CHRONIC KIDNEY DISEASE MINERAL BONE DISORDER IN CHILDREN

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Abstract. Childhood and adolescence are critical times for the development of all organs and systems. Achievement of optimal bone mass in this period is thought to be the best predictor for bone health in the adult life. In children, nutrition, physical activity, growth, endocrine and metabolic function is mandatory for a normal skeleton development and cardiovascular system. Disordered mineral and bone metabolism associated with chronic kidney disease causes important obstacles to final adult height, bone strength and cardiovascular integrity that may contribute to chronic morbidity. As kidney function decreases, a progressive deterioration in mineral homeostasis emerge, with an abnormal serum and tissue concentrations of phosphorus and calcium, and changes in circulating levels of hormones. Therefore, treatment target of MBD includes maintaining optimal serum parameters for calcium, phosphorus and parathyroid hormone according to stage of CKD, in order to improve growth, high-turnover bone disease and prevent cardiovascular calcifications.

Key words: chronic kidney disease, metabolic bone disorder, children

Introduction

Childhood and adolescence are critical times for the development of a life-long bone health and cardiovascular system. Bone growth involves a complex coordination of varied cell activities that are under the direct influence of a range of hormones and growth factors along with mineral metabolism that may be profoundly disturbed in chronic kidney disease. This affects normal growth and favors cardiovascular calcifications that are indeed less prevalent than in adult population, but remains a leading cause of mortality. The close connection between phosphocalcic metabolism disturbances, the treatment for correcting this alterations and vascular calcifications has led to a new and elaborate approach of chronic kidney disease in order to improve patients outcome. The term “renal osteodistropy” fails to describe this complex association of physiopathological elements and the need to find an appropriate term was implied. Therefore, Kidney Disease: Improving Global Outcomes (KDIGO) established that the term ‘CKD–Mineral and Bone Disorder (CKD–MBD)’ should be used to describe the broader clinical syndrome encompassing mineral, bone, and calcific cardiovascular abnormalities that develop as a complication of CKD. CKD-MBD is defined as being a systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following: (a) abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism; (b) abnormalities in bone turnover, mineralization, volume, linear growth, or (c) strength vascular or other soft-tissue calcification. “Renal osteodistropy” on the other hand, describes only the bone impairment as a single complication of CKD that can be quantified by bone biopsy which describes three histologic parameters: three key histologic descriptors: bone turnover, mineralization, and volume (TMV) and has been recommended in all patients with CKD. Although the histomorphometry of bone biopsy is the only available method for evaluate all three parameters, it is not routinely performed.

This review is intended to emphasize the current approach of mineral and bone disorder in children and the new therapeutically strategies, along with their impact on reducing mortality and improving long term outcome.

Secondary hyperparathyroidism – pathogenesis and the importance of serum parathyroid hormone values in CKD-MBD

