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THE BONE KIDNEY AXIS

Michel Baum

Department of Pediatrics and Medicine, University of Texas Southwestern Medical Center

This issue of Current Opinion in Pediatrics is devoted to how renal disease affects bone and how factors secreted by bone can affect the kidney. A discussion of bone biology and disease may not seem to fit into the nephrology section of the Journal but these organs are integrally related. Normal kidney function is necessary for bone health and bone growth and even mild chronic kidney disease impacts bone mineralization as well as calcium and phosphate homeostasis.

Calcium and phosphate are substrates for mineralization of bone matrix and thus the formation of bone. Under normal conditions an adult is in calcium and phosphate balance so that the amount of calcium and phosphate absorbed from the intestine is equal to that excreted in the urine. Children are in positive balance for both calcium and phosphate for growth including bone growth. Inadequate substrates for mineralization yields unmineralized osteoid resulting in rickets in children and osteomalacia in adults.

Calcium and phosphate levels are tightly regulated by several hormones including 1,25 dihydroxyvitamin D₃, parathyroid hormone and FGF-23 and these hormones also regulate the serum concentration of each other [1]. Thus dysregulation of one hormone in this axis results in the dysregulation of all. The final step of active vitamin D synthesis is 1 α -hydroxylase that occurs in the kidney, which is stimulated by hypophosphatemia. Active 1,25 dihydroxyvitamin D₃ acts on the intestine to increase the absorption of calcium and phosphate. 1,25 dihydroxyvitamin D₃ also inhibits PTH secretion while stimulating the secretion of FGF23; a phosphaturic hormone secreted by osteocytes. PTH secretion is augmented by hypocalcemia and acts to increase serum calcium by stimulating osteoclasts to resorb bone, increasing 1,25 dihydroxyvitamin D₃ production and increasing renal calcium reabsorption. Each of these processes will result in an increase in serum calcium. PTH inhibits renal phosphate reabsorption and increases FGF23. FGF23 inhibits PTH secretion, decreases 1- α -hydroxylase, the enzyme responsible for synthesis of 1,25 dihydroxyvitamin D₃ and increases inactivation of 1,25 dihydroxyvitamin D₃ by stimulating 24-hydroxylase. The net effect of this balancing act is to provide stable calcium and phosphate levels while providing calcium and phosphate for bone formation.

All of the hormones listed above are either synthesized or have an action on the kidney. It is not surprising that chronic kidney disease causes dysregulation of all of these hormones. The first hormone to increase in chronic kidney disease is FGF23 [2]. It is not clear what the stimulus is for osteocytes to increase the production and liberation of FGF23 with renal

insufficiency. Since FGF23 inhibits renal phosphate transporters, it would seem likely that the stimulus would be an increase in serum phosphate. Indeed, hyperphosphatemia is a stimulus for FGF23 secretion and a major problem for patients with severe chronic kidney disease; however serum FGF23 levels increase with mild kidney dysfunction even before there is an increase in serum phosphate. As renal disease becomes more severe, there is an increase in serum phosphate due to an imbalance between dietary intake and the ability of the kidney to excrete phosphate. Renal tubular injury and the increase in FGF23 result in a decrease in serum 1,25 dihydroxyvitamin D₃ levels. The increase in serum phosphate will result in a decrease in ionized calcium and in conjunction with low 1,25 dihydroxyvitamin D₃ levels, there is an increase in serum parathyroid hormone. The net result is low 1,25 dihydroxyvitamin D₃ and high serum phosphate, PTH and FGF23 levels. The low levels of 1,25 dihydroxyvitamin D₃ will result in an osteoid mineralization defect called osteomalacia in adults and rickets in children. Children with chronic kidney disease not only have deformed bones but also suffer from short stature, which is in part due to abnormal bone growth. Even children with mild to moderate chronic kidney disease have been found to have abnormal bone mineralization [3]. Chronic hyperparathyroidism can result in bone resorption. The bone disease resulting from hyperparathyroidism is called osteitis fibrosa cystica.

