Citation: IBMS BoneKEy **9**, Article number: 243 (2012) | doi:10.1038/bonekey.2012.243

www.nature.com/bonekey

NEWS

From diagnosis to etiology: understanding the causes of rickets

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International Bone and Mineral Society, Chicago, IL, USA.

IBMS BoneKEy **9,** Article number: 243 (2012) | doi:10.1038/bonekey.2012.243; published online 19 December 2012

A recent *IBMS BoneKEy* webinar dissected the molecular factors and metabolic pathways physicians should consider in their assessments

Introduction

Determining the causes of rickets is a complicated task for clinicians, as children who present with similar clinical, radiographic and histological features of the disease may in fact have quite different underlying pathophysiology. This etiological variability can result from a number of different mineral and hormonal alterations. How best to interpret those alterations on the way to pinpointing the origins of rickets was the focus of '*Diagnostic Challenges in Rare Metabolic Bone Disorders in Childhood*' (http://www.nature.com/bonekey/webinars/index.html?key=webinar16), a recent *IBMS BoneKEy* webinar presented by Dr Craig Langman, the Isaac A Abt MD Professor of Kidney Diseases at the Feinberg School of Medicine, Northwestern University and Head, Kidney Diseases at the Ann and Robert H Lurie Children's Hospital of Chicago in IL, USA. Dr Langman showed that abnormalities in levels of calcium, parathyroid hormone (PTH), phosphate, vitamin D, fibroblast growth factor-23 (FGF-23) and alkaline phosphatase can each have a role in rickets, and illustrated the steps physicians should take to arrive at a correct understanding of the genesis of the disease. The presentation was followed by a panel discussion moderated by Dr Catherine Gordon, from Children's Hospital Boston, and featuring panelists Dr Thomas Carpenter, from Yale School of Medicine, and Dr Matthew Warman, also from Children's Hospital Boston.

Vitamin D

Dr Langman first turned to vitamin D metabolism (see Langman[1] for review), disturbances of which are a well-recognized cause of rickets. He noted four main ways in which those disturbances can lead to rickets. First, pediatric patients may exhibit deficiencies in the parent compound vitamin D because of a lack of sunlight, a lack of dietary intake or reduced gastrointestinal absorption. Second, abnormalities in liver metabolism of vitamin D into calcidiol (25(OH)D), the major circulating form of vitamin D, can also play a role, because of chronic liver disease, decreased enterohepatic circulation resulting from cholestatic diseases or use of therapeutic drugs or xenobiotics. Third, altered kidney metabolism of calcidiol into calcitriol (1α,25$(OH)_2D_3$), the hormonal form of vitamin D, can also have a role, due to chronic kidney disease (CKD), chronic metabolic acidosis, a lack of the CYP27B1 enzyme in the kidney that converts calcidiol into calcitriol or because of alterations in FGF-23 (see below). Finally, abnormalities in the binding of calcitriol to the vitamin D receptor, or abnormalities in the subsequent activity of this receptor, can also lead to rickets.

To discern the causes of rickets, physicians can measure levels of the various vitamin D metabolites. 'If the substrate 25(OH)D is low, a vitamin D intake issue, an absorption issue, a liver production problem or excess enterohepatic losses may be at work,' Dr Langman explained. 'When the substrate 25(OH)D is either normal or slightly increased, a calcitriol synthesis defect—and if one measured 1,25 dihydroxyvitamin D3, it would be very low or absent—or a calcitriol action defect, because of the vitamin D receptor mutation, may be involved. And in that latter circumstance, one would have markedly elevated calcitriol,' Dr Langman said.

