Management Of Bone Disease In Children On Peritoneal Dialysis
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Abstract: Abnormalities in mineral metabolism and bone structure are a common complication in chronic kidney disease (CKD) that may develop prior to any clinical manifestations of renal failure and institution of peritoneal dialysis. The effects of abnormal bone and mineral metabolism on endochondral ossification during growth result in complications in the epiphyseal region that are unique to the children with CKD. There are several forms of renal osteodystrophy, including osteitis fibrosa cystica, adynamic bone disease, and osteomalacia. In some patients, there is evidence of more than one type, which is called mixed osteodystrophy. In most clinical settings, it is not necessary to identify the specific form of renal osteodystrophy but rather determine if bone turnover activity is high or low. In most children with stage 5 disease, the combination of dietary phosphate restriction, phosphate binders, and active vitamin D therapy is required to maintain normal age-appropriate serum phosphate value and a serum PTH concentration that is no more than two to four times normal. In children, several observational studies have shown that calcium-based phosphate binders are effective and safe in lowering serum phosphate and PTH levels.

Key words: Renal osteodystrophy, continuous peritoneal dialysis, phosphate binders, PTH.

Introduction:
Abnormalities in mineral metabolism and bone structure are a common complication in chronic kidney disease (CKD) including children on dialysis (1). Renal osteodystrophy is an early, and inevitable pervasive consequence of CKD that may develop prior to any clinical manifestations of renal failure. However, the effects of abnormal bone and mineral metabolism on endochondral ossification during growth result in complications in the epiphyseal region that are unique to the children with CKD. Abnormalities in mineral metabolism and bone structure are a common complication in CKD (1). The changes that occur in the homeostatic mechanisms that regulate serum concentrations of calcium, phosphate, vitamin D, and parathyroid hormone (PTH) lead to development of renal osteodystrophy or renal bone disease. In children with CKD, renal osteodystrophy results in significant morbidity. Some of them are similar to those seen in adults with CKD (eg, fractures, bone pain, and avascular necrosis) but others are unique to children (eg, growth failure and skeletal deformities).

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STAGES OF CHRONIC RENAL DISEASE — Many of the complications of CKD (including renal osteodystrophy) can be prevented or delayed through early detection and treatment. This observation has led to the development of a staging system by the KDOQI working group that is based upon the estimated glomerular filtration rate and is independent of the primary renal diagnosis. This staging system is used to help guide management of metabolic abnormalities in children with CKD (2).

Stage 1 — Normal glomerular filtration rate (GFR) 90 mL/min per 1.73 m2
Stage 2 — GFR between 60 to 89 mL/min per 1.73 m2
Stage 3 — GFR between 30 and 59 mL/min per 1.73 m2
Stage 4 — GFR between 15 and 29 mL/min per 1.73 m2
Stage 5 — GFR of <15 mL/min per 1.73 m2 or requires dialysis treatment.

The management of bone disease should start at the time of initiation of peritoneal dialysis in these children. Children with CKD stage 2 usually have no signs or symptoms of bone abnormalities. However, these children may have evidence of abnormalities on laboratory testing (eg, decreased serum calcitriol [1,25 dihydroxyvitamin D] and elevated serum PTH) (3). This period should be used to counsel the child and family about CKD and its impact on bone metabolism. We need to emphasize the importance of laboratory monitoring and discuss future interventions that will prevent renal osteodystrophy.
Subtle signs of renal osteodystrophy begin to be observed when the GFR decreases to 50 percent of normal (stage 3 disease). These children should be monitored for evidence of bone disease by physical examination and laboratory evaluation. Physical findings include muscle pain, weakness, and bony changes such as varus and valgus deformities of the long bones. Laboratory abnormalities of bone metabolism (eg, elevated PTH) are common in stage 3 disease and require therapeutic interventions.

TYPES — There are several forms of renal osteodystrophy, including osteitis fibrosa cystica, adynamic bone disease, and osteomalacia. In some patients, there is evidence of more than one type, which is called mixed osteodystrophy.

In a series of 51 children undergoing dialysis, the prevalence of the different types of bone disease was as follows: normal histology (37%), adynamic bone disease (27%), osteitis fibrosa cystica (24%), mixed osteodystrophy (10%), and osteomalacia (2%) [4]. In children with CKD stages 2 to 4, osteitis fibrosa cystica is the most common form of renal osteodystrophy.

(a) Osteitis fibrosa cystica — Osteitis fibrosa cystica results from secondary hyperparathyroidism. Bone biopsies of affected patients demonstrate increased bone turnover activity and defective mineralization compared to normal bone. The aim of therapy is to prevent secondary hyperparathyroidism, thus preventing osteitis fibrosa cystica.

