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The consequences of chronic kidney disease on bone metabolism and growth in children

Justine Bacchetta[1,2,3], Jérôme Harambat[4], Pierre Cochat[1,2], Isidro B. Salusky[5] and Katherine Wesseling-Perry[5]

[1]Centre de Référence des Maladies Rénales Rares, Service de Néphrologie et Rhumatologie Pédiatriques, Hôpital Femme Mère Enfant, Bron, France, [2]Université de Lyon, Lyon, France, [3]Institut de Génomique Fonctionnelle de Lyon (IGFL), Ecole Normale Supérieure, Lyon, France, [4]Unité de Néphrologie Pédiatrique, Hôpital Pellegrin et Université de Bordeaux, Bordeaux, France and [5]Department of Pediatrics, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA

Correspondence and offprint requests to: Justine Bacchetta; E-mail: justine.bacchetta@chu-lyon.fr

Abstract

Growth retardation, decreased final height and renal osteodystrophy (ROD) are common complications of childhood chronic kidney disease (CKD), resulting from a combination of abnormalities in the growth hormone (GH) axis, vitamin D deficiency, hyperparathyroidism, hypogonadism, inadequate nutrition, cachexia and drug toxicity. The impact of CKD-associated bone and mineral disorders (CKD–MBD) may be immediate (serum phosphate/calcium disequilibrium) or delayed (poor growth, ROD, fractures, vascular calcifications, increased morbidity and mortality). In 2012, the clinical management of CKD–MBD in children needs to focus on three main objectives: (i) to provide an optimal growth in order to maximize the final height with an early management with recombinant GH therapy when required, (ii) to equilibrate calcium/phosphate metabolism so as to obtain acceptable bone quality and cardiovascular status and (iii) to correct all metabolic and clinical abnormalities that can worsen bone disease, growth and cardiovascular disease, i.e. metabolic acidosis, anaemia, malnutrition and 25(OH)vitamin D deficiency. The aim of this review is to provide an overview of the mineral, bone and vascular abnormalities associated with CKD in children in terms of pathophysiology, diagnosis and clinical management.

Keywords: bone; chronic kidney disease; growth; paediatrics; vascular calcifications

Introduction

Growth retardation, decreased final adult height and renal osteodystrophy (ROD) are common complications of childhood chronic kidney disease (CKD), resulting from a combination of factors, such as resistance to growth hormone (GH), modifications of the GH-insulin-like growth factor type 1 (IGF1) axis, vitamin D deficiency, hyperparathyroidism, hypogonadism, malnutrition and drug toxicity (corticosteroids, calcineurin inhibitors) [1, 2]. Not only do these complications impact overall quality of life through their effects on both physical and mental well-being in children with CKD, but also alterations in mineral metabolism and bone disease are linked to cardiovascular disease, contributing to a significant decrease in life expectancy.

Reflecting the complex interplay between bone disease, mineral metabolism and cardiovascular disease in patients with renal dysfunction, the CKD mineral and bone disorder (CKD–MBD) is a term used to describe one or a combination of the following: (i) abnormalities of calcium, phosphorus, parathyroid hormone (PTH) or vitamin D metabolism, (ii) abnormalities in bone histology, linear growth or strength and (iii) vascular or other soft tissue calcification [3]. The impact of CKD–MBD in children may be immediate (biological disequilibrium of calcium/phosphate/vitamin D metabolism determinants) or delayed (growth retardation, CKD–MBD, fractures, vascular calcifications, increased morbidity and mortality) [4]. In contrast, the term ROD currently refers specifically to the different bone lesions as defined by bone histomorphometry. The bone and growth consequences of CKD have been highlighted in a cohort of 249 young Dutch adults with onset of end-stage renal failure before the age of 14 years: in this cohort, 61% of patients had severe growth retardation, 37% severe bone disease (as defined by at least one of the following conditions: deforming bone abnormalities, chronic pain related to the skeletal system, disabling bone abnormalities, aseptic bone necrosis and low-traumatic fractures) and 18% disabilities resulting from bone impairment [5]. In addition, evidence of vascular calcifications has been demonstrated in young adult dialysis patients with ESRD therapy initiated in childhood [6, 7].