The kidneys intervenes in calcium homeostasis by converting the storage form of vitamin D (25-hydroxyvitamin D3) through 1α hydroxylase enzyme, to the active form of vitamin D (1,25 dihydroxyvitamin D, calcitriol) that stimulates intestinal calcium absorption. It is was known that suppression of calcitriol synthesis occurs early in the evolution of CKD, before alterations in calcium, phosphorus and PTH can be detected and thought to be caused by progressive reduction of renal mass function. New studies changed this concept, by outlining that the suppression effect on 1α hydroxylase exercised by circulating fibroblast growth factor 23 (FGF23) leads to a more important decrease in calcitriol synthesis than the loss of renal mass. FGF23 is a hormone produced by osteocyte that expresses its...
action by a mandatory activating coreceptor named Klotho whose actions may be directly linked with vascular calcifications and therefore an increased mortality rate[21]. Their synergic action is to decrease renal proximal tubular phosphate reabsorption (that varies from 85% in normal kidney to under 15% in patients that have stage 4-5 CKD)[13] maintaining a normal phosphorus balance in early stages of CKD and to suppress the renal 1 α hydroxylase receptor, as a result of that lowering the synthesis of calcitriol (that will successively decrease gastrointestinal phosphate absorption)[14,15]. Several studies in children are consistent with data from the adult population and supports that [16-20] "increases FGF23 may be the first detectable biochemical evidence for an abnormal regulation of mineral ion homeostasis while glomerular filtration rate is merely normal, leading to the early decline in 1, 25(OH)2vitamin D levels"[2]. The decrease of calcitriol leads to an insufficiency of intestinal calcium absorption and as a result, the serum levels of PTH start to elevate[22]. This adjustment mechanism of PTH manages to maintain a normal calcium balance in early stage of CKD, by stimulating bone release. As a consequence of bone resorption though, it appears also an increasing level of serum phosphorus[2]. As long as the adaptive mechanisms and glomerular filtration rate are not severe damaged, a normal homeostasis can be maintained as a result of high levels of PTH. When glomerular filtration rate decreases, on the other hand, excretion of phosphorus is altered and hyperphosphatemia occurs causing a further suppression of calcitriol[23] and a stimulation of additional PTH release[24,25]. As kidney function reduces, appears an increasingly need of PTH levels in order to maintain an adequate mineral and bone metabolism. As a result of chronic exposure to high levels of PTH, accumulation of biologically active PTH fragments[27,28] and downregulation of the PTH receptor[28] we confront a resistance of the parathyroid gland, have as a result high levels of PTH, a parathyroid hyperplasia which is difficult to reverse[24]. Hypocalcemia, hyperphosphatemia, lower levels of 1,25(OH)2D3 and changes in normal feedback of PTH due to a hyperplastic gland, have as result secondary hyperparathyroidism with a great impact on growth, development and long outcome of the children (bone deformities, fractures and soft tissue calcifications)[4, 30-34].

The importance of maintaining the serum levels of PTH in the optimal target ranges[2] depending on the stage of CKD is implied, considering its central role in the pathophysiology of this complex disease. Therefore, a detailed monitoring PTH along with calcium, phosphorus and alkaline phosphatase activity is recommended beginning with stage 2 of CKD in children[4]. Target levels of PTH depending on CKD staging are suggested. Unfortunately there is still an important controversy regarding the optimal levels of PTH in pre-dialysis CKD, and the "current recommendations by the National Kidney Foundation suggest that levels be maintained between 200 and 300 pg/ml[35], the European Pediatric Dialysis Group suggests that values between two- and threefold the upper limit are optimal in dialyzed children[36], and a much broader range—between two- and nine times the range for normal individuals—is recommended by the Kidney Disease: Improving Global Outcome (KDIGO) foundation for patients treated with maintenance dialysis[4]".

Abnormalities in bone turnover, mineralization, volume and linear growth in children

Bone disease in pediatric population with CKD has been a primary concern for physicians, because of the great impact that it has on a growing organism and in the sense of finding the most suitable treatments and better understanding of its physiopathology. The most suitable tool that evaluates the bone disorder by three key histologic descriptors: bone turnover, mineralization, and volume, is the bone biopsy. Nevertheless, it is not routinely performed (because it does not predict the risk of fracture or type of osteodistrophy), unless patients with CKD present pathological fractures, persisten bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and prior to therapy with bisphosphonates[4].

The most frequent bone lesion that is observed in children with early stages of CDK is high bone turnover, which is due to a high exposure of circulating PTH that activates excessively the osteoblasts and osteoclasts with consequences in bone structure and strength[37-39]. This is a cause for alterations in bone histology and may evolve to periarticular fibrosis or "osteitis fibrosa cystica"[40]. Over-suppression of PTH levels by excessive treatment or prolonged dialysis, on the other hand, has also a great impact on bone histology, in the sense of lowering the bone turn-over, a state named "adynamic renal osteodistrophy." This condition is characterized by a lack of bone cellularity, a reduced bone formation rate, normal osteoid volume, a high risk for vascular calcifications (due to a high calcium and alkaline phosphate levels) and severe growth impairment[2,41,42].