The treatment for these problems seems relatively easy. We can replace 1,25 dihydroxyvitamin D₃. We ask our patients to limit phosphate-containing foods (milk, cheese, dark colas, meat, beans etc. which are all the good things we love to eat) and take phosphate binders, which are both unpalatable and/or relatively ineffective. These measures should help control the hyperphosphatemia and increase the 1,25 dihydroxyvitamin D₃ levels, which in turn will decrease PTH. The levels of FGF23 will also decrease but nonetheless remain elevated. The armamentarium of drugs to control hyperparathyroidism includes calcium mimetics that activate the calcium sensing receptor and decrease PTH secretion. However, there is some concern that these drugs may not be safe in children. If one is successful in controlling the increase in parathyroid hormone secretion, the patient is not out of the woods, as over aggressive therapy can cause a decrease in osteoblast and osteoclast activity resulting in low bone turnover or adynamic bone disease. The current management of patients with chronic kidney disease is to normalize the serum 1,25 dihydroxyvitamin D₃, calcium and phosphate levels. The optimal level of PTH in patients with chronic kidney disease is not clear as over aggressive management resulting in normal levels may cause adynamic bone disease. Renal osteodystrophy in children is discussed in this issue of Current Opinion in Pediatrics by Drs. Markus Kemper and Michael van Husen.

Chronic kidney disease and renal osteodystrophy can result in poor growth. The cause for the poor growth is multifactorial. In patients with chronic kidney disease, poor growth not only affects the patient's quality of life, but is also a risk factor for morbidity and mortality. Unfortunately, catch up growth to normal stature is rarely achieved despite nutritional support, growth hormone therapy and even after renal transplantation. Drs. Ingulli and Mak discuss this topic.

The leading cause of death in both adults and children with end stage renal disease is cardiovascular disease [4]. Elevated levels of FGF23 have been associated with left

ventricular hypertrophy and death in patients with chronic kidney disease [5–7]. It is now apparent that vascular disease is of a different type in patients with chronic kidney disease than that of elderly people who have subendothelial lipid accumulation. Patients with chronic kidney disease have medial calcification due to the fact that smooth muscle cells develop characteristics of osteocytes and lay down hydroxyapatite [8]. Even children with end stage renal disease have been found to have coronary artery calcification [4]. Prevention of cardiovascular disease and arterial calcification is now a prime focus in the care of children with chronic kidney disease. However, besides an increase in serum phosphate and elevated calcium phosphate product, the factors leading to the generation of arterial calcification are unknown. This topic is discussed in the review by Drs. Paoli and Mitsnefes.

The problems with bone mineralization encountered in patients with chronic kidney disease are not cured by renal transplantation. First, kidney transplant is almost often placed in a patient with preexisting bone disease. Second, the high FGF23 and PTH levels do not normalize immediately after transplant and can result in severe and prolonged hypophosphatemia. Third, glucocorticoids are used in most immunosuppression protocols for a period of time resulting in impaired bone formation and growth. In addition, calcineurin inhibitors can cause renal magnesium wasting and hypomagnesaemia, which can inhibit PTH secretion and the action of PTH on bone. Many of the above problems improve with time and improved growth can be achieved after renal transplantation but nonetheless patients with end stage renal disease that develops early in life often do not achieve their height potential and are at risk for fractures. Finally, while we are always hopeful that a renal transplant will last, there are often acute rejections that are treated with high dose steroids and chronic rejection leading to chronic kidney disease resulting in the same metabolic bone disease discussed above. Drs. Dieter Haffner and Ulrike Schuler discuss this topic in this issue.

Another renal manifestation of bone disease is nephrolithiasis, which is not uncommon in children. Nephrolithiasis is associated with osteoporosis; a major risk factor for fractures. Once a patient has a stone the likelihood of recurrence is high. Most renal stones are composed of calcium oxalate or calcium phosphate. There are several strategies for the prevention of nephrolithiasis. An increase in fluid intake is important in preventing renal stone formation. In most cases one can reduce urinary calcium excretion with a low sodium diet, though the use of potassium citrate and thiazide diuretics are often necessary. The incidence of nephrolithiasis is increasing and pediatricians should be aware of the presenting symptoms and how to treat this condition. Drs. Schwaderer, Kusumi and Ayoob discuss the risk factors for hypercalciuria, renal stones and its link to osteoporosis (ref).

The bone-kidney axis reaches beyond chronic kidney disease and renal stones. Especially relevant to children are genetic diseases resulting in altered production or action of several hormones including FGF23, PTH and 1,25 vitamin D₃ [9]. In addition, mutations in one of the renal phosphate transporters kidney designated NaPi2c results in hereditary hypophosphatemic rickets with hypercalciuria, while mutations in NaPi2a results in Fanconi syndrome. The renal phosphate loss with NaPi2c mutations result in hypophosphatemia and rachitic bone changes. These genetic disorders of phosphate metabolism are discussed in the article by Jyothsna Gattineni.

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