The aim of this review is therefore to provide an overview of the mineral, bone and vascular abnormalities associated with CKD in children in terms of pathophysiology, diagnosis and clinical management.

Physiology of normal growth and bone formation

Linear growth is a unique feature of childhood, occurring through the modelling of new bone by skeletal accretion and longitudinal growth in the growth plate. In this process, chondrocytes play a key role, as well as GH [8, 9]. One-third of the total growth occurs during the first 2 years of life, on a primarily nutrition-dependent basis [8]. Later childhood is marked by a lesser, although constant, growth velocity (5–7 cm/year), driven primarily by the actions of GH and thyroid hormone. At the onset of puberty, oestrogen and testosterone induce a second increase of growth velocity. During growth, the epiphyseal cartilage goes through a process of progressive maturation, and when no additional epiphyseal cartilage remains to provide further long bone growth, bone fusion occurs between the shaft and the epiphysis, ending the linear growth process [10].

GH, also termed 'somatotropin', is a 191-amino acid hormone with anabolic effects on multiple tissues including stimulation of body growth and protein synthesis and modulation of the carbohydrate, lipid and protein metabolism [10]. GH is the key endocrine factor regulating post-natal growth: the pulsatile release of GH by the somatotrope cells of the anterior pituitary gland is stimulated by the hypothalamic GH-releasing hormone and regulated by several other factors [10]. GH has a short half-time in blood (<20 min); therefore, the effects of GH on almost all tissues of the body, are mediated primarily through hepatic intermediate substances (somatomedins) including somatomedin C (or IGF1), although, in mouse models, GH itself has been shown to have some direct actions on pubertal skeletal development, as well [11]. IGF1 is also an anabolic hormone; it is transported in plasma bound to six different IGF-binding proteins (IGFBP) to increase its half-life and exerts its biological effect when binding to its specific tyrosine kinase receptor (IGF1-R) [8]. In healthy children, the most prevalent IGFBP is IGFBP3, accounting for 75% of the circulating IGFs [8].

Bone formation in children occurs by two distinct mechanisms: the first one is similar to that observed in adults (i.e. skeletal remodelling of existing mineralized tissue that is controlled by osteoclasts and osteoblasts), whereas the second one is specific to the paediatric population (i.e. modelling of new bone by skeletal accretion and longitudinal growth from the growth plate, through the action of chondrocytes) [9]. The growth plate is an avascular tissue between the epiphyses and metaphyses of long bones; endochondral bone formation corresponds to its progressive replacement by bone. The regulation of this process is complex, with a key role for GH and the PTH/PTH-related protein-receptor (PTHrP) axis [12]. GH exerts at least four main actions on the growth plate: (i) an increased local production of IGF1 that will later acts in a paracrine manner to stimulate the clonal expansion of proliferating chondrocytes, (ii) a positive effect on cellular differentiation, converting chondrocytes into osteogenic cells, (iii) an increased rate of cellular proliferation and (iv) an increased deposition of proteins by the chondrocytic and osteogenic cells, leading to further bone growth [10, 12].