(b) Adynamic bone disease — Adynamic bone disease is characterized by low osteoblastic activity and bone formation rates. It represents the major bone lesion seen in children who require dialysis therapy and is related to excess suppression of the parathyroid gland (due to the administration of calcium-containing phosphate binders and vitamin D analogues) [4]. These patients typically have a low serum intact PTH concentration (eg, <100 pg/mL), which is frequently accompanied by an elevated serum calcium. Adynamic bone disease is uncommon among predialysis patients. In the past, adynamic bone disease also resulted from aluminum toxicity due to the administration of aluminum-containing phosphate binders. Adynamic bone disease increases the risk for fractures and metastatic calcification. It is best treated by allowing the intact PTH level to rise to increase bone turnover by decreasing or discontinuing the dose of the calcium-based phosphate binders and/or vitamin D therapy.

(c) Osteomalacia — Osteomalacia is a low turnover bone lesion that is characterized by an increased volume of unmineralized bone. It is characterized by reductions in bone turnover, the number of bone-forming and bone-resorbing cells, and an increase in the volume of unmineralized bone. In the past, this disorder resulted from aluminum toxicity due to the administration of aluminum-containing phosphate binders, which are no longer recommended. Osteomalacia is now much less common (4) and, when it occurs, is thought to reflect vitamin D deficiency.

(d) Mixed osteodystrophy — Bone lesions in patients with mixed osteodystrophy include elements of both high and low bone turnover.

(e) Other factors — Other factors that may impact on renal osteodystrophy in children include corticosteroid therapy, metabolic acidosis, hypophosphatemia (due to excessive dietary phosphate restriction or use of phosphate binders), nutritional vitamin D deficiency, medications that interfere with vitamin D metabolism (eg, anticonvulsants), and prolonged immobilization.

Diagnosis

Bone biopsy is the gold standard for establishing the type of renal osteodystrophy. In most clinical settings, it is not necessary to identify the specific form of renal osteodystrophy but rather determine if bone turnover activity is high or low. In children with CKD stage 5 on chronic peritoneal dialysis (CPD), a combination of serum PTH and calcium can distinguish between high (eg, osteitis fibrosa cystica) and low (eg, adynamic bone disease) turnover bone disease (5,6). In one study of children on chronic peritoneal dialysis, a serum PTH level >200 pg/mL and a serum calcium value <10 mg/dL (2.5 mmol/L) identified patients with high turnover bone disease from secondary hyperparathyroidism with 85 percent sensitivity and 100 percent specificity (5). Serum PTH concentrations <200 pg/mL and serum calcium value >10 mg/dL (2.5 mmol/L) were 100 percent sensitive but only 79 percent specific for identifying patients with adynamic bone lesions. In another study of children on hemodialysis, all patients with a serum PTH concentration >125 pg/mL and a serum calcium value <10 mg/dL (2.5 mmol/L) had either osteitis fibrosa or mixed osteodystrophy.

Indications for bone biopsy are not well established because clinical situations, in which having the diagnosis of bone disease is helpful, have not been identified. The K/DOQI guidelines suggest that a bone biopsy be considered to determine the type of renal osteodystrophy and guide therapy.
in children with stage 5 disease in whom there are nontraumatic bone fractures, suspected aluminum exposure, or persistent hypercalcemia with serum PTH between 400 and 600 pg/ml (1). In children with CKD stage 2 to 4, the most likely form of renal osteodystrophy is osteitis fibrosa cystica and a bone biopsy is not routinely needed. In these patients, an elevated serum PTH concentration is indicative of increased bone turnover disease.

Management

The goals of therapy are to prevent phosphate retention, hypovitaminosis D, and hypocalcemia. Management is focused on early detection and correction of these abnormalities because each contributes to the development of secondary hyperparathyroidism, which causes renal osteodystrophy.

Monitoring — Serum concentrations of calcium, phosphate, and PTH should be measured on an ongoing basis in all children with CKD, even those with mild disease who often have evidence of abnormalities in bone metabolism. Early detection of bone metabolic abnormalities ensures that therapeutic interventions can be initiated, thereby preventing or minimizing renal osteodystrophy.

For calcium and phosphorus measurements, the K/DOQI guidelines recommend monthly measurements in Stage 5 disease whereas PTH measurements should be done, at least every three months.

If therapy is initiated to correct serum abnormalities or to treat renal osteodystrophy, laboratory evaluation should be performed more frequently to ensure a response to therapy or to identify the need to adjust therapy.

