Bone Complications of Cystinosis

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Cystinosis is recognized as a systemic disease because of mutations in the gene encoding cystinosin, the lysosomal cystine exporter.[1] In the nephropathic form that affects infants and young children, the kidney Fanconi syndrome leads to metabolic acidosis, hypophosphatemia attributable to phosphaturia, and reduced synthesis of the active metabolite of vitamin D, 1,25-dihydroxyvitamin D_3, also known as calcitriol. These resultant biochemical abnormalities do not allow the adequate mineralization of osteoid made by the osteoblast and result in a classic feature of nephropathic cystinosis, rickets.[2] In addition, it has been recognized recently that cystinosin is expressed by osteoblasts, and mutations in cystinosin may lead to a reduction in the ability of osteoblast precursor cells to transform into mature osteoblasts capable of synthesizing osteoid, thus, leading to defective mineralization.[3]

Contemporary treatment of patients with rickets in cystinosis includes provision of pharmacologic phosphate salts, correction of the metabolic acidosis with supplemental alkali, and generally, provision of calcitriol.[4] Experimental evidence provides rationale that cystine-depleting therapy with cysteamine bitartrate helps to restore osteoblast function toward normal as well.[3] Thus, the contemporary infant with nephropathic cystinosis should have rickets treated and cured within a short time after the diagnosis is made.

Some reports of copper deficiency have arisen in nephropathic cystinosis as a consequence of the kidney Fanconi syndrome loss of urinary copper.[5] Copper is an essential co-factor in collagen fibril arrangement and in osteoid mineralization. At present, it remains unknown whether we should be supplementing copper to our patients with nephropathic cystinosis, but it is hoped that emerging studies will help direct this soon.

As patients with cystinosis now routinely survive well into adulthood years, additional challenges to life-long bone health have emerged and will be reviewed herein.

Defective Remodeling

We maintain bone health in both the pediatric and the adult years by remodeling existing bone.[6] This process involves osteoclastic resorption over a short period of a few weeks, followed by a more prolonged osteoblastic mineralization of the resorbed space. Given the defect that may exist in the osteoblast in cystinosis, one might posit that an excess of resorption would occur, relative to bone formation. This is termed a low turnover bone state and is predictive of both diminished bone mass and the presence of microfractures (inadequate remodeling repair).

Excess fractures have been seen in limited series of patients with nephropathic cystinosis, including both before and after a kidney transplant.[7-9] Bone mass has also not been reported in large series, but individual cases and limited reports have indicated lower bone mass than normal, although controls with children having chronic kidney disease (CKD) from other diseases than cystinosis have not been included.

CKD-Mineral Bone Disorder

This term has been applied to the complex interactions between the biochemical abnormalities of CKD (including nephropathic cystinosis), the bone defects of CKD apart from those laboratory abnormalities, and the unique vascular calcification that occurs with progressive CKD, whether imaged in adults by spiral computed tomography studies, or in children and adolescents, evidenced by altered vessel measurements (carotid intimal-medial diameter, as one example).[10] CKD-mineral bone disorder (MBD) leads to excess bone fractures, various forms of heart disease, and excess mortality. Most of the data have been demonstrated in adults with CKD, but recent studies have confirmed these hypotheses in children as well.[11] To date, there is no specific study of CKD-MBD in nephropathic cystinosis, but there is no reason to assume that there would be less of the entity in it than in other children with CKD.

There are some theoretical issues in nephropathic cystinosis that might worsen CKD-MBD compared with other children with CKD of differing etiology. For

CKD	Chronic kidney disease
MBD	Mineral bone disorder

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example, it is well understood that as kidney function declines, the phosphate-responsive hormone, fibroblast growth factor-23 (FGF-23), rises in the blood. FGF-23 has been linked independently with excess mortality, heart disease, and progression of CKD itself in adult studies.[12] What might occur in nephropathic cystinosis with long-term phosphate salt administration? The kidney Fanconi syndrome persists quite late into the course of patients with CKD with nephropathic cystinosis, so cessation of phosphate salts leads to hypophosphatemia. Studies are needed about FGF-23 in cystinosis, especially because we recognize that calcitriol administration is an additive factor to FGF-23 elevations in CKD.

