Review

Bone Disorders in Pediatric Chronic Kidney Disease: A Literature Review

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Review

Bone Disorders in Pediatric Chronic Kidney Disease: A Literature Review

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Simple Summary: Mineral and bone disorder (MBD) is usually prevalent in pediatric patients with chronic kidney disease (CKD) and is correlated with meaningful morbidity. CKD may cause disorders in bone remodeling/modeling, which are more evident in the growing skeleton, expressing as short stature, bone pain and deformities, fractures, slipped epiphyses and ectopic calcifications. Although evaluation of bone health is a crucial part in the clinical care of children with CKD, it persists as main challenge for paediatricians.

Abstract: Intense changes of mineral and bone metabolism are frequent in chronic kidney disease (CKD) and represent an important cause of morbidity and reduced quality of life. These disorders have conventionally been defined as renal osteodystrophy and classified based on bone biopsy, but due to a lack of bone biopsy data and validated radiological methods to evaluate bone morphology in children, it has been challenging to effectively assess renal osteodystrophy in pediatric CKD; the consequence was a suboptimal management of bone disorders in children. CKD-mineral and bone disorder (CKD-MBD) is a new expression used to describe a systemic disorder of mineral and bone metabolism as a result of CKD. CKD-MBD is a triad of biochemical imbalances of calcium, phosphate, parathyroid hormone and vitamin D, bone deformities and soft tissue calcification. This literature review aims to explore the pathogenesis, diagnostic approach, and treatment of CKD-MBD in children and the effects of renal osteodystrophy on growing skeleton, with a specific focus on the biological basis of this peculiar condition.

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1. Introduction

Chronic renal failure is defined by intense changes of the ordered metabolic sequences, which usually assurance cellular integrity and metabolic homeostasis [1].

The kidney plays a significant role in the regulation of calcium, inorganic phosphate, parathyroid hormone, calcitonin, and vitamin D metabolism. Adults and children with progressive loss of renal parenchyma suffer from modifications in bone metabolism with resultant osteodystrophy [2]. Renal osteodystrophy is the term used to delineate the bone morphology related with chronic kidney disease (CKD) [3]. It represents a variety of skeletal lesions that range from high-turnover conditions (osteitis fibrosa and mild lesions of secondary hyperparathyroidism) to low-turnover bone diseases (osteomalacia and adynamic lesions) [4].

In 2006, the KDIGO (Kidney Disease Improving Global Outcomes) have introduced the including term of chronic kidney disease-mineral and bone disorder (CKD-MBD) to describe this clinical entity [5]. MBD is the triad of biochemical abnormalities (of calcium, phosphate, parathyroid

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hormone (PTH) and 1,25-dihydroxyvitamin D), bone abnormalities (short stature, reduced mineralization, and increased risk of fractures) and extra-skeletal calcification [6].

Complications of CKD-MBD include vascular calcification, stroke, skeletal fractures, and increased risk of death. Increased FGF23 and PTH concentrations, and 1,25 dihydroxy vitamin D (1,25(OH)2D) deficiency, support the pathogenesis of CKD-MBD [7].

Due to the absence of bone biopsy data and validated radiologic methods to evaluate morphology of the bone, it has been difficult to adequately assess renal osteodystrophy in pediatric CKD. This has directed a suboptimal management of bone disorders in children.

This literature review aims to explore the pathogenesis, diagnostic approach, and treatment of CKD-MBD in children and the effects of renal osteodystrophy on growing skeleton, with a specific focus on the biological basis of this peculiar condition.

2. Methods and Results

We achieved a literature research of the past 15 years to find renal osteodystrophy related studies and reports; the following electronic databases were systematically searched: PubMed, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL).

The research strings were:

- Renal AND osteodystrophy
- Renal AND bone
- Bone mineral AND renal
- Bone disorder AND renal
- CKD-MBD AND children

Papers were only included in the present review if they focused on pediatric population (ranging from 0 month to 18 years old). Only English-written publications were included. The current investigation mainly concentrated on randomized placebo-control studies, but case-control studies, retrospective and prospective observational studies, and systematic reviews and meta-analysis were evaluated as well.

The article selection method was supported independently by three reviewers (LC, SF and LDS).

All significant articles discovered were further scrutinized for extra references not appeared in the preliminary examination.

Review or commentary papers without original data were eliminated, whereas their contents were used for clarification of collected information.

All papers not noticeably concerning osteodystrophy or CKD-MBD were similarly excluded.

The quality of the trials was thoroughly evaluated and the following potential biases have been assessed: random classification group (selection bias), similarity of patients at baseline concerning the most significant prognostic indicators (homogeneity bias), allocation hiding (selection bias), blinding of workers (performance bias), blinding of outcome valuation (detection bias), partial outcome data (attrition bias), evading of co-interventions (co-intervention bias), report of drop out (drop out bias).

A total of 50 papers were encountered in the literature search. Among them, after the application of inclusion and exclusion criteria, 42 papers were selected, while 8 papers were excluded.

2.1. Pathogenesis

The pathogenesis and natural hystory of CKD-MBD is mainly connected to secondary hyperparathyroidism [8]. Renal failure causes hypocalcaemia and hyperphosphatemia. The first one is due to reduced 1-alpha-hydroxylation of 25-hydroxyvitamin D, which leads to low intestinal absorption of calcium. Hypocalcaemia stimulates parathyroid glands to produce more PTH. On the other hand, reduced glomerular filtration rate (GFR) causes phosphate retention, which stimulates the osteocytes to secrete FGF23. These pathways lead to increase phosphaturia by PTH action on renal phosphate sodium co-transporter and mobilize calcium out of bone, affecting its mineralization

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[9]. Moreover, FGF23 inhibits WNT pathways, which contribute to bone degradation and consequent higher fracture risk [10].

In the last decade, new mechanisms and regulatory molecules have been identified, including alpha-Klotho, FGF-23 and its receptor, vitamin D receptors, sclerostin, Ca-sensitive receptors and decarboxylated osteocalcin, which have allowed us to shed greater light on the pathogenesis of CKD-MBD. While the "traditional" factors seem to become relevant only in the advanced stages of CKD, the new ones would already act in the early stages of kidney disease [11,12].

It is now believed that the first alteration in the initial stages of CKD-MBD is the increase in circulating levels of FGF-23; therefore, the dosage of this factor can represent an important marker for early identification of alterations in mineral and bone metabolism. It is not fully understood which is the first stimulus that induces an increase in FGF-23 levels. In the first instance it is believed that it follows (or is contextual) a reduction in the production of alpha-Klotho, a transmembrane protein that regulates the activation of FGF-23 receptors at the level of the target organs (kidney and parathyroid).and osteocytes, and whose levels modulate those of growth factor through a negative feedback mechanism. In the later stages of CKD, the progressive reduction of renal function is accompanied by a strong increase in FGF-23 levels, together with hyperphosphatemia, calcitriol deficiency and hypocalcemia. These mechanisms result in persistently elevated PTH values, usually seen when GFR values decrease below 50 mL/min/1.73 m^2 [8].

Blood calcium levels decrease not only as a consequence of calcitriol deficiency, but also of phosphate (P) retention and development of bone resistance to PTH action. Hypocalcemia represents an important stimulus to PTH secretion, mediated by calcium sensitive receptors (CaSR), highly expressed in parathyroid cells. However, over the long term, vitamin D receptors and CaSRs develop resistance to the stimulus, which can lead to hyperplasia of the parathyroid glands (tertiary hyperparathyroidism) in some patients.

Finally, although in the early stages elevated FGF-23 levels inhibit PTH secretion, keeping PTH levels low, it is believed that, in advanced stages of CKD, parathyroid cells become resistant to this stimulus.

These pathogenetic mechanisms lead to an alteration of the turnover, mineralization and bone volume, with consequent alterations of development of histomorphometric of the bone, responsible in childhood for poor growth and in adulthood for osteomalacia to fibrous osteitis. In particular, hyperparathyroidism increases bone turnover, mainly by inducing the expression of RANKL (Receptor Activator of Nuclear factor Kappa B Ligand) on the surface of osteoblasts, with consequent differentiation of the latter into osteoclasts. The simultaneous lack of calcitriol, causing a serious lack of bone mineralization, leads to the growth of bone with a reduced mineral mass and therefore more exposed to the risk of fractures.

Furthermore, it is recent knowledge that the maturation of the skeleton is accompanied by the development of muscle mass. In particular, it is believed that the latter anticipates bone development, representing a crucial element for bone health during childhood and adolescence (musculoskeletal axis).

Patients with CKD show muscle atrophy and weakness in 7-20% of cases, especially in the advanced stages of the disease. The resulting osteo-sarcopenia exposes them to a greater risk of fractures, disability and hospitalization. Again, vitamin D deficiency and elevated PTH levels have a negative effect on muscle. The effect is a marked reduction in muscle strength, currently well documented in children with CKD.

Furthermore, the inflammatory process increases muscle proteolysis and promotes the expression of myostatin (a factor limiting muscle growth). Anorexia, frequent in these subjects, contributes to the depletion of muscle mass [8].

2.2. New classification

Biochemical anomalies in the serum levels of phosphorus, calcium, PTH, and vitamin D lead to multiple bone alterations in patients with CKD. Both the laboratory modifications and the bone

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deformities contribute to vascular calcification [13]. All three of these processes are strictly connected and justify the significant morbidity and mortality in patients with CKD.

Traditionally, renal osteodystrophy has always been classified only according to a small subset of indicators associated with mineral and bone disorders in CKD as stated above. On the contrary, the modern definition should include all the following three main features: serum biomarkers, noninvasive imaging (in order to assess extra-skeletal calcification), and bone anomalies.

The KDIGO (Kidney Disease: Improving Global Outcomes) sponsored a summit in 2005 on the reconsideration of the current descriptive terminology for this pathophysiologic process [5]. The conference suggested that the term renal osteodystrophy be used solely to describe the abnormal bone disease, histologically documented, associated with CKD [14]. In order to diagnose renal osteodystrophy, the gold standard is represented by a bone biopsy, which also allows to properly classify this entity. Interestingly, the summit also stated that renal osteodystrophy should only be considered as one of the many elements referrable to a new clinical entity or syndrome named chronic kidney disease–mineral and bone disorder (CKD-MBD). In fact, the conference agreed that the definition of CKD-MBD should include elements of abnormal mineral metabolism, altered bone configuration and structure, and extra skeletal calcification documented with clinical, biochemical and imaging findings.

The early KDIGO guideline on CKD-MBD was then published in 2009 [15]. New evidence was then revised at the 2013 KDIGO Controversies Conference, and in 2017, KDIGO released a clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of CKD-MBD [16–18].

2.3. Abnormalities of bone in CKD

Bone remodeling is a physiologic process in both adults and children and disorders of mineral metabolism are related to abnormal bone [13].

As for macrostructure, skeletal deformity is frequent in children with CKD-MBD and is typical of rapidly growing bones. Therefore, rickets radiographically presents with slipped epiphyses and other deformities such as bow-legs and knock-knees [9,19]. In addition, the impaired quality of the bone in CKD is the major cause of hip fractures in patients undergone dialysis [13,20].

On the other hand, inadequate vitamin D supplementation, imbalance of serum calcium and phosphate and metabolic acidosis contribute to poor mineralization, with histologic findings of osteomalacia, typical of children affected by CKD-MBD [21].

Although bone biopsy is still considered the gold standard to diagnose CKD-MBD, its use is predominantly implicated just in clinical research, because of its invasive nature and the current incapability of pathology laboratories to interpret results [21].

In fact, before 1990, the most frequent skeletal lesion found at bone biopsy were the increased bone formation and osteoclast and osteoblast activity and number, characteristic of secondary hyperparathyroidism [21,22]. However, the use of phosphate binding agents and the iatrogenic reduction of PTH serum concentration have histologically led to adynamic bone, with low or normal bone formation rate and reduced number of osteoclasts and osteoblasts [23]. Currently different Authors are studying the clinical implications of this new histologic findings, which is still not clear [21].

2.4. Assessing bone mineralisation

In children with CKD it is necessary to assess a clinical history and achieve a physical examination to find CKD-MBD-related bone disease. The frequency of evaluation is based on the principal cause and stage of CKD, the age of the patient, the symptoms, the existence of comorbidities and level of abnormalities in previous CKD-MBD measures. More numerous assessment during periods of rapid growth in infancy and adolescence is needed (Table 1).

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Table 1. Suggested interval of clinical, biochemical, and radiological assessment (in months) of CKD-MBD in children by CKD stage and age.

Age	Assessments	Mild CKD	Moderate CKD	Severe CKD and dialysis
0-1 y	Clinical evaluation	1-3	0.5-2	0.25-1
	Biochemicals (Ca, P, HCO3-, PTH, ALP)	3-6	1-3	0.25-1
	Biochemicals (25OH)	6	3-6	3
	X-rays	Only if clinical signs	Only if clinical signs	Only if clinical signs
1-3 y	Clinical evaluation	3-6	1-3	0.5-2
	Biochemicals (Ca, P, HCO3-, PTH, ALP)	3-6	1-3	0.5-1
	Biochemicals (25OH)	6-12	3-6	3
	X-rays	Only if clinical signs	Only if clinical signs	Only if clinical signs
>3 y	Clinical evaluation	3-6	1-3	1-3
	Biochemicals (Ca, P, HCO3-, PTH, ALP)	6	3-6	1-3
	Biochemicals (25OH)	6-12	3-6	3
	X-rays	Only if clinical signs	Only if clinical signs	Only if clinical signs
Puberty	Clinical evaluation	3-6	1-3	1-3
	Biochemicals (Ca, P, HCO3-, PTH, ALP)	6	3-6	1-3
	Biochemicals (25OH)	6-12	3-6	3
	X-rays	Only if clinical signs	Only if clinical signs	Only if clinical signs

In children with CKD, further examinations to calculate linear growth rate are also needed; in particular, infants with CKD G2–G5D should have their length measured at least quarterly, while children with CKD G2–G5D should be evaluated for linear growth at least annually [13].

Biochemical markers show low sensitivity and specificity. As a marker of CKD-MBD, dosage of serum and ionized calcium, phosphate, alkaline phosphatase, PTH and 25(OH)D should be evaluated in children with CKD Stages 2–5D. Furthermore, it is necessary to monitor serum bicarbonate levels frequently and to maintain them within the normal range. The severity of anomalies, the age, signs and symptoms and concomitant treatments, and the stage and progression of CKD should define the frequency of monitoring the disease. Age-related normal ranges of serum calcium, phosphate, alkaline phosphatase and CKD stage dependent PTH target ranges should be considered in the identification and management of bone disease in pediatric CKD.

Age-dependent normal values for different markers of bone and mineral metabolism and CKD stage-dependent PTH target ranges proposed by international guideline committees are based on CALIPER study [18,24,25].

The 2017 KDIGO guidelines recommended examining serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity at the beginning of CKD G3a. In children, they suggested this checking beginning in CKD G2. They stated to use trends in PTH rather than absolute 'target' values to guide therapy as to start or stop treatments to lower PTH. If trends of PTH are inconsistent, a bone biopsy may be contemplated.

Bone imaging and histology are variably used to assess bone disease in CKD, but there are limited evidence-based studies to encourage their use in routine clinical practice.

Conventional X-rays can only roughly assess radiological findings, such as bone mineralization. Those children affected by bone pain, doubted atraumatic fractures and genetic diseases with a documented bone involvement should be assessed with this exam.

DXA, Peripheral Quantitative Computed Tomography (pQCT), High-Resolution peripheral Quantitative Computed Tomography (HR-pQCT), Magnetic Resonance Imaging (MRI) and

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ultrasound are remarkable for researches [7,26], but there is no evidence to mention them as routine screening exams for bone health or evaluation of fracture risk in pediatric CKD patients.

The 2009 KDIGO CKD-MBD guideline noted that DXA BMD does not differentiate among categories of renal osteodystrophy. Furthermore, no findings have assessed the connection between DXA results and fractures, and so the KDIGO 2017 update does not offer specific recommendations for DXA use in children [18].

Table 2. Comparing bone imaging techniques in children with CKD-MBD.

	Plain radiography	**DXA**	**QCT, pQCT and HR-pQCT**	**MRI**	**US**
Main evaluated parameters	Gross evaluation of mineralization	Bone mineral density and body composition	Bone microarchitecture, biomechanics and volumetric mineralization; prediction of fracture risk	Bone microarchitecture, volumetric mineralization and soft tissue evaluation (bone muscle unit)	Cortical bone evaluation
Skeletal site	All skeleton	Hip, distal radius, lumbar spine, all skeleton	Hip, distal radius, distal tibia	Distal radius, distal tibia, calcaneus, hip, spine, all skeleton	Tibia
Availability	++++	++++	++	++	+++
Cost	+	+	++	+++	+
Radiation exposure	Yes	Yes, minor	Yes, minor	No	No
Presence of reference data	Present	Present	Present	Absent	Absent
Main concerns	Observer dependent interpretation, bidimensionality, low sensitivity	Bidimensionality, underestimation of mineralization, low resolution, difficult follow up of growing bones	No consensus regarding the drawing of the reference line and main regions of interest	No consensus regarding the main regions of interest	Operator dependent

The advice to execute a bone biopsy is based on the prospect it may modify treatment and the choice to administer antiresorptive therapy. Since this is infrequently, if ever done in children with CKD, the role of bone biopsies remains debatable [27].

According to the literature, a bone biopsy is suggested in those cases where laboratory and clinical results do not confirm an underlying osseous disease. Given the complex interpretation of the specimens, it should be considered to send the samples to experienced centers for a proper histomorphometric assessment. In fact, a proper diagnosis is mandatory in order to let the physician tailor a specific therapeutic strategy for the patient [24].

2.5. Cardiovascular manifestations and vascular calcification

Cardiovascular disease is the major cause of mortality in CKD [28]. The intricate nature of renal, bone, and cardiovascular diseases was retitled as mineral and bone disorder of chronic kidney disease to comprehend how bone disease drives vascular calcification and concur the development of long-term cardiovascular complications. Recent data suggest that a good management of the bone disease can increase and improve cardiovascular disease status [29].

Patients with CKD showed an increased risk of coronary artery disease due to calcium deposition and consequent arterial stiffening, in addition to left ventricular dysfunction with

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concomitant heart failure and arrhythmias. Children and young adults with CKD or on dialysis mature vascular calcification even as BMD rises, with the most significant vascular alterations in young people with no linear growth [30].

While evidently affected by the traditional risk factors for development of cardiovascular disease, patients with CKD are also disturbed by non-traditional risk factors, including calcium overloading related to a forceful management of secondary hyperparathyroidism [31].

Recent data have shown that a considerable number of patients with CKD are lacking of vitamin D on a nutritional basis, in addition to the known decrease in the kidney-produced active metabolite during progressive CKD. Vitamin D analogues are central in cardiovascular health. Pilot studies suggest that vitamin D therapy for secondary hyperparathyroidism may confer a cardiac protection and decrease mortality. Attention to osteodystrophy care in chronic kidney disease should also include heart health [32].

Furthermore, there is an amplified risk of obesity and metabolic syndrome among kidney transplant beneficiaries, which negatively affects cardiovascular and renal outcomes in these patients.

Cardiometabolic risk factors are usual in pediatric kidney transplant recipients. Approximately one-fifth of patients have metabolic syndrome, and left ventricular hypertrophy is much more common among patients with metabolic syndrome [33–35].

2.6. Diagnosis and management of mineral and bone disorders in infants under 2 years with CKD

During the first years of life, the need for calcium (Ca) and phosphate (P) is particularly elevated and infants with CKD are specifically at risk of developing mineralization and/or ossification disorders. In this context, achieving an adequate balance is a complex process, especially due to rapid bone growth and possible nutritional issues [4,36].

In fact, infants affected by CKD exhibit persistent abnormal creatinine levels above the 97.5th percentile in the first 12 months of life and an estimated glomerular filtration rate (eGFR) < 90 mL/min per 1.73 m2 by the Schwartz formula [37,38].

Given the complexity of the diagnostic process, a step-by-step approach is suggested and here described.

The first evaluation is a clinical one, which is performed systematically assessing height, weight and head circumference and comparing them with the centile growth charts. Clearly, also the corrected gestational age, CKD stage, comorbidities and the MBD severity have to be recorded.

The latter should also be kept in consideration in the subsequent step, that is the evaluation of CKD-MBD biochemical markers, which are: Ca, P, ALP, PTH, 25(OH)D, HCO3. Management is not established on an individual laboratory value, but on all available CKD-MBD markers. Biomarkers' evaluation has a double meaning, as they can be used both as a diagnostic tool and as a therapeutic target, which is different according to the specific marker. In fact, it is essential to maintain serum Ca, P, alkaline phosphate, and HCO3 within the age-related normal ranges in this age group. Regarding PTH levels, they have to be maintained within the CKD-stage related target ranges. Finally, it is recommended the maintenance of 25(OH)D within the target range reported in older children.

Clinical and biochemical evaluations are easily accessible and thus should be frequently re-evaluated, adjusting the therapy. In particular, we did already mention the possible difficulties of food intake, thus diet plays a key-role in the maintenance of the corrected calcium and phosphate intake.

It is necessary to regularly evaluate the dietary intake of calcium and phosphorus in newborns with CKD, maintaining the resulting levels within the limits of the recommended dietary intake (SDI) in infants with CKD. A low-phosphate diet should not compromise protein or calcium intake, adding phosphate binders if necessary.

The nutritional values of premature newborns can be used as an indication to modulate the diet of premature newborns suffering from CKD. As with premature infants, full-term infants with CKD also require vitamin D supplementation from birth, maintaining serum 25(OH)D levels within a target range of 75-120 nmol/L. Recommendations in this specific age group suggest taking the lowest dose of active vitamin D analogues orally to achieve normal calcium and PTH concentrations.

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If elevated PTH values persist, recommendations indicate oral calcium supplementation. Acute hypocalcemia should be managed with intravenous calcium at all ages. In case of hypercalcemia, sevelamer carbonate should be considered and, in case of persistent hyperphosphatemia, supplementation with P 350 after optimizing dietary phosphate intake. Phosphate supplementation is essential in newborns with CKD, modulating their dietary intake, without compromising total protein intake. If serum phosphate is not controlled despite appropriate dietary adjustments, it is recommended to start therapy with phosphate binders.

In infants on dialysis, recommendations suggest increasing dialysate calcium concentrations to preserve calcium serum concentrations. It is also indicated to optimize dialysis in infants with persistently uncontrolled secondary hyperparathyroidism and/or hyperphosphatemia. In this group of patients, if severe and persistent hyperparathyroidism is found, with normal or elevated calcium levels despite optimization of the diet or supplementation with vitamin D, Cinacalcet is recommended with caution.

While clinical and biochemical evaluations do not put at risk these young patients, the topic of radioprotection has to be carefully approached in the diagnostic evaluation of infants with CKD. In fact, plain X-rays are only recommended when the physician has a clinical doubt of rickets or other osseous anomalies and they should not be routinely prescribed. Case-by-case evaluations should be made regarding infants with genetic diseases and their need for radiological monitoring in case of bone disturbances.

Finally, a parathyroidectomy might be considered when all medical management of secondary hyperparathyroidism have failed [39].

2.7. Treatment

The prevention and the treatment of secondary hyperparathyroidism, with a good balance of phosphoremia and calcemia, is the principal aim of CKD-CMD therapy [8].

As for phosphate, free-calcium binders, such as sevelamer, are currently the first choice for pediatric patients affected by renal failure when dietary regimen is not sufficient, but also calcium carbonate and calcium acetate are frequently used, with special monitoring of serum calcium concentration [21]. Besides, magnesium-based compounds are not frequently used use in paediatric CKD because of the risk of hyperkalemia, hypermagnesemia and diarrhea. Although aluminum comprehending agents are active in binding phosphorus, they have been limited because of cumulative bone marrow, skeletal and central nervous system toxicity [21].

The use of calcimimetic such as cinacalcet in order to reduce PTH secretion is partially limited due to the few available evidence about its use in children with chronic renal failure [40,41].

Finally, vitamin D supplementation is really important in this population, as its deficiency contributes to CKD-MBD progression. Recent guidelines suggest administering vitamin D analogues (ergocalciferol or cholecalciferol) in children with CKD 2-5D who have persistently increased serum PTH concentrations [42] when serum 25(OH) D levels are below 30 ng/ml [8]. Active vitamin D analogues (calcitriol, alfacalcidol, paricalcitol or doxercalciferol) should be used in case of serum PTH above target range and serum 25(OH)D over 30 ng/ml, with contextual absence of hypercalcemia and hyperphosphatemia [8]. Daily oral calcitriol is secure and well tolerated by these patients, with a low incidence of consequent hypercalcemia [42]. Different Authors agree that vitamin D analogues should be administered in the lowest dose to achieve target PTH concentrations and maintain normal serum calcium concentration, performing monthly controls of blood PTH, calcium and phosphate in the first three months and every 3 months thereafter [42]. Clinicians should start with an intensive replacement phase of three months and a subsequent maintenance phase. The treatment should be discontinued when 25(OH) D concentration is over 48 ng/ml or if the child is hypercalcemic [8,42].

Conclusions and Future Perspectives

Pediatric CKD is a vigorous and multifaceted disease with exclusive aspects that diverge this population from adults. Due to rapid bone growth and efforts with nutrition, an acceptable control of CKD-MBD in infants is especially challenging.

The pediatric nephrology research group did estimable and exhilarating efforts in concentrating on this group, and evidence-based management of this population is growing, but for now there are still very few high-quality findings to guide evidence-based practice.

In future, it may be necessary to define the targets for the principal biomarkers in this age group in case of CKD, especially PTH, 25(OH)D, and ALP. Studies to establish the true calcium necessities in infants for optimal bone quality and without a risk of vascular calcifications are needed. Evaluating the incidence and risk factors for fractures in children with CKD and on dialysis is crucial. Moreover, it would be important to detect the required quantity of Ca intake and the best PTH target range, which consent normal turnover and mineralization (determined by histology, imaging and biomarker studies) without deteriorating vascular calcifications. More data to establish if urinary calcium excretion in healthy infants and those with CKD can be used to estimate optimal calcium intakes are necessary. Evaluate the importance of cortical bone assessment in bone biopsy cores to expect fracture risk and evaluate the sensitivity and specificity of DXA to predict fracture risk in pediatric CKD would be crucial in the future. Further investigations are also required to find novel CKD-MBD serum biomarkers, that would allow a more precise indirect evaluation of bone histomorphometry, cell maturation and skeletal mineralization. At the same time, innovative techniques should be addressed to the assessment of osseous qualitative and biomechanical properties, such as microarchitecture, accumulated microscopic damage and the quality of collagen and the size of mineral crystals.

Finally, our understanding of a link between mineral disturbances and vascular calcification in CKD requires further study. An important issue for future research is to find a balance of calcium and phosphate intake in young patients, in order to optimize skeletal mineralization while reduce the risk of vascular calcification due to excessive calcium intake. An accurate estimation of the real-time changes in bone mineral balance may guide treatments based on the individual's state of bone turnover and mineralization.

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