Mineralization of bone is another histologic parameter that is altered in chronic kidney disease. The mineralization of bone is essential for its hardness and strength, and its normal development depends on an elaborate process in which crystals of calcium phosphate are produced and placed in a well established architecture. If this process is not properly regulated, the result can be a concomitant increase in osteoid volume and osteoid maturation time[3]. The researchers have found that a central pawn in the correct mineralization is inorganic pyrophosphate, which inhibits abnormal calcification. Levels of pyrophosphate are controlled by at least three other molecules: nucleotide pyrophosphatase phosphodiesterase 1 (NPP1), which produces pyrophosphate outside the cells; ankylosis protein (ANK), which transports it from the cell's interior to the cell surface; and tissue nonspecific alkaline phosphatase (TAP), which decrease pyrophosphate in the extracellular environment, keeping its levels in control[43]. It is important to know that all this molecules are influenced by more than one biochemical parameter, which includes PTH, calcium, alkaline phosphate, FGF-23[45,49] and also can be altered by medication that
we use with the intention to avoid disturbances of bone metabolism like active vitamin D sterols[44]. This is the reason why mineralization defects are high prevalent in pediatric CKD and is present even though the turn-over of the bone is normal, on early stages of CKD[45,46].

Children with chronic kidney disease have also abnormalities in bone volume, first of all because of the high levels of PTH which is an anabolic steroid with an impact on trabecular bone, leading to an increased bone volume, trabecular volume and width[47-48].

Another problem that has a severe impact on children’s outcome is linear growth failure. More than one third of CKD pediatric patients have a height deficit (under the 3rd percentile) even with a moderate renal function. This is caused by a multitude of factors like renal osteodistrophy, metabolic acidosis, chronic inflammation, difficulties in alimentation, functional hypogonadism and disturbances in endocinial axe of insulin like GF1[4]. Guidelines strongly recommend the usage of human recombinant growth hormone (rhGH) therapy after resolution of malnutrition and biochemical abnormalities (PTH levels has to be monitored and controlled during therapy)[4], considering the degree of CKD, the growth potential and control of the osteodistrophy[2,50].

**Cardiovascular consequences in CKD-MBD**

Even in early stages of CKD (when the first hormonal systems to modify are FGF-23 and osteocalcin[11,53]) disturbances in mineral metabolism and loss of mesenchymal-cell anabolism influence the cardiovascular system, starting with a loss of vascular smooth muscle phenotype[51]. This leads to a decrease in vascular smooth muscle differentiation thus progressively losing its contractility[54,55]. This defect of contractility determines vascular stiffness, which is the cause of systolic high pressure and consequent left ventricular hypertrophy, an important manifestation in children with CKD[55]. Another effect of CKD-MBD is vascular calcification, in which a pathophysiological role may have disturbances in mineral metabolism and loss of mesenchymal-cell anabolism influence the cardiovascular system, starting with a loss of vascular smooth muscle phenotype[51]. This leads to a decrease in vascular smooth muscle differentiation thus progressively losing its contractility[54,55]. This defect of contractility determines vascular stiffness, which is the cause of systolic high pressure and consequent left ventricular hypertrophy, an important manifestation in children with CKD[55]. Another effect of CKD-MBD is vascular calcification, in which a pathophysiological role may have vitamin D, FGF23 and hyperphosphatemia.

Different methods are used to assess the extent of cardiovascular damage in adults, but the methods still need to be standardized for the use in pediatric population. Carotid intima-media thickness and aortic pulse wave velocity are the most used methods to assess cardiovascular disorders in children, but they fail to describe vascular minimal changes in early stages of CKD[56].

**Therapeutic agents in CKD-MBD**

The therapy in pediatric CKD-MBD has an important role in controlling mineral metabolism, with the goal of improving linear growth, reducing bone fragility and deformities, increasing quality of life and reducing vascular calcifications[2].

The management includes maintaining serum calcium and phosphorus in normal limits, thereby maintaining appropriate PTH levels for CKD stage, preventing hyperplasia of the parathyroid glands, limiting extraskeletal calcification and preventing the accumulation of toxins like β2-microglobulin and aluminum[57].

Phosphorus control implies a combination of therapeutic agents like phosphate-binders and rigorous diet, in order to maintain its levels within the normal range, regarding the association of phosphorus and cardiovascular morbidity[57].

**Phosphate binders** can be classified in calcium-containing salts (calcium carbonate, calcium citrate and calcium acetate)- that are used to lower hyperphosphatemia and also as an additional source of calcium- and calcium-free phosphate binders (sevelamer hydrochloride, lanthanum carbonate, magnesium carbonate, stabilized polynuclear iron hydroxide and ferric polymaltose complex) that were developed to minimize the calcification risk and lowering the toxicity of calcium-containing salts[57].

Calcium-containing salts, as calcium carbonate, are proved to balance the phosphorus serum levels, by adjusting the dose proportional to the phosphorus content of the meal[34]. High doses, on the other hand, may lead to hypercalcemia (frequent in patients treated with vitamin D or adynamic bone disease[58]), an increase progression of vascular calcifications and rigidity and neurologic toxicity (aluminum hydroxide)

Sevelamer hydrochloride has the same effect on phosphorus levels as calcium-containing salts, but lowers the progression of vascular calcifications and improves the cardiac outcome by its action on cholesterol (lowers serum cholesterol levels and LDL cholesterol and increases HDL cholesterol) and has no side-effect as hypercalcemia. For preventing acidosis that may appear in treatment with sevelamer hydrochloride, has been introduced a new form named sevelamer carbonate[57,59]. Lanthanum carbonate is also a calcium-free phosphate binder, with the same effects as sevelamer, but because lanthanum is a heavy metal, has side effects as renal toxicity and accumulation in tissues and is not approved for children use[60].

**Vitamin D therapy**

Low levels of 1, 25-dihydroxy vitamin D (calcitriol) and hyperphosphatemia play a central role in secondary parathyroidism[30,61,62]. Providing adequate intake of vitamin D while controlling dietary phosphorus restriction has been shown to suppress successfully PTH levels[63,64].

KDOQI guidelines recommend vitamin D deficiencies to be treated with different doses of ergocalciferol or cholecalciferol depending of the stage of the deficiency, for 6 months[64].

Calcitriol and alfacalcidol express their effect on mineral metabolism by increasing the intestinal and renal calcium absorption, by increasing skeletal sensitivity for PTH and increasing FGF-23 levels, suppressing this way PTH levels, improve dialysed patients outcome, improve systolic pressure and reduce proteinuria and fibrosis in pre-dialysis patients[57,65,66]. This indirect mechanism of increasing FGF-23 levels may have consequences in time, by increasing cardiovascular risk[45]. Also, in association with calcium-based binders, active vitamin D sterols can lead in hypercalcemia and hyperphosphatemia, with an increased risk of tissue calcifications[57,67].

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In order to minimize the side effect of hypercalcemia but maintaining a good impact on PTH levels, new molecules were developed: 22-oxacalcitrol, paricalcitol and doxercalciferol. Despite the beneficial effects on secondary parathyroidism, these new molecules seem not to improve bone mineralization[57]

Calcimimetics

Cinacalcet is a molecule that activates calcium sensing receptor, and it reduces PTH, FGF-23, phosphorus and calcium levels, inhibits parathyroid hyperplasia and controls bone mineralization[57,68]. Unfortunately there is still a lack of clinical trials in pediatric population with CKD in using calcimetics, and the effects of this molecules on growth and cardiovascular protection are still to be investigated[58].

Parathyroidectomy for secondary hyperparathyroidism

Surgical parathyroidectomy is "the definitive therapy to manage uncontrolled"[70] secondary hyperparathyroidism and it is considered only when all medical therapies have failed. There are not well defined indications for this surgical intervention, especially in children, since cinacalcet therapy is largely used[71]. Nevertheless, KDOQI guidelines recommend parathyroidectomy in severe cases of hyperparathyroidism (iPTH > 88mol/L) associated with hypercalcemia or hyperphosphatemia that are not responding to treatment, bone pathological fractures, vascular calcification or pruritus[63,70,71].

Discussion

Chronic kidney disease and mineral bone disorder is an important health problem, that affects an increasing number of pediatric patients, and has a powerful impact on child development and quality of life. New research bring to the front-line new molecules and hormones that are involved in mineral metabolism and cardiovascular health, new therapies are still undergoing clinical trials which makes us hopeful in treating this complex disorder. Also, an important thing to follow is starting more clinical trials in pediatric population, because there are striking differences between an adult organism and a growing one.

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