotein 1 (DMP1). The ASARM region of DMP1 binds to and is degraded by *PHEX* and the other end binds to the integrin. Attachment to the integrin signals intracellular degradation of FGF23 into C- and N-terminal fragments that are released from the osteocyte. Thus, x-linked mutations in *PHEX* or homozygous autosomal mutations in DMP1 will result in increased FGF23 production, leading to hypophosphatemia and hypomineralization.

Two other recessive forms of hypophosphatemic rickets have been described. The enzyme ENPP1 (ectonucleotide pyrophosphatase/phosphodiesterase family member) combines phosphates to form pyrophosphate and manages the Pi to pyrophosphate ratio in bone and other locations. Its dysfunction results in ectopic calcifications in the aorta, kidney, and joints. The connection to the elevated FGF23 levels sometimes observed in this disease is not clear. The third recessive form is due to mutations in the kinase FAM20C. It is typically lethal, but of the few survivors, one case of rickets with elevated FGF23 levels has been reported.

Several genetic diseases involving somatic mosaicisms are associated with hypophosphatemic rickets. In one, epidermal nevus syndrome, excess FGF23 either is produced by the skin lesion(s) or its production is induced in bone cells by another biochemical made in the skin lesion. Typically patients have too many lesions to remove to achieve a cure.

Some children with McCune-Albright syndrome, due to an activating mutation in the *GNAS* gene involved G protein signaling, have bone lesions that produce excess FGF23. Thus, their skeletal disease can be multifactorial. The hypophosphatemic rickets component could be cured if only a few bone FGF23-producing lesions are present and can be identified and removed.

Tumor-associated osteomalacia was the first to give rise to the concept that the body produced phosphaturic molecules

TABLE 2. **Differential Diagnosis: Hormonal Disorders Resulting in Low Calcium and/or Phosphorous Levels**[a]

	FGF23 EXCESS	VITAMIN D DEFICIENCY[b]	1α-HYDROXYLASE DEFICIENCY	VITAMIN D RESISTANCE	HYPOPARATHYROIDISM	PSEUDOHYPOPARATHYROIDISM
Calcium	N	N/L	L	L	L	L
Phosphorous	L	L	L	L	H	H
Alkaline phosphatase	H	H	H	H	N	H
PTH	N	H	H	H	N	H
25-vitamin D	N	L	N	N	N	N
1,25-dihydroxyvitamin D	N/L	L/N/H	L	H	L	L

Abbreviations: FGF23= fibroblast growth factor 23, H=high, L=low, N=normal, PTH=parathyroid hormone.
[a]*N, L, and H refer to reference range values in healthy populations.*
[b]*Vitamin D deficiency can be defined biochemically by a 25-hydroxyvitamin D level less than 20 ng/mL (<50.0 nmol/L) alone without other biochemical abnormalities. This table indicates the eventual expected biochemical consequences of vitamin D deficiency.*

other than PTH. These were termed phosphatonins. With the discovery of FGF23 it soon became evident that these mesenchymal tumors produced this protein in abundance. Being small and difficult to locate, treatment is often similar to that for the congenital forms of hypophosphatemic rickets. However, if located, surgical excision is curative.

Evaluation

Laboratory and radiographic findings consistent with biochemical and radiologic rickets are typically seen. An inappropriately elevated intact FGF23 level for the degree of hypophosphatemia is highly suggestive of the diagnosis, and this can often be confirmed by appropriate genetic analyses (Table 2).

Treatment

Definitive treatment to reduce FGF23 levels is not available. Historically, treatment has aimed to improve the biochemical profile through supplementation with oral Pi and calcitriol, ie, to chase urinary Pi losses with more Pi intake. Calcitriol is used to enhance Pi absorption. Too much of a Pi dose will induce diarrhea; too much Pi over time will cause a secondary hyperparathyroidism, resulting in further bone demineralization. Too much calcitriol will cause hypercalciuria, increasing the risk of nephrocalcinosis, renal stones, and hypercalcemia. Because the absorption and excretion of a dose of Pi is rapid, multiple doses are needed to be spread throughout the waking period of the day, optimally 6 times a day. Calcitriol can be given once or twice a day. This is a difficult regimen to follow, and few families are fully adherent with the regimen. In addition, orthopedic care with bracing may help straighten the lower extremities, potentially avoiding the need for later corrective surgery.