Phosphate — As the child ages, the normal range of phosphorus values decreases phosphorus retention begins in the early stages of CKD and plays a central role in the development of hyperparathyroidism. The clinical correlate of these pathophysiologic changes is that a child with CKD stage 2 and 3 disease has an elevated serum PTH but a serum phosphorus that, although increased, remains within the normal range. When the GFR falls below 30 mL/min per 1.73 m2 (stage 4 disease), hyperphosphatemia will usually occur unless appropriate therapy is given.

In children, the K/DOQI practice guidelines recommend that in Stage 5 (GFR <15 mL/min per 1.73 m2 or dialysis requirement) — The serum phosphorus should be maintained between 4 to 6 mg/dL (1.29 to 1.93 mmol/L) in children 1 to 12 years of age and between 3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L) in adolescents.

In children with CKD, two therapeutic interventions to attain and maintain the targeted serum phosphorus concentration include restriction of dietary phosphorus and the use of calcium-based phosphate binders. In controlled studies of both children and adults, dietary phosphorus restriction results in decreased serum PTH and increased serum 1,25-dihydroxyvitamin D (calcitriol) concentrations (7,8). Conversely, an intake of phosphorus that is twice the Dietary Reference Intake in children with CKD stage 3 increases serum PTH and decreases serum 1,25-dihydroxyvitamin D (7). As a result of these studies, the K/DOQI practice guidelines recommend restricting dietary phosphorus in children with CKD who have an elevated serum PTH level to 100 percent of the Dietary Reference Intake (DRI) for age. 0 to 0.5 years - 100 mg/day 0.5 to 1 year - 275 mg/day 1 to 3 years - 460 mg/day 4 to 8 years - 500 mg/day 9 to 19 years - 1250 mg/day. Dietary phosphorus is restricted to 80 percent DRI if the serum PTH is above the target range and the serum phosphate concentration is above the age-appropriate normal range) (1): 0 to 0.5 years - 80 mg/day 0.5 to 1 year - 220 mg/day 1 to 3 years - 368 mg/day 4 to 8 years - 400 mg/day 9 to 19 years - 1000 mg/day. After the initiation of dietary restriction, serum phosphorus should be monitored at least every three months in children with CKD stages 3 and 4, and monthly in those with CKD stage 5. Studies in children with CKD report no association of dietary phosphorus restriction with poor linear growth (9-12). However, serum phosphorus concentrations below the target range for age should be avoided because of the potential adverse effects of hypophosphatemia on linear growth. Compliance with dietary phosphate restriction in children is poor as most of their favorite foods are rich in phosphate. Thus, despite attempts to restrict phosphorus intake, phosphate binders often become necessary to prevent phosphate absorption from the gastrointestinal tract.

In children, several observational studies have shown that calcium-based phosphate binders are effective and safe in lowering serum phosphate and PTH levels (13-15). In contrast to this general recommendation, calcium-based phosphate binders should not be used as the sole agent in patients who are hypercalcemic (serum calcium >10.2 mg/dL). The preferred drug in this setting is sevelamer (Fosesta, acceterol), a noncalcium and nonaluminum phosphate binder (16). It may be used alone or in conjunction with a calcium-containing phosphate binder. With the concern that calcium-
containing phosphate binders may contribute to soft tissue calcification, noncalcium and nonaluminum phosphate binders are used more frequently as initial therapy in adults. In children, data are limited comparing sevelamer to calcium-containing agents. Until further studies demonstrate the safety and efficacy of sevelamer in children, it should be reserved for children with hypercalcemia (1,17).

Calcium and vitamin D — In children with CKD, the homeostatic mechanisms that maintain normal serum calcium and 1,25-dihydroxyvitamin D (calcitriol) concentrations are disrupted. In children, calcitriol (1,25-dihydroxyvitamin D) has been reported in observational studies to decrease serum PTH concentrations and improve the linear growth of children with CKD (18,19). The K/DOQI practice guidelines recommend the following evaluation for detection and treatment of vitamin D deficiency (1). In children with stage 2 to 4 disease (GFR of 15 to 89 mL/min per 1.73 m2) and serum PTH values above the target range for the stage of CKD, serum 25-hydroxyvitamin D concentrations should be measured. If serum 25-hydroxyvitamin D is <30 ng/mL (75 nmol/L), treatment with ergocalciferol should be started. Reassessment of serum 25-hydroxyvitamin D is recommended three months after the initiation of therapy. If serum 25-hydroxyvitamin D is >30 ng/mL (75 nmol/L) in children with stage 2 to 4 disease, treatment with calcitriol should be started only if the serum PTH is above the target range, and the serum calcium level is <10 mg/dL (2.37 mmol/L) and the serum phosphorus level is less than age-appropriate upper limits for the stage of CKD. The recommended starting dose is based on the body weight of the child:

Weight <10 kg — 0.05 microgram every other day
Weight between 10 and 20 kg — 0.1 to 0.15 microgram per day
Weight >20 kg — 0.25 microgram per day

Hypercalcemia — Children with CKD who are treated with vitamin D therapy and calcium-containing phosphate binders may develop hypercalcemia. If total serum calcium values exceed 10.2 mg/dL (2.55 mmol/L), the dose of calcium-based phosphate binders should be reduced and/or therapy changed to sevelamer. Vitamin D therapy should also be discontinued until the serum calcium returns to the targeted range and then restarted with an appropriate dose adjustment.

Parathyroid hormone — High bone turnover seen in osteitis fibrosa and mixed osteodystrophy is a result of secondary hyperparathyroidism.

Serum PTH concentration is inversely correlated with renal function and is almost always elevated when the glomerular filtration rate falls below 60 mL/min per 1.73 m2 (4). Although the optimal serum PTH values in children with CKD are uncertain, the K/DOQI guidelines recommend targeted levels of serum intact PTH in

Stage 5 disease to be 200 to 300 pg/mL

The management and prevention of secondary hyperparathyroidism is complex and requires frequent monitoring and adjustment of therapy. The initial step is to correct phosphate retention by dietary restriction usually combined with either calcium-containing phosphate binders and/or sevelamer.

This is followed by either calcium supplementation and/or vitamin D therapy. In the early stages of CKD, the clinician also should assess and replenish 25 hydroxyvitamin D (if the level is low) with oral ergocalciferol or cholecalciferol prior to initiating therapy with calcitriol. In most children with stage 5 disease, the combination of dietary phosphate restriction, phosphate binders, and active vitamin D therapy is required to maintain normal age-appropriate serum phosphate value and a serum PTH concentration that is no more than two to four times normal. Severe secondary hyperparathyroidism requiring parathyroidectomy is rare in children.

Complications

The sequelae of renal osteodystrophy in children include growth retardation, musculoskeletal deformities, and soft tissue calcification (1).

Growth failure — Growth failure in children with CKD is multifactorial in origin. Potential contributing factors in addition to renal osteodystrophy include chronic metabolic acidosis, anorexia, inadequate caloric intake, and inadequate insulin-like growth factor. The relative importance of these factors in growth failure is uncertain. However, treatment is aimed at correcting all correctable abnormalities.

There is evidence of increased growth after interventions such as vitamin D therapy and normalization of serum PTH concentrations (18,19). In addition to these standard goals of the treatment of CKD as described above, growth hormone therapy is also effective. The data supporting this conclusion are presented separately.

Musculoskeletal deformities — Children with renal osteodystrophy are at increased risk for nontraumatic
fractures. In addition, other skeletal deformities may develop, given that these children can be vitamin D deficient, hypophosphatemic, acidotic, on drugs that induce cytochrome P450 pathways, etc. In children with CKD, the growth plate is vulnerable to injury with disruption of the connection between the epiphyseal plate and the metaphysis (20,21). This abnormality, along with hyperparathyroid erosions of bone, puts the child at an increased risk for slipped epiphysis and genu valgum.

Soft tissue and vascular calcification — Soft tissue calcifications (also called calcinosis) can lead to long-term morbidity in patients with CKD. The sites include vascular, ocular, periarticular, and visceral calcifications and may be severe enough to produce calciphylaxis. Soft tissue calcification can involve the vasculature, including the coronary arteries (22-24). In an attempt to minimize the risk of soft tissue and vascular calcification, the K/DOQI guidelines recommend that the calcium phosphate product be maintained below the following values (1): Less than 55 mg2/dL2 in children older than 12 years of age; Less than 65 mg2/dL2 in children younger than 12 years of age. This is best achieved by maintaining the serum level of phosphate within the target range and keeping the serum calcium within the normal range for the laboratory, generally between 8.8 and 9.7 mg/dL.

Conclusions:

In children with CKD, abnormalities in bone metabolism occur early affecting those with mild to moderate renal disease and is universal. If untreated, these patients will develop renal bone disease (renal osteodystrophy) as their renal failure progresses. Renal osteodystrophy can present as several different pathologic forms and includes osteitis fibrosa, adynamic bone disease, osteomalacia, and mixed osteodystrophy. Management (frequency of monitoring and therapeutic interventions) is based upon the child’s level of kidney function. Therapy focuses on prevention of phosphate retention and hypovitaminosis D.

References:


