

Renal Phosphate Wasting Disorders: Clinical Features and Pathogenesis

By Lori A. Brame, Kenneth E. White, and Michael J. Econs

Rickets and osteomalacia are associated with hypophosphatemia in several disease states, including X-linked hypophosphatemic rickets, autosomal-dominant hypophosphatemic rickets, and tumor-induced osteomalacia. Recent advances in the understanding of these diseases include discovery of mutations in the genes encoding human phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX) and fibroblast growth factor 23 (FGF-23) and the finding of overproduction of FGF-23 and other proteins including matrix extracellular phosphoglycoprotein (MEPE) and frizzled-related protein 4 (FRP-4) in tumor-induced osteomalacia. Research is ongoing to better define how these proteins relate to each other and to the sodium-phosphate cotransporter in both normal and abnormal phosphate metabolism. New and improved therapies for disorders of phosphate metabolism, osteomalacia, and rickets will develop as our knowledge of phosphate metabolism grows. © 2004 Elsevier Inc. All rights reserved.

ABNORMALITIES OF PHOSPHATE and vitamin D metabolism and primary renal tubular defects are among the factors that lead to the final common disease states of rickets in children and osteomalacia in both children and adults.¹ In developed nations where vitamin D deficiency is relatively uncommon, inherited renal phosphate-wasting disorders are frequently the cause of osteomalacia and rickets. Recent advances in the understanding of several genetic disorders of phosphate metabolism and one acquired condition of hypophosphatemia have shed light on the underlying pathophysiology of rickets and osteomalacia. This article reviews the clinical and laboratory manifestations of several isolated renal phosphate wasting disorders (see Table 1), including X-linked hypophosphatemic rickets (XLH), autosomal-dominant hypophosphatemic rickets (ADHR), hereditary hypophosphatemic rickets with hypercalciuria (HHRH), and tumor-induced osteomalacia (TIO). A disorder of the chloride channel CLC-5 responsible for Dent's disease is reviewed separately in this issue by Dr. Scheinmann. We describe how the search for the genes and acquired factors responsible for these disorders has furthered our understanding of bone and phosphate metabolism and explore the implications these discoveries have for potential treatments.

ISOLATED RENAL PHOSPHATE WASTING DISORDERS

XLH

XLH is a relatively common cause of rickets, with a prevalence of approximately 1 in 20,000. It is inherited in an X-linked dominant manner, with no evidence of a gene dosage effect, imprinting, or genetic anticipation.² The disease is highly pene-

trant but has a wide range of expressivity.³ In other words, those carrying the mutation are likely to have the disease, but the severity of disease and specific clinical manifestations are variable, even among members of the same family. Manifestations of XLH include short stature, bone pain, tooth abscesses, enthesopathy, and lower-extremity deformities. Progressive enthesopathy (calcification of tendon insertions, ligaments, and joint capsules) can occur, with pain and limitation of motion contributing significantly to disability.⁴ Hypophosphatemia secondary to renal phosphate wasting is the hallmark of the disease. Renal phosphate wasting is measured by the tubular maximum reabsorption of phosphate per glomerular filtration rate. Other laboratory manifestations are as outlined in Table 1. Serum calcitriol (1,25-dihydroxy vitamin D) concentrations, which increase in the setting of hypophosphatemia in normal individuals, are inappropriately normal or low in patients with XLH. Radiographic changes of rickets, which can include fraying, widening, and cupping of the metaphyseal ends of long bones, are often but not always present in children.⁵ Adults can have a variety of radiographic findings depending on disease severity. These findings can include pseudofractures, osteoarthritis, and enthesopathic

From the Departments of Medicine and Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN.

Supported by National Institutes of Health grants R01AR42228, R01DK063934, and K24-AR02095.

Address reprint requests to Michael Econs, MD, 549 North Clinical Dr, Clinical Building 459, Indianapolis, IN 46202.

E-mail: mecons@iupui.edu

© 2004 Elsevier Inc. All rights reserved.

0270-9295/04/2401-0006\$30.00/0

doi:10.1053/j.semnephrol.2003.08.016

Table 1. Summary of Clinical and Biochemical Findings

	XLH	ADHR/HBD	HHRH	TIO
Calcium	N	N	N	N
Phosphorus	L	L	L	L
TmP/GFR	L	L	L	L
Alkaline phosphatase	N-H	N-H	H	H
iPTH	N*	N	LN	N
Calcitriol	N	N	H	L-N
Urine Ca ⁺⁺	L-N	L-N	H	L-N
Penetrance	Complete	Incomplete	Unknown	NA

* Occasionally pretreatment iPTH is high.

Abbreviations: TMP, tubular maximum reabsorption of phosphate; GFR, glomerular filtration rate; iPTH, intact parathyroid hormone; NA, not applicable; H, high; L, low; N, normal; N-H, normal to high; L-N, low to normal.

changes.^{4,6} Osteomalacia is present on bone biopsy examination.