Growth Hormone Resistance and Bone

CKD itself is a state of growth hormone resistance on the skeleton, including the absence of normal bone growth and bone remodeling.[13] Studies of the effect of recombinant human growth hormone in nephropathic cystinosis have demonstrated normal responses with regard to growth, but no studies have carefully examined changes on bone density or fracture incidence.[14] More recently, reports of frank growth hormone deficiency has been documented in some patients with nephropathic cystinosis.[15]

Challenges in Adolescence to Bone Health

Several hormonal disturbances in the adolescent patient with nephropathic cystinosis may occur that could compromise optimal bone health. The adolescent growth spurt is dependent, in part, on gonadal steroids, estrogen and testosterone, in female and male patients, respectively.[16] Although CKD itself may alter ovarian secretion of estrogen, there appears no additional disturbance in female patients with nephropathic cystinosis itself. The same cannot be said for male patients with cystinosis, as up to 70% of all male patients may be hypogonadal, with reduced testosterone secretion, and diminished effects on increasing bone density at the time of the adolescent growth spurt.[4] At present, there are no large series of male patients with cystinosis treated with testosterone and subsequent effects on bone.

Less than optimal treatment for nephropathic cystinosis may produce a state of frank hypothyroidism. Adequacy of thyroid hormone is an essential co-factor for optimal bone health overall.[17] Again, we are without sufficient data to fully understand this process in patients with nephropathic cystinosis. Recent series of patients with cystinosis, however, suggests that the true prevalence of hypothyroidism is decreasing, and it is hoped, therefore, this component of bone health challenge will be eliminated.[4]

Changes in Neuromuscular Function

There is a tight integration between bone and overlying muscle to achieve normal bone health in all individuals. Diminished muscle tone is associated with lowered bone mass regionally at the site of the disordered muscle activity and excess fractures.[18] As the natural history of nephropathic cystinosis evolves with more patients surviving well into the adolescent years and beyond with muscle dysfunctions, it is possible that the underlying bone in the distal extremities may be challenged. Such changes in bone could result in deformities, fractures, and bone pain, but we have no specific understanding of how to best treat the underlying bone yet. It is hoped that new studies will be designed to use advanced imaging techniques that include high-resolution peripheral quantitative computed tomography to help understand the physiology of this new disorder.

Challenges to Bone Health after Kidney Transplantation

Medications used to assure optimal outcomes after kidney transplantation, as well as pre-existing CKD-MBD from before transplantation, contribute to challenge optimal bone health.[19-21] Corticosteroids are well known to be associated with excess bone fractures and osteoporosis in children and adults. Potent calcineurin-inhibition may add to that fracture potential as well. Few contemporary series of patients with nephropathic cystinosis exist to clarify the pathways to meet this challenge to optimal bone health, but it does appear in general that limitation of corticosteroid exposure is important.

Bone Marrow Transplant and Bone Health

As innovative therapies to the treatment of patients with nephropathic cystinosis in the near future may include bone marrow or stem cell transplantation, it should be recognized that for other diseases, such procedures have substantial bone morbidity associated with it.[22] Such factors that impair bone health include the use of medications (corticosteroids, calcineurin inhibition) and perhaps preconditioning with radiotherapy, which itself may be toxic to bone.

Alternatively, stem cell and marrow transplantation may provide normal precursors for bone cell development and, thereby, overcome the mutations in cystinosis inherent in the osteoblast of affected patients. The balance between these beneficial and potentially harmful effects should be studied carefully in the future.

Toxicity from Cystine-Depleting Agents

The use of cysteamine bitartrate in doses higher than currently recommended has led to a specific vascular defect, linked pathophysiologically to altered collagen cross-linking.[23] Whether this same defect in collagen cross-linking occurs in bone as well remains uncertain but should be borne in mind if such extreme dosing is contemplated.

Bone Toxicity Related to Proton-Pump Inhibition

Epidemiologic studies in adults have linked the chronic use of proton-pump inhibitors to excess bone fractures.[24] It is unknown if this pertains to the pediatric or adolescent patient in general, and no studies have evaluated such therapies in any population with nephropathic cystinosis. As a general rule, it seems prudent that such medications should be limited to as short a time as possible for therapeutic benefit and avoidance of potential bone toxicity.

Summary and Recommendations

Bone is one of the systemic organs affected by nephropathic cystinosis, both as part of the effects of the cystinosin mutation, as well as from some of the therapies used in different parts of the disease through the life cycle. Consideration must be given to optimize bone health throughout the lifespan of patients with nephropathic cystinosis to improve their quality of life. ■

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