Several drugs are under investigation that use antibodies against either FGF23 or the FGF receptor. Because the FGF receptors are responsive to many FGFs, this broad-based approach would seem to be riskier than a more specific targeting of the core problem of excess FGF23. Preliminary reports from a phase 3 trial in adults using burosumab, a monoclonal antibody against FGF23, seem to be promising in improving serum Pi levels and the clinical status of the hypophosphatemic patients. (12)

Summary

- Based on strong evidence, vitamin D comes from the diet and sunlight. It is activated by the liver and kidney. (2)
- Based on expert opinion, pediatric vitamin D reference ranges are controversial. (4)
- Based on strong evidence, rickets is inadequate mineralization in a growing bone. There are multiple risk factors for vitamin D–deficient rickets. (4)
- Based on strong evidence, laboratory findings in the different types of rickets can point to the etiology, the most common of which is nutritional. (6)
- Based on expert opinion, there are multiple protocols for treating nutritional rickets, and nonnutritional forms are treated differently. (7)
- Based on strong evidence, parathyroid hormone (PTH) is regulated by changes in serum calcium levels and signals through a G protein–coupled receptor. (8)
- Based on strong evidence, PTH acts at the bone and kidney to raise serum calcium levels (13)(14). Whereas phosphorus is also released from bone in response to PTH, phosphorus excretion is increased in the kidney with the net effect of lowering the serum phosphorus level (15).
- In hypoparathyroidism, low PTH levels result in low serum calcium levels. Signs include Chvostek and Trousseau signs, and severe hypocalcemia can cause tetany and seizures. (2)
- Based on strong evidence, primary hypoparathyroidism can be due to inherited disorders or acquired by neck surgery, autoimmune disease, or metal or tumor infiltration. (2)
- Based on strong evidence, pseudohypoparathyroidism is a disorder of PTH resistance characterized by low serum calcium levels despite elevated PTH levels. Type 1a is caused by mutations in *GNAS1* and is associated with Albright hereditary osteodystrophy. Type 1b is caused by defects in *GNAS1* imprinting and does not result in osteodystrophy. Treatment is with calcium and calcitriol. (11)
- Based on strong evidence, fibroblast growth factor 23 (FGF23) helps regulate plasma phosphate concentration (16). High phosphate and 1,25-dihydroxyvitamin D levels are its stimulators (17).
- Based on strong evidence, FGF23 decreases the production of cotransporters in the kidney that normally prevent phosphate wastage, and it downregulates the production of 1,25-dihydroxyvitamin D, which increases gut absorption (17).
- Based on strong evidence, there are multiple causes, most genetic, of excess FGF23 production, all leading to hypophosphatemia and ultimately rickets. (17)

References for this article are at http://pedsinreview.aappublications.org/content/41/1/3.

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1. You are caring for a 5-year-old boy who is brought to your office for a health supervision check. His mom states that she was recently diagnosed as having vitamin D deficiency. You decide to check a vitamin D level on the child. His level comes back at 18 ng/mL (44.9 nmol/L; reference range, 50–80 ng/mL [124.8–199.7 nmol/L]). His mother really does not want him to take medications even if it is vitamins, and she prefers to try homeopathic methods first. She asks how much sun exposure he should get to achieve sufficiency? Which of the following is the most appropriate length of time of midday summer sunlight exposure of sunscreen-free skin that you would recommend in this patient?
   A. 5–10 minutes.
   B. 20–30 minutes.
   C. 45–55 minutes.
   D. 60–70 minutes.
   E. 70–90 minutes.