ADHR

ADHR is a less common heritable form of isolated renal phosphate wasting and rickets than XLH, but the exact prevalence is unknown. Similar to XLH, disease expression even within families is variable, but in contrast to XLH, penetrance is incomplete. Clinical and laboratory manifestations of ADHR vary from person to person and are similar to those of XLH in those who present in childhood. Adults typically complain of bone pain, fatigue, and/or weakness, and some have evidence of pseudofractures or stress fractures. Renal phosphate wasting and inappropriately normal calcitriol concentrations are the predominant laboratory findings in ADHR, with other laboratory findings as described in Table 1.⁷ Analysis of a large kindred with 23 affected individuals showed 2 general patterns of disease. One group presented with renal phosphate wasting and rickets as children, and the other group presented with renal phosphate wasting after puberty. All members of the kindred with onset of disease after puberty were women, and several of these individuals first manifested symptoms shortly after pregnancy. These individuals complained of bone pain, weakness, and insufficiency fractures, but did not have lower-extremity deformities. Two men with documented childhood hypophosphatemia and rickets later lost the renal phosphate-wasting defect. It is unknown at this time what other genetic, hormonal, or environmen-

tal factors allow for postpubertal resolution or development of disease. Two unaffected adults with the ADHR mutation are examples of incomplete penetrance of the disease.⁷

Hypophosphatemic Bone Disease

Hypophosphatemic bone disease is a disorder described by Scriver et al.⁸ They reported 5 small kindreds with renal phosphate wasting, short stature, and lower-extremity deformities but no radiographic evidence of rickets. In 1 kindred there was a male-to-male transmission, consistent with autosomal-dominant inheritance. Given the variable disease expression in ADHR, it may be tempting to speculate that ADHR and hypophosphatemic bone disease are one and the same disease. However, when sequencing of the coding region of the gene responsible for ADHR was performed in patients with hypophosphatemic bone disease, no mutation was identified.⁹

HHRH

HHRH was first described by Tieder et al¹⁰ in 1985 in members of a consanguineous Bedouin tribe. Similar to the disease entities described earlier, HHRH is characterized by hypophosphatemia. However, HHRH is distinguished by increased calcitriol concentrations and suppressed parathyroid hormone levels. Affected individuals also have markedly elevated urine calcium excretion with increased intestinal absorption of phosphorus and calcium, which can lead to nephrolithiasis. Clinically, affected individuals have rickets and short stature. Further analysis of the kindred revealed 21 members with an intermediate phenotype, suggesting an autosomal-codominant mode of inheritance. Those individuals with an intermediate phenotype had hypercalciuria, mild hypophosphatemia, and increased calcitriol levels, but no evident bony abnormalities.¹¹

TIO

TIO, also termed *oncogenic hypophosphatemic osteomalacia*, is an acquired disorder of renal phosphate wasting. Clinical manifestations are proximal muscle weakness, bone pain, and fatigue. Children with open epiphyses and TIO have the lower-extremity disorders characteristic of rickets, whereas adults with TIO develop fractures and pseudofractures. Muscle weakness can be profound, and patients may become bedridden by the

time the diagnosis is established.¹² Laboratory abnormalities are similar to those in XLH and ADHR. The associated tumors often are benign, but can be quite difficult to localize. Positron emission tomography scans, octreotide scans, and other functional imaging modalities often are necessary for localization. Tumors usually are mesenchymal, but other tumor types have been described, including hemangiopericytomas, odontogenic maxillary tumors, fibromas, angiosarcomas, prostate and small cell carcinomas, osteoblastomas, and hematologic malignancies.¹³ Removal of the tumor, if the tumor can be found, cures the renal phosphate wasting and osteomalacia.¹³

PATHOPHYSIOLOGY

Hyp Mice and the Phex Gene

A murine model known as Hyp has been essential to our understanding of hypophosphatemic rickets. The Hyp mouse is characterized by renal phosphate wasting, growth retardation, and impaired bone mineralization.¹⁴ Corresponding to the inappropriately normal calcitriol levels in humans with XLH, 25-hydroxyvitamin D-1 α -hydroxylase activity in the Hyp mouse is inappropriately low for the level of hypophosphatemia.¹⁵ Hyp mice also have a primary osteoblast defect.¹⁶

To evaluate whether the phosphate wasting results from a primary renal defect or whether the phosphate wasting is the result of a humoral factor that alters phosphate transport in the renal proximal tubule, Meyer et al¹⁷ performed parabiosis experiments using Hyp and normal mice. In these experiments, Hyp mice were joined surgically to normal mice. Vascular channels developed between the 2 animals, allowing for cross-circulation. The normal mice showed progressive hypophosphatemia and renal phosphate wasting. After separation, plasma phosphate levels of the control mice normalized within 24 hours with subsequent rebound hyperphosphatemia. To further address this issue, Nesbitt et al¹⁸ performed renal cross-transplantation between Hyp and normal mice. Nephrectomized Hyp mice received normal kidneys, which then began wasting phosphorus. Normal mice transplanted with Hyp kidneys maintained normal phosphorus metabolism, with normal phosphorus levels and no renal phosphate wasting. The humoral factor suggested by the 2 experiments described earlier has been termed *phosphatonin*.¹⁹

The HYP consortium identified the gene responsible for XLH in 1995 by a positional cloning approach. The gene is called PHEX, for phosphate-regulating gene with homologies to endopeptidases on the X chromosome.^{20,21} Shortly after PHEX was identified, a deletion in the 3' end of the murine Phex gene was found in the Hyp mouse. There is 91% homology between the mouse and human gene DNA, and 96% homology between the mouse and human protein.^{21,22} PHEX codes for a 749-amino acid protein, a member of the M13 family of membrane-bound metalloproteases. Other members of this family include neutral endopeptidase and endothelin converting enzymes 1 and 2.^{20,23} Previously described proteins in this metalloprotease family are known to activate or to degrade various peptide hormones,^{24,25} and thus it is likely that PHEX does the same.