Changes in mineral metabolism with progressive CKD

Since bone consists primarily of calcium and phosphorus, in the form of hydroxyapatite, it is not surprising that alterations in mineral metabolism, as occur with progressive CKD, lead to bone disease. The earliest biochemical abnormality in CKD is an increase in circulating fibroblast growth factor 23 (FGF23) levels [13]. FGF23, in conjunction with its co-receptor, Klotho, activates FGF receptor 1 (FGFR1) and acts on the kidney to induce renal phosphate wasting and to suppress renal 1α-hydroxylase activity. FGF23 also acts on the parathyroid gland and may play a role in suppressing PTH levels [14]. FGF23 is stimulated by phosphate and $1,25(OH)_2$vitamin D and, in both adults and children, and FGF23 increases as glomerular filtration rate (GFR) decreases, with elevations in circulating concentrations occurring in very early stages of CKD, prior to any apparent alterations in circulating mineral content [15, 16]. This increase could be explained by different factors, including a decreased renal clearance of FGF23, a compensatory mechanism to excrete an increased phosphate load, a response to treatment with active vitamin D analogues, and/or a compensatory mechanism to the loss of the kidney-secreted Klotho protein. Although these increased circulating levels of FGF23 in patients with CKD consist almost exclusively of the intact, active form of the molecule [17], it is not clear whether the biological effects of FGF23 are increased or decreased in the context of decreased kidney function [18, 19]. Indeed, decreased expression of FGFR1 and Klotho in parathyroid cells from dialysis patients and a resistance to the suppressive effects of FGF23 on PTH in uraemic rats suggest that parathyroid gland FGF23 signalling pathway is downregulated in both animals and humans with CKD observations which may explain, at least in part, the refractory secondary hyperparathyroidism observed in CKD patients [20–22]. On the other hand, as FGF23 levels increase, tubular phosphate reabsorption increases and $1,25(OH)_2$-vitamin D synthesis decreases, suggesting that FGF23 signalling remains intact in the kidney.

Subsequently, abnormalities in other parameters of mineral metabolism progressively appear. During mild CKD (stages 2 and 3), calcitriol levels decline in response to increased FGF23 concentrations. Since calcitriol suppresses PTH secretion, declining $1,25(OH)_2$vitamin D levels are followed, in moderate (stages 3 and 4) CKD, by increasing PTH concentrations and by loss of pulsatility in PTH secretion [23]. Ultimately, in late stage 4 CKD, hypocalcaemia and hyperphosphataemia develop in response to decreased intestinal calcium absorption (from critically low calcitriol concentrations) and decreased phosphate excretion (from critically low renal mass), respectively [13]. Finally, 25(OH)vitamin D deficiency, which is prevalent worldwide, likely also contributes to the development of secondary hyperparathyroidism. Patients with CKD are particularly prone to 25(OH) vitamin D deficiency (currently defined by values below 30 ng/mL or 75 nmol/L), due to several combined factors including decreased sunlight exposure, relative scarcity of

vitamin D in occidental diets, lack of supplementation in vitamin D due to the current underestimation for recommended daily intake and increased body fat mass in populations [24]. Recent data from four studies in children have documented a 40–77% prevalence of 25(OH) vitamin D deficiency/insufficiency in children with CKD [25]. In addition to providing a substrate for the formation of calcitriol, thus indirectly suppressing PTH levels, Ritter *et al*. [26] recently identified that 25(OH)vitamin D continues to directly suppress PTH synthesis even when parathyroid gland 1alpha hydroxylase is inhibited, thus demonstrating a direct effect of 25(OH)vitamin D on PTH synthesis, independent of $1,25(OH)_2$vitamin D. Moreover, a recent placebo-controlled randomized trial demonstrated that ergocalciferol was able to delay the onset of secondary hyperparathyroidism in paediatric patients with predialysis CKD [27]. 25(OH)vitamin D likely also has a direct effect on bone biology, independent of its effects on mineral metabolism; indeed, Priemel *et al*. [25] demonstrated in a cohort of 675 deceased adults that pathological mineralization defects could occur when the serum 25(OH) vitamin D level was below 30 ng/mL. New roles of vitamin D in global health have also recently been highlighted: vitamin D may represent a protective factor against infections, autoimmune diseases, cardiovascular diseases and cancer [28].