Phosphate

Like alterations in vitamin D metabolism, changes in phosphate metabolism (see Prié *et al.*[2] for review) can also cause rickets. Dr Langman opened his discussion of phosphate by noting that growing children exhibit a net balance of phosphate of about 300 mg per day that is delivered to bone and muscle. The kidney is the key site for homeostatic control of phosphate balance, where proximal tubule cells reabsorb phosphate through sodium-phosphate cotransport proteins. Although PTH and FGF-23 control the transport of phosphate in the kidney, Dr Langman stressed that there are hormone-independent causes of disorders characterized by low serum phosphate concentrations. 'For example, in humans, there are at least three known mutations in sodium-phosphate cotransporters leading to hypophosphatemia with or without kidney stone formation and/or bone demineralization that includes rickets. In this circumstance in general, PTH and FGF-23 levels are normal,' he said. He further noted that additional mutations observed in other disorders of proximal renal tubule function including

Dent's disease, Lowe syndrome and cystinosis can also result in hypophosphatemic rickets.

Hormonal regulation of phosphate is nonetheless extremely important, and here Dr Langman focused on FGF-23, a hormone that has received increasing attention over the last few years from both bone and kidney specialists. FGF-23 is a protein made by osteocytes, bone's most plentiful cell type, and signals primarily via a protein called Klotho, but also by Klotho-independent means. Furthermore, FGF-23 can be influenced by a number of phosphate-regulating genes. For instance, mutations in phosphate regulating endopeptidase homolog, X-linked (*PHEX*) cause X-linked dominant hypophosphatemic rickets, whereas mutations in dentin metalloproteinase-1 (*DMP-1*) lead to autosomal-recessive hypophosphatemic rickets. Finally, mutations in *FGF-23* itself lead to autosomal-dominant hypophosphatemic rickets.

Dr Langman next illustrated how dietary phosphate intake affects FGF-23 levels, and the homeostatic adjustments the body makes to keep phosphate at normal levels. On one hand, high dietary phosphate intake increases osteocyte production of FGF-23, which then acts in the kidney via Klotho to decrease the production of calcitriol; FGF-23 accomplishes this by increasing levels of an enzyme, 24-hydroxylase, which pushes calcitriol to be metabolized into an inactive product. In addition, FGF-23 also acts in the kidney to reduce the efficiency of the sodium-phosphate cotransporters of which Dr Langman spoke earlier in his presentation. The end result is increased excretion of phosphate in the urine, along with a reduction in calcitriol so that dietary phosphate will no longer be absorbed at a high level. On the other hand, low dietary phosphate intake decreases osteocyte production of FGF-23. As a result, there is reduced Klotho-dependent signaling by FGF-23 in the kidney, followed by increased calcitriol production and increased efficiency of phosphate absorption by the sodium-phosphate cotransporters. Consequently, decreased excretion of phosphate in the urine is observed, which increases phosphate balance, as does the increase of calcitriol.

Although the body thus has homeostatic mechanisms that use FGF-23 to maintain a normal phosphate balance, alterations of FGF-23 levels are observed in certain disease states. In particular, Dr Langman pointed to CKD-mineral bone disorder (CKD-MBD). CKD is now viewed as a state of Klotho deficiency, which increases FGF-23 production via a bone–kidney mechanism that is still incompletely understood. As expected, the end result of increased FGF-23 levels is increased urinary excretion of phosphate, a reduction in the phosphate balance and a reduction in calcitriol. This further results in secondary hyperparathyroidism that is characteristic of CKD-MBD.

However, in terms of phosphate metabolism, clinicians seeking to ascertain the causes of rickets must pay attention not only to phosphate and FGF-23 levels, but also to calcium levels. For instance, Dr Langman pointed to Jansen syndrome, a disease caused by activating mutations in the PTH/PTH-related peptide receptor. Patients with Jansen syndrome exhibit a dwarfing phenotype, along with hypercalcemia.

Consequently, Dr Langman said that in order for physicians to use the current understanding of phosphate metabolism to determine the causes of rickets, the key is to consider phosphate levels, FGF-23 levels and calcium levels (**Figure 1**). 'If phosphate is low, FGF-23 is reduced and calcium is normal, there may be a primary defect in the proximal tubule transport of phosphate, or in rare circumstances, there may be dietary phosphate depletion in neonates,' he explained. 'When phosphate is low but FGF-23 is high and calcium is normal, hypophosphatemic rickets may result from genetic causes. Last, when phosphate is low, FGF-23 is high, and calcium is high in the absence of PTH in the blood, think of Jansen syndrome, and when phosphate levels are either normal or even slightly increased, FGF-23 is markedly elevated, and calcium is normal or slightly low, think of chronic kidney disease as a cause of rickets,' he said.

More than minerals and hormones

Dr Langman next turned to two diseases characterized by a rickets-like phenotype, but without the concomitant mineral or hormonal abnormalities characteristic of other forms of rickets. In the case of hypophosphatasia (HPP; see Mornet[3] for review), defective mineralization of bone and/or teeth results from an inability to produce normal levels of tissue-nonspecific alkaline phosphatase, an enzyme that supplies phosphate necessary to form hydroxyapatite during bone mineralization; hundreds of mutations have been identified in the alkaline phosphatase gene (see previous *IBMS BoneKEy* webinar on *The Role of Phosphatases in the Initiation of Skeletal Mineralization*; http://www.nature.com/bonekey/webinars/index.html?key=webinar10). 'In patients with hypercalcemic forms of rickets with very low to absent levels of alkaline phosphatase, physicians should consider HPP as a cause,' Dr Langman said. Recently, an enzyme replacement therapy for HPP was developed to correct the deficiency of alkaline phosphatase in bone, and a clinical trial published in 2012[4] found this approach to be effective in rescuing the rachitic bone phenotype observed in infants and young children with life-threatening HPP.

Like patients with HPP, patients with osteogenesis imperfecta (see Forlino *et al.*[5] for review) can also present with a rickets-like phenotype. Osteogenesis imperfecta, which is characterized by low bone mass, decreased bone strength and increased bone fragility, results from defects in collagen. In dominant forms of osteogenesis imperfecta, defects in the

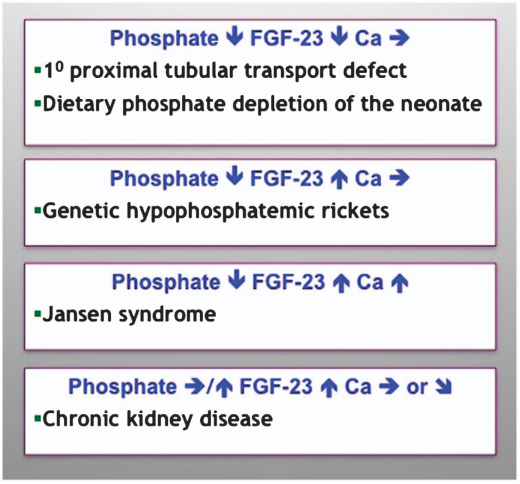

Figure 1 Phosphate metabolism in the differential diagnosis of rickets. Figure provided courtesy of Dr. Craig Langman.

quantity or structure of type I procollagen are the culprit, whereas recessive forms result from a deficiency of proteins that alter posttranslational modifications of collagen or collagen folding. In the clinic, 'when calcium is normal and the patient is rachitic, but has no other mineral abnormalities, physicians should think of osteogenesis imperfecta,' Dr Langman said.

In summary, ascertaining the causes of rickets is a complex undertaking for the physician. A number of different factors, including mineral, hormonal and enzymatic abnormalities can all have an important role in causing the disease. Doctors must carefully consider all of those factors, and use the appropriate tests, which should measure calcium, phosphate, vitamin D, PTH, FGF-23 and alkaline phosphatase levels, to arrive at the right diagnosis. The central message of '*Diagnostic Challenges in Rare Metabolic Bone Disorders in Childhood*' was that patients with rickets are in fact a heterogeneous group, and so only a multifaceted assessment will suffice.

Conflict of Interest

The author declares no conflict of interest.

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