PHEX is expressed in low levels in bone and teeth,^{21,26} and to an even lesser extent in lung, brain, muscle, and gonads.^{21,27} However, no PHEX expression has been found in the kidney.²¹ A primary osteoblast defect has been suspected as the cause of disordered mineralization of extracellular matrix and phosphorus wasting.²⁸⁻³² Two groups of investigators have made transgenic mice that overexpress Phex in the osteoblast, one using the osteocalcin promoter and the other a pro- α 1(I) collagen gene promoter.³³⁻³⁵ Surprisingly, when recombined on to the Hyp background, neither transgene had an appreciable effect on serum phosphorus or 1,25(OH)₂ vitamin D concentrations. These groups independently found that the skeletal abnormalities partially reversed, but the underlying renal phosphorus wasting persisted. Their findings suggest that PHEX/Phex expression in cells other than the osteoblast is important for renal phosphate homeostasis, whereas the skeletal disturbances observed in XLH may be caused at least partially by local interactions of PHEX and its substrates.

Many mutations of PHEX have been described in different families with XLH, including deletions, frame shifts, and missense and nonsense mutations.³⁵ Despite the fact that XLH is inherited in an X-linked dominant manner, which normally suggests a gain of function disorder, the PHEX mutations are inactivating, or loss of function, mutations. Clearly, the phosphaturic humoral factor phosphatonin suggested by the Hyp mouse cross-transplant and parabiosis experiments is not PHEX. However, it is possible that in normal in-

dividuals, PHEX functions to directly or indirectly degrade or, less likely, to decrease production of phosphatonin. Loss of function of PHEX/Phex in XLH and Hyp mice thus may lead to higher concentrations of phosphatonin, which may subsequently cause renal phosphate wasting.³⁵

Humoral Factors

In 2000, the ADHR consortium used a positional cloning approach to identify the abnormal gene responsible for ADHR, fibroblast growth factor 23 (FGF-23).³⁶ Three missense mutations affecting 2 arginines at positions 176 and 179 of the FGF-23 protein were discovered in 4 unrelated kindreds with ADHR. Because FGF-23 is expressed at very low levels in normal tissues, Northern blots containing RNA from 16 different human and mouse tissues failed to reveal expression of FGF-23. Reverse-transcription polymerase chain reaction from RNA of a variety of normal human tissues indicated that FGF-23 is expressed in low levels in heart, liver, and thyroid/parathyroid tissues.⁹

Just as a humoral factor termed phosphatonin is proposed to be the mechanism of phosphaturia in XLH and Hyp mice, a circulating factor has been implicated as the cause of hypophosphatemia and renal phosphate wasting in patients with TIO. Evidence for this theory comes from observation that phosphate metabolism normalizes when the underlying tumor is removed. Kumar³⁷ proposed a set of criteria defining a phosphatonin to guide the search for this substance or substances in TIO. He proposed that a phosphatonin should inhibit renal phosphate transport, inhibit formation of calcitriol, and be expressed in tumor tissues causing TIO. As well, for a substance to be considered a phosphatonin, the blood concentrations of that substance should be increased in patients with TIO and decrease after removal of the tumor, with a corresponding resolution in phosphate wasting.³⁷

In light of the clinical similarity between ADHR and TIO, White et al³⁸ examined tumor tissue from 6 different tumors associated with TIO for FGF-23 expression. Northern and Western blots showed that these tumors have a high level of expression of FGF-23 messenger RNA and protein, several orders of magnitude higher than that of normal tissues. Shimada et al³⁹ independently confirmed the findings of White et al³⁸ by obtaining complementary DNA clones abundantly expressed in a tumor causing TIO and comparing the prevalence of the

tumor transcripts with the levels of the messenger RNAs in the normal tissue surrounding the tumor. Those most frequently expressed were dentine matrix protein 1, heat shock protein-90, osteopontin, matrix extracellular phosphoglycoprotein (MEPE), and a novel sequence they termed *OST311*. *OST311* was determined to be identical to FGF-23.^{9,40} Nude mice implanted with Chinese hamster ovary cells transfected with MEPE or dentine matrix protein 1 failed to manifest hypophosphatemia. However, nude mice transfected with FGF-23 tumor cells developed hypophosphatemia, renal phosphate wasting, increased alkaline phosphatase levels, and inappropriately low calcitriol levels with decreased expression of 1- α -hydroxylase activity compared with control mice. They also showed growth retardation and osteomalacia.³⁹ Furthermore, when recombinant FGF-23 was injected into mice, the mice developed hypophosphatemia and renal phosphate wasting. In subsequent studies, Shimada et al⁴¹ injected FGF-23 into mice and found a decrease in the primary sodium phosphate cotransporter responsible for phosphate reabsorption, *Npt2a*, as well as a reduction in 1- α -hydroxylase messenger RNA. These findings indicate that FGF-23 functions as a regulator of *Npt2a* expression and of calcitriol synthesis. Furthermore, investigators have documented that patients with tumor-induced osteomalacia and increased FGF-23 levels, in whom a clinical cure is achieved with surgical resection, have had dramatic decreases in FGF-23 concentrations after surgery.^{42,43} Thus, there is substantial support for the hypothesis that FGF-23 is a phosphatonin.

Although FGF-23 has been the best-characterized tumor protein product associated with TIO, it is not the only one. Jan de Beur et al⁴⁴ identified at least 10 genes consistently overexpressed in tumors from patients with TIO relative to patients with mesenchymal tumors but without TIO. MEPE, frizzled-related protein 4 (FRP-4), dentine matrix protein 1, FGF-23, and PHEX were among these overexpressed genes. Of note, studies are underway with MEPE and FRP-4 to determine their potential roles in phosphate homeostasis. Rowe et al⁴⁵ found high levels of MEPE expression in TIO tumor samples, low levels of expression in bone marrow and brain, and very low expression in lung, kidney, placenta, and 3 of 11 control tumors. However, when Shimada et al³⁹ implanted Chinese hamster ovary cells that were

stably transfected with MEPE into mice, the mice did not develop renal phosphate wasting. In addition, the knockout mouse for OF45, the murine homolog to MEPE, does not have an obvious phenotype with regard to phosphorus homeostasis.⁴⁶ However, OF45 knockout mice develop increased bone mass, indicating that MEPE may be an important regulator of bone formation. It is possible that MEPE plays a role in the skeletal changes seen in TIO.

FRP-4 may contribute to renal phosphate wasting in TIO and thus is another candidate phosphatonin. Preliminary work reported by Vassiliadis et al⁴⁷ indicated that FRP-4 inhibits sodium-dependent phosphate transport in opossum kidney cells. In addition, preliminary work by Berndt et al⁴⁸ showed phosphaturia in mice receiving an infusion of recombinant FRP-4. These results indicate that additional proteins may have phosphatonin-like activity; however, further study is necessary before drawing any final conclusions.

FGF-23, ADHR, and XLH

Based on the discovery that high levels of FGF-23 production in TIO lead to hypophosphatemic osteomalacia and/or rickets and that missense mutations in the gene encoding FGF-23 caused a similar phenotype in 4 unrelated families with ADHR, it was hypothesized that the mutations of FGF-23 in ADHR lead to increased activity of FGF-23, possibly through decreased cleavage of the expressed FGF-23 protein.^{38,39} The mutations in ADHR replace arginine (R) residues 176 or 179 at a subtilin-like proprotein convertase cleavage site (RXXX motif), making alterations in FGF-23 protein cleavage a likely mechanism of enhanced FGF-23 activity in ADHR.^{9,49} When native FGF-23 was transfected into cell lines, 2 bands were seen on Western blot analysis, corresponding to the full-length protein and the C-terminal cleavage product.^{44,54,58} However, when the FGF-23 mutants were transfected into cell lines, Western analysis detected only the full-length FGF-23. These results indicate that the ADHR mutations stabilize the FGF-23 protein, preventing cleavage at the RXXX site.⁴⁹

Given the phenotypic similarity of XLH and ADHR, it seems logical that an interaction between PHEX and FGF-23 might exist. Whether or not FGF-23 is a substrate for PHEX is controversial. Bowe et al⁵⁰ incubated wild-type FGF-23 and

ADHR mutant FGF-23 in media with and without PHEX. Proteolysis of wild-type FGF-23 occurred when incubated with PHEX, but mutant FGF-23 remained intact. However, Guo et al were unable to show cleavage by PHEX of an FGF-23 peptide that encompassed arginines 176 and 179.⁵¹ Whether the peptides truly have the same conformation as the native FGF-23 intact molecule is unknown. Recently, Yamazaki et al⁴² reported FGF-23 levels in 6 individuals with XLH and confirmed PHEX mutations. Five of the 6 had FGF-23 levels higher than those of 104 healthy controls. Using a different FGF-23 assay, Jonsson et al⁵² showed FGF-23 levels to be higher than in healthy controls in 13 of 21 patients with XLH. Clearly, more research in this area is needed to elucidate the relationship between PHEX and FGF-23.

Sodium Phosphate Cotransporter

Extracellular phosphate homeostasis is maintained by intestinal absorption and renal excretion. Absorption of phosphate occurs throughout the small intestine by both active transport and passive diffusion. Absorption is proportional to phosphate intake, with approximately 60% to 70% of phosphate being absorbed in normal circumstances. Calcitriol is a major regulator of phosphate absorption.^{53,54}

Renal handling of phosphate is dependent on phosphate concentrations in the glomerular ultrafiltrate as well as tubular reabsorption. In the proximal convoluted tubule, the sodium phosphorus cotransporter NPT2a regulates reabsorption.⁵⁵ NPT2a, and thus hormone sodium-dependent phosphate reabsorption, is regulated by parathyroid hormone. In rat studies, administration of parathyroid hormone caused Npt2a removal from the apical membrane of proximal tubular cells into intracellular lysosomes, where the protein is degraded. In addition to its effects on Npt2a intracellular sorting, parathyroid hormone decreases Npt2a gene transcription.^{56,57} Hyp mice have an approximate 50% reduction in Npt2a message and protein expression that is not mediated by parathyroid hormone.⁵⁸ This implies that loss of PHEX leads to diminished NPT2a/Npt2a through one or more intermediate steps.

Genetic evidence for the importance of NPT2a in humans recently has been published. Prie et al⁵⁹ studied individuals with hypophosphatemia, renal

phosphate wasting, and nephrolithiasis or bone demineralization. Of 20 patients analyzed, 2 were found to be heterozygous for mutations in the NPT2a gene. The daughter of one patient was heterozygous for a mutation as well, and had hypophosphatemia, renal phosphate wasting, and a history of fracture. The discovery of a mutation in the NPT2a gene in humans correlating with hypophosphatemia and renal phosphate wasting confirms the importance of NPT2a in phosphate metabolism in humans. However, given that 18 of the 20 patients analyzed by Prie et al⁵⁹ did not have a mutation on NPT2a, other transport or regulatory proteins must play an important role. Further study will better define the role of NPT2a in phosphorus metabolism in humans.

Integration

The sum of the evidence to date supports the theory that ADHR is caused by mutations in the FGF-23 molecule that prevent proteolysis of FGF-23 by serine proteases (subsulin-like proprotein convertases). As FGF-23 accumulates, it results in phosphate wasting. In patients with TIO, FGF-23 is secreted in such large amounts that it may overwhelm subsulin-like proprotein convertase-mediated proteolysis, and phosphate wasting results from the large circulating FGF-23 concentration. Mutations in PHEX in patients with XLH lead to increased FGF-23 levels, and animal studies support diminished Npt2a activity. It is possible that wild-type PHEX directly or indirectly results in degradation of FGF-23, so that the loss of function PHEX mutations observed in XLH lead to an accumulation of intact FGF-23. Accumulation of FGF-23 then may diminish NPT2a protein in the proximal tubule, ultimately preventing renal phosphate reabsorption and causing hypophosphatemia.

TREATMENT

Treatment of XLH and ADHR is similar, although no data exist on optimal treatment for ADHR.⁶⁰ High doses of calcitriol are combined with high-dose phosphate supplementation until growth is complete. To minimize diarrhea and gastrointestinal upset from the phosphate, the dose should be increased gradually. Serum calcium, phosphorus, creatinine, and urine calcium and creatinine are monitored to allow titration of the calcitriol and phosphate dosage. It is not usually possible to normalize serum phosphorus values, and

normalization of serum phosphorus should not be a therapeutic goal. Excess phosphate replacement will lead to secondary hyperparathyroidism, and excess calcitriol can cause hypercalciuria and hypercalcemia. Nephrocalcinosis appears to be more correlated to phosphorus dose than vitamin D dose,⁶¹ but a balance of phosphorus and vitamin D replacement is needed to prevent side effects. Therefore, if administration of phosphate or calcitriol is stopped, the other should be discontinued as well.⁶⁰ Nephrocalcinosis and tertiary hyperparathyroidism are potentially serious complications of therapy, but are balanced by the benefits of correction of rickets, improved growth, and diminished bowing of the lower extremities.⁶²⁻⁷² Because of the potential for serious side effects, therapy should be supervised by a physician experienced in the treatment of hypophosphatemic rickets. Treatment of adults is more controversial, but often is recommended in adults with pseudofractures and/or bone pain. Therapy has not been shown to reverse or slow the rate of progression of enthesopathy. HHRH is treated somewhat differently; phosphate supplementation is an effective treatment, but calcitriol is avoided because calcitriol levels in this disease already are increased. Definitive treatment of TIO is removal of the tumor. If the tumor cannot be found, the disease manifestations can be improved with phosphate supplementation and calcitriol administration as described earlier for XLH.⁶⁰

Recent characterization of FGF-23 suggests potential for new therapeutic options in rare diseases such as ADHR and TIO as well as the more common XLH. If FGF-23 is the primary phosphaturic factor in these diseases, then development of an FGF-23 receptor antagonist may correct the underlying defects without the risks for nephrocalcinosis and secondary/tertiary hyperparathyroidism and the inconvenience associated with current therapy. Development of such a receptor antagonist will be aided by ongoing studies aimed at FGF-23 receptor identification. Alternative modes of treatment to be considered are therapies aimed at decreasing the concentration of bioavailable FGF-23, such as administration of a circulating decoy receptor that would bind excess FGF-23 or administration of a soluble PHEX protein.

The discovery of FGF-23 has enhanced our understanding of disordered phosphate metabolism. As the relationships between PHEX, NPT2a, FGF-

23, MEPE, FRP-4, and other proteins are further defined, insight into normal phosphate metabolism will allow more targeted treatment of the underlying disorders leading to osteomalacia and rickets.

The knowledge gained from these uncommon diseases may even suggest novel treatments for bone and mineral problems encountered in more common disorders such as chronic kidney disease.

REFERENCES

- Bell NH: Osteomalacia and rickets, in Becker KL, (ed): Principles and Practice of Endocrinology and Metabolism. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 615-623
- Whyte MP, Schranck FW, Armamento-Villareal R: X-linked hypophosphatemia: A search for gender, race, anticipation, or parent of origin effects on disease expression in children. *J Clin Endocrinol Metab* 81:4075-4080, 1996
- Winters RW, Graham JB, Williams TF, et al: A genetic study of familial hypophosphatemia and vitamin d resistant rickets with a review of the literature. *Medicine* 70:215-217, 1991
- Polisson RP, Martinez S, Khoury M, et al: Calcification of entheses associated with x-linked hypophosphatemic osteomalacia. *N Engl J Med* 313:1-6, 1985
- Econs MJ, Feussner JR, Samsa GP, et al: X-linked hypophosphatemic rickets without "rickets." *Skeletal Radiol* 20:109-114, 1991
- Hardy DC, Murphy WA, Siegel BA, et al: X-linked hypophosphatemia in adults: Prevalence of skeletal radiographic and scintigraphic features. *Radiology* 171:403-414, 1989
- Econs MJ, McEnery PT: Autosomal dominant hypophosphatemic rickets/osteomalacia: Clinical characterization of a novel renal phosphate-wasting disorder. *J Clin Endocrinol Metab* 82:674-681, 1997
- Scriver CR, MacDonald W, Reade T, et al: Hypophosphatemic nonrachitic bone disease: An entity distinct from x-linked hypophosphatemia in the renal defect, bone involvement, and inheritance. *Am J Med Genet* 1:101-117, 1977
- Autosomal dominant hypophosphatemic rickets is associated with mutations in FGF23. The ADHR consortium. *Nat Genet* 26:345-348, 2000
- Tieder M, Modai D, Samuel R, et al: Hereditary hypophosphatemic rickets with hypercalciuria. *N Engl J Med* 312:611-617, 1985
- Tieder M, Modai D, Shaked U, et al: "Idiopathic" hypercalciuria and hereditary hypophosphatemic rickets. Two phenotypical expressions of a common genetic defect. *N Engl J Med* 316:125-129, 1987
- Ryan EA, Reiss E: Oncogenous osteomalacia. Review of the world literature of 42 cases and report of two new cases. *Am J Med* 77:501-512, 1984
- Drezner MK: Tumor-induced osteomalacia, in Favus MJ, (ed): Primer on the Metabolic Bone Disease and Disorders of Mineral Metabolism. Philadelphia, Lippincott Williams & Wilkins, 1999, pp 331-337
- Eicher EM, Southard JL, Scriver CR, et al: Hypophosphatemia: Mouse model for human familial hypophosphatemic (vitamin d-resistant) rickets. *Proc Natl Acad Sci U S A* 73:4667-4671, 1976
- Lobaugh B, Drezner MK: Abnormal regulation of renal 25-hydroxyvitamin d-1 alpha-hydroxylase activity in the x-linked hypophosphatemic mouse. *J Clin Invest* 71:400-403, 1983
- Ecarot-Charrier B, Glorieux FH, Travers R, et al: Defective bone formation by transplanted hyp mouse bone cells into normal mice. *Endocrinology* 123:768-773, 1988
- Meyer RA Jr, Meyer MH, Gray RW: Parabiosis suggests a humoral factor is involved in x-linked hypophosphatemia in mice. *J Bone Miner Res* 4:493-500, 1989
- Nesbitt T, Coffman TM, Griffiths R, et al: Crosstransplantation of kidneys in normal and hyp mice. Evidence that the hyp mouse phenotype is unrelated to an intrinsic renal defect. *J Clin Invest* 89:1453-1459, 1992
- Econs MJ, Drezner MK: Tumor-induced osteomalacia—unveiling a new hormone. *N Engl J Med* 330:1679-1681, 1994
- A gene (PEX) with homologies to endopeptidases is mutated in patients with x-linked hypophosphatemic rickets. The HYP consortium. *Nat Genet* 11:130-136, 1995
- Beck L, Soumounou Y, Martel J, et al: Pex/pex tissue distribution and evidence for a deletion in the 3' region of the pex gene in x-linked hypophosphatemic mice. *J Clin Invest* 99:1200-1209, 1997
- Strom TM, Francis F, Lorenz B, et al: Pex gene deletions in gy and hyp mice provide mouse models for x-linked hypophosphatemia. *Hum Mol Genet* 6:165-171, 1997
- Francis F, Strom TM, Hennig S, et al: Genomic organization of the human PEX gene mutated in X-linked dominant hypophosphatemic rickets. *Genome Res* 7:573-585, 1997
- Xu D, Emoto N, Giaid A, et al: Ece-1: A membrane-bound metalloprotease that catalyzes the proteolytic activation of big endothelin-1. *Cell* 78:473-485, 1994
- Welches WR, Brosnihan KB, Ferrario CM: A comparison of the properties and enzymatic activities of three angiotensin processing enzymes: Angiotensin converting enzyme, prolyl endopeptidase and neutral endopeptidase 24.11. *Life Sci* 52:1461-1480, 1993
- Ruchon AF, Marcinkiewicz M, Siegfried G, et al: Pex mRNA is localized in developing mouse osteoblasts and odontoblasts. *J Histochem Cytochem* 46:459-468, 1998
- Grieff M, Mumm S, Waeltz P, et al: Expression and cloning of the human x-linked hypophosphatemia gene cDNA. *Biochem Biophys Res Commun* 231:635-639, 1997
- Lajeunesse D, Meyer RA Jr, Hamel L: Direct demonstration of a humorally-mediated inhibition of renal phosphate transport in the hyp mouse. *Kidney Int* 50:1531-1538, 1996
- Ecarot B, Glorieux FH, Desbarats M, et al: Defective bone formation by hyp mouse bone cells transplanted into normal mice: Evidence in favor of an intrinsic osteoblast defect. *J Bone Miner Res* 7:215-220, 1992
- Ecarot B, Caverzasio J, Desbarats M, et al: Phosphate transport by osteoblasts from x-linked hypophosphatemic mice. *Am J Physiol* 266:E33-E38, 1994
- Ecarot B, Glorieux FH, Desbarats M, et al: Effect of 1,25-dihydroxyvitamin D3 treatment on bone formation by transplanted cells from normal and X-linked hypophosphatemic mice. *J Bone Miner Res* 10:424-431, 1995
- Xiao ZS, Crenshaw M, Guo R, et al: Intrinsic mineralization defect in Hyp mouse osteoblasts. *Am J Physiol* 275:E700-E708, 1998
- Bai X, Miao D, Panda D, et al: Partial rescue of the hyp

phenotype by osteoblast-targeted PHEX (phosphate-regulating gene with homologies to endopeptidases on the x chromosome) expression. *Mol Endocrinol* 16:2913-2925, 2002

34. Liu S, Guo R, Tu Q, et al: Overexpression of PHEX in osteoblasts fails to rescue the Hyp mouse phenotype. *J Biol Chem* 277:3686-3697, 2002

35. DiMeglio LA, White KE, Econs MJ: Disorders of phosphate metabolism. *Endocrinol Metab Clin North Am* 29:591-609, 2000

36. Econs MJ, McEnery PT, Lennon F, et al: Autosomal dominant hypophosphatemic rickets is linked to chromosome 12p13. *J Clin Invest* 100:2653-2657, 1997

37. Kumar R: Tumor-induced osteomalacia and the regulation of phosphate homeostasis. *Bone* 27:333-338, 2000

38. White KE, Jonsson KB, Carn G, et al: The autosomal dominant hypophosphatemic rickets (*adhr*) gene is a secreted polypeptide overexpressed by tumors that cause phosphate wasting. *J Clin Endocrinol Metab* 86:497-500, 2001

39. Shimada T, Mizutani S, Muto T, et al: Cloning and characterization of *fgf23* as a causative factor of tumor-induced osteomalacia. *Proc Natl Acad Sci U S A* 98:6500-6505, 2001

40. Yamashita T, Yoshioka M, Itoh N: Identification of a novel fibroblast growth factor, FGF-23, preferentially expressed in the ventrolateral thalamic nucleus of the brain. *Biochem Biophys Res Commun* 277:494-498, 2000

41. Shimada T, Muto T, Hasegawa H, et al: FGF-23 is a novel regulator of mineral homeostasis with unique properties controlling vitamin D metabolism and phosphate reabsorption. *J Bone Miner Res* 17:S168, 2002 (abstr)

42. Yamazaki Y, Okazaki R, Shibata M, et al: Increased circulatory level of biologically active full-length *fgf-23* in patients with hypophosphatemic rickets/osteomalacia. *J Clin Endocrinol Metab* 87:4957-4960, 2002 (abstr)

43. Jonsson KB, Zahradnik R, Larsson T, et al: FGF-23 is a circulating factor that is elevated in oncogenic osteomalacia and x-linked hypophosphatemic rickets. *J Bone Miner Res* 17: 158, 2002 (suppl 1)

44. Jan De Beur SM, Finnegan RB, Vassiliadis J, et al: Tumors associated with oncogenic osteomalacia express genes important in bone and mineral metabolism. *J Bone Miner Res* 17:1102-1110, 2002

45. Rowe PS, de Zoysa PA, Dong R, et al: MEPE, a new gene expressed in bone marrow and tumors causing osteomalacia. *Genomics* 67:54-68, 2000

46. Gowen LC, Petersen DN, Mansolf AL, et al: Targeted disruption of the osteoblast/osteocyte factor 45 gene (*OF45*) results in increased bone formation and bone mass. *J Biol Chem* 278:1998-2007, 2003

47. Vassiliadis J, Jan de Beur SM, Bowe AE, et al: Frizzled related protein 4 expression is elevated in tumors associated with oncogenic osteomalacia and inhibits phosphate transport in vitro. *J Bone Miner Res* 16:S225, 2001 (abstr, suppl 1)

48. Berndt TJ, Vassiliadis J, Reczek D, et al: Effect of the acute infusion of frizzled related protein 4 (*FRP-4*), a protein highly expressed in tumors associated with osteomalacia, on phosphate excretion in vivo. *J Bone Miner Res* 17:S158, 2002 (abstr, suppl 1)

49. White KE, Carn G, Lorenz-Depiereux B, et al: Autosomal-dominant hypophosphatemic rickets (*adhr*) mutations stabilize *fgf-23*. *Kidney Int* 60:2079-2086, 2001

50. Bowe AE, Finnegan R, Jan de Beur SM, et al: Fgf-23 inhibits renal tubular phosphate transport and is a *phex* substrate. *Biochem Biophys Res Commun* 284:977-981, 2001

51. Guo R, Liu S, Spurney RF, et al: Analysis of recombinant *phex*: An endopeptidase in search of a substrate. *Am J Physiol* 281:E837-E847, 2001

52. Jonsson KB, Zahradnik R, Larsson T, et al: Fibroblast growth factor 23 in oncogenic osteomalacia and x-linked hypophosphatemia. *N Engl J Med* 348:1656-1667, 2003

53. Rizzoli R, Fleisch H, Bonjour JP: Role of 1,25-dihydroxyvitamin D3 on intestinal phosphate absorption in rats with a normal vitamin D supply. *J Clin Invest* 60:639-647, 1977

54. Lee DB, Walling MW, Brautbar N: Intestinal phosphate absorption: Influence of vitamin D and non-vitamin D factors. *Am J Physiol* 250:G369-G373, 1986

55. Murer H, Biber J: Molecular mechanisms of renal apical na/phosphate cotransport. *Annu Rev Physiol* 58:607-618, 1996

56. Kempson SA, Lotscher M, Kaissling B, et al: Parathyroid hormone action on phosphate transporter mRNA and protein in rat renal proximal tubules. *Am J Physiol* 268:F784-F791, 1995

57. Kronenberg HM: Npt2a—the key to phosphate homeostasis. *N Engl J Med* 347:1022-1004, 2002

58. Tenenhouse HS, Beck L: Renal Na(+)-phosphate cotransporter gene expression in X-linked Hyp and Gy mice. *Kidney Int* 49:1027-1032, 1996

59. Prie D, Huart V, Bakouh N, et al: Nephrolithiasis and osteoporosis associated with hypophosphatemia caused by mutations in the type 2a sodium-phosphate cotransporter. *N Engl J Med* 347:983-991, 2002

60. Tenenhouse H, Econs MJ: Mendelian hypophosphatemia, in Scriver CR, (ed): *The Metabolic and Molecular Basis of Inherited Disease*. New York, McGraw-Hill, 2001, pp 5039-5068

61. Taylor A, Sherman NH, Norman ME: Nephrocalcinosis in x-linked hypophosphatemia: Effect of treatment versus disease. *Pediatr Nephrol* 9:173-175, 1995

62. Balsan S, Tieder M: Linear growth in patients with hypophosphatemic vitamin d-resistant rickets: Influence of treatment regimen and parental height. *J Pediatr* 116:365-371, 1990

63. Blydt-Hansen TD, Tenenhouse HS, Goodyer P: *Phex* expression in parathyroid gland and parathyroid hormone dysregulation in x-linked hypophosphatemia. *Pediatr Nephrol* 13: 607-611, 1999

64. Goodyer PR, Kronick JB, Jequier S, et al: Nephrocalcinosis and its relationship to treatment of hereditary rickets. *J Pediatr* 111:700-704, 1987

65. Verge CF, Lam A, Simpson JM, et al: Effects of therapy in x-linked hypophosphatemic rickets. *N Engl J Med* 325:1843-1848, 1991

66. Reid IR, Hardy DC, Murphy WA, et al: X-linked hypophosphatemia: A clinical, biochemical, and histopathologic assessment of morbidity in adults. *Medicine (Baltimore)* 68: 336-352, 1989

67. Firth RG, Grant CS, Riggs BL: Development of hypercalcemic hyperparathyroidism after long-term phosphate supplementation in hypophosphatemic osteomalacia. Report of two cases. *Am J Med* 78:669-673, 1985

68. Drezner MK, Lyles KW, Haussler MR, et al: Evaluation of a role for 1,25-dihydroxyvitamin d3 in the pathogenesis and

treatment of x-linked hypophosphatemic rickets and osteomalacia. *J Clin Invest* 66:1020-1032, 1980

69. Rasmussen H, Pechet M, Anast C, et al: Long-term treatment of familial hypophosphatemic rickets with oral phosphate and 1 alpha-hydroxyvitamin d3. *J Pediatr* 99:16-25, 1981

70. Glorieux FH, Marie PJ, Pettifor JM, et al: Bone response to phosphate salts, ergocalciferol, and calcitriol in hypophosphatemic vitamin d-resistant rickets. *N Engl J Med* 303:1023-1031, 1980

71. Harrell RM, Lyles KW, Harrelson JM, et al: Healing of bone disease in x-linked hypophosphatemic rickets/osteomalacia. Induction and maintenance with phosphorus and calcitriol. *J Clin Invest* 75:1858-1868, 1985

72. Chesney RW, Mazess RB, Rose P, et al: Long-term influence of calcitriol (1,25-dihydroxyvitamin d) and supplemental phosphate in x-linked hypophosphatemic rickets. *Pediatrics* 71:559-567, 1983