The impact of altered bone metabolism on growth in children with CKD

Growth retardation in CKD

In paediatric patients with CKD, growth failure develops early in the course of CKD and affects up to 35% of this population; by the time of renal transplantation, a significant proportion of children present with severe short stature [29–32]. The aetiology of this poor growth is multifactorial and includes both potentially modifiable factors (e.g. protein and calorie malnutrition, anaemia, metabolic acidosis, hypothyroidism and salt wasting) and less modifiable factors such as abnormalities in the GH–IGF1 axis, resistance to GH, ROD and therapies [31, 33, 34]. However, despite the correction of these factors, many children with CKD continue to grow poorly [33]. Altered GH metabolism and organ resistance to GH have been implicated as major contributors to growth retardation in CKD, as summarized in Table 1 [8, 35–38]. In teenagers with CKD, the loss of the pulsatile release of the gonadotropin-releasing hormone also explains the delay and the shortening of the pubertal growth spurt, in association with a reduced growth velocity [8].

The contribution of ROD to growth failure

Bone evaluation in CKD children remains challenging [1] since (i) the metabolism of bone biomarkers is not well known during CKD, with an accumulation of most of bone biomarkers as GFR decreases [39, 40]; (ii) bone biomarkers vary according to age and gender in a paediatric population [41]; and (iii) the only bone imaging technique that is widely available (i.e. dual X-ray absorptiometry or DXA) is a poor metric for assessing bone status in CKD, as recently discussed in international paediatric guidelines [42, 43]. However, childhood and adolescence are critical periods for bone mass gain since about 90% of peak bone mass is acquired before the age of 18 years and a decreased peak bone mass may induce an increased risk of fractures and osteoporosis during adulthood [44]. Bone biopsy from the anterior iliac crest after double-tetracycline labelling (10–15 mg/kg per day, taken orally three times a day during two 2-day periods separated by a 12-day free interval) remains the reference standard to evaluate bone status in CKD patients [45]. Even though it is rarely performed in clinical practice, it is the only available technique leading to an accurate evaluation of ROD [46]. Histomorphometry allows the diagnosis of the different skeletal lesions of ROD [47]; some reference values established in children with normal renal function have been described [48, 49]. In all cases, histomorphometric results should be reported using the terminology established by the Nomenclature Committee of the American Society for Bone and Mineral Research [50], and by the TMV classification system established by the KDIGO

Table 1. The impairment of the GH/IGF1 axis in CKD children

Type of impairment	Mechanism
GH metabolism	High normal GH secretion rate (attenuated IGF1 feedback and increased number of GH secretory bursts) Decreased serum levels of free GH (normal to elevated levels of circulating GH but increased binding proteins) Increased half-life of GH (decreased metabolic clearance)
Skeletal resistance to GH	Decreased receptor expression in target organs (mainly the liver)[a]
Cellular resistance to GH	Defect in the post-receptor GH-activated JAK/STAT pathway(up-regulation of SOCS pathway) inducing a decreased expression of downstream genes (mainly IGF1)
IGF1 metabolism	Normal serum IGF1 levels (decreased in end-stage renal disease) but decreased free bioactive IGF1 Increased circulating levels of inhibitory IGFBP (IGFBP1, IGFBP2, IGFBP4, IGFBP6) Normal circulating levels of stimulatory IGFBP (IGFBP3) Net decrease in IGF1 bioactivity, and further decreased IGF1-receptor activation
Cellular resistance to IGF1	Resistance to the post-receptor signal transduction inducing a decreased tyrosine kinase activity

[a]Since the GH-binding protein is a cleaved product of the GH receptor and since its serum level correlates with spontaneous growth rate and response to GH therapy, it has been hypothesized that it could be an indirect indicator of GH sensitivity, but there are still controversies concerning its potential use as a marker of GH receptors at the tissue level.

Table 2. The spectrum of ROD according to the TMV classification [51]

	Turnover	Mineralization	Volume
Osteomalacia (OM)	Low	Abnormal	Low to normal
Adynamic bone (AD)	Low	Normal	Low to normal
Mild hyperparathyroid related bone disease (HPT)	Mild	Normal	Normal to high
Mixed uraemic osteodystrophy (MUO)	High	Abnormal	Normal
Osteitis fibrosa (OF)	High	Normal	High

working group to specifically define ROD [51], as summarized in Table 2 [52].