2. A 15-year-old boy comes to your office for a sports physical. He just finished summer football camp and is looking forward to starting the fall football season. His medical history is significant for anemia and seizures, for which he has been taking phenytoin and a multivitamin. His height and weight are at the 90th percentile, and his body mass index is 25. His blood pressure is 110/65 mm Hg. There is a strong family history of type 2 diabetes, hyperlipidemia, and hypertension. You decide to obtain some laboratory tests on him and find that his 25-hydroxyvitamin D level is 9 ng/mL (22.5 nmol/L; reference range, 20–50 ng/mL [49.9–124.8 nmol/L]). Which of the following is the most likely reason for this 25-vitamin D level?
   A. Decreased sun exposure.
   B. Light skin color.
   C. Malabsorption.
   D. Nutritional deficiency.
   E. Seizure medication.

3. A 4-year-old boy, new to your practice, is brought by his parents for a health supervision visit. His developmental assessment shows that he is not using 3-word sentences, and he did not walk until he was 2 years of age. He is less than the 5th percentile for weight and height. Mom states that he often complains of pain in his legs but is able to walk without support. His mom follows a vegan diet and feeds him the same. She reports that he is a very picky eater. You obtain a 25-hydroxyvitamin D level, which is found to be 5 ng/mL (12.5 nmol/L; reference range, 20–50 ng/mL [49.9–124.8 nmol/L]). You order radiographs of his legs. Which of the following radiographic findings are most consistent with this diagnosis in this patient?
   A. Growth plate widening with metaphysis flaring and fraying.
   B. Focal bony lysis or cortical loss.
   C. Lesion in the metaphysis or diaphysis with a well-defined serpentiginous border.
   D. Multiple fractures in different stages of healing.
   E. Spiral fracture of the tibia.

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This journal-based CME activity is available through Dec. 31, 2022, however, credit will be recorded in the year in which the learner completes the quiz.

2020 *Pediatrics in Review* is approved for a total of 30 Maintenance of Certification (MOC) Part 2 credits by the American Board of Pediatrics (ABP) through the AAP MOC Portfolio Program. *Pediatrics in Review* subscribers can claim up to 30 ABP MOC Part 2 points upon passing 30 quizzes (and claiming full credit for each quiz) per year. Subscribers can start claiming MOC credits as early as October 2020. To learn how to claim MOC points, go to: http://www.aappublications.org/content/moc-credit.

4. You are evaluating a 2-month-old boy for new-onset transient seizures, muscle cramps, muscle spasms, and facial twitching. On physical examination you notice that he has hypertelorism, down-slanting eyes, low-set ears, a prominent nose with a squared nasal root, and micrognathia. Which of the following laboratory study results are most consistent with his symptoms and his underlying genetic disorder?

   A. High PTH, high calcium.
   B. High PTH, low calcium.
   C. High PTH, normal calcium.
   D. Low PTH, high calcium.
   E. Low PTH, low calcium.

5. A 5-year-old boy is brought to your clinic for evaluation of new-onset fatigue. Initial laboratory studies show a serum phosphorous level of 2 mg/dL (0.7 mmol/L). On physical examination he is small for age but otherwise a normal child. A diet recall reveals that he is a picky eater and eats only chicken nuggets, cheese, and beans. Based on this patient's clinical and laboratory findings and on your knowledge of the 3 hormones that are largely responsible for phosphate homeostasis in humans, you speculate that his fibroblast growth factor 23 hormone is likely activated. Which of the following are the most likely alterations in serum phosphorous and calcitriol levels to result from an elevated fibroblast growth factor 23 hormone level in this patient?

   A. High serum phosphorous, high calcitriol.
   B. High serum phosphorous, low calcitriol.
   C. High serum phosphorus, normal calcitriol.
   D. Low serum phosphorous, high calcitriol.
   E. Low serum phosphorous, low calcitriol.