ROD is characterized by alterations in bone turnover, mineralization and volume; these three components should be evaluated independently to characterize the different subtypes of ROD, as defined by the K-DIGO in 2006 and summarized in Table 2 [51]. High bone turnover (secondary hyperparathyroidism, *osteitis fibrosa cystica*) is the primary skeletal lesion of paediatric ROD, and is present in virtually all untreated incident paediatric dialysis patients. This lesion is caused by a long-term exposure to high serum PTH levels and $1,25(OH)_2$vitamin D deficiency. In contrast, low-turnover lesions (i.e. adynamic bone disease) may occur as a result of excess treatment with vitamin D analogues and calcium salts and are characterized by low PTH and alkaline phosphatase levels as well as high serum calcium levels. Low bone turnover has been associated with an increased risk of vascular calcifications, fractures and more severe growth retardation [3, 53].

Defects in skeletal mineralization are also prevalent in paediatric patients with CKD—occurring in 30% in stage 2 CKD and increasing in prevalence as CKD progresses, even though bone turnover remains normal in the earliest CKD stages and becomes apparent while GFR decreases [13]. Nearly 80% of dialysis patients display some defect in skeletal mineralization, a problem that is not corrected by traditional therapy with vitamin D sterols and phosphate binders [54]. Although alterations in skeletal mineralization (i.e. rickets) contribute to increased fracture rates, bone deformities and growth retardation in children with normal renal function, their exact role in these clinical symptoms in children with CKD, remains to be elucidated [3]. In contrast to bone turnover and mineralization, assessment of bone amount and structure are best assessed via imaging techniques [55]. Although widely used in paediatric populations, the areal measurement of bone mineral density (BMD) by DXA has three major limitations in paediatric CKD populations: (i) its reliance on areal density rather than volumetric density that can be modified only by growth; (ii) its inability to distinguish between trabecular and cortical bone that can be independently damaged in CKD; and (iii) its inability to evaluate trabecular microarchitecture whereas it is a strong determinant of bone quality [39, 43]. In contrast, new imaging techniques, including bone magnetic resonance imaging or high-resolution peripheral quantitative computed tomography have led to an improvement in bone evaluation with an assessment of both compartmental volumetric densities and trabecular microarchitecture [56–58]. These bone imaging devices are particularly challenging in children, whose bones continually grow in size, shape and mass [59]; however, they present several advantages, namely, safety and low radiation exposure. At this time, these techniques are not widely available and their exact role in paediatric CKD patients remains to be defined [60–64].

Clinical management of growth retardation in children with CKD

Control of ROD

In clinical practice, the recent guidelines on abnormalities of bone and mineral metabolism in CKD have established that a regular monitoring of calcium, phosphorus, PTH and alkaline phosphatase should be performed at regular intervals [65]. Since both adynamic bone and severe hyperparathyroidism increase the severity of growth retardation [3], current guidelines suggest that serum PTH and bone-specific alkaline phosphatase values be used for the evaluation of bone disease (KDIGO guidelines, evidence 1C in adults and 2D in children), with serum PTH values kept within a range appropriate to the stage of CKD [66]. Unfortunately, PTH values are poor predictors of ROD, likely due to a combination of factors including the development of end-organ resistance to the hormone as CKD progresses and an accumulation of PTH fragments as renal function declines [67]. Thus, a bone biopsy should be performed for the following indications: unexplained fractures, persistent bone pain, unexplained hypercalcaemia, possible aluminium toxicity and before bisphosphonates therapy [65]. Table 3 summarizes the targets of PTH serum levels according to the different stages of CKD, according to the 2009 KDIGO international guidelines [65]; however, optimal targets depend on the geography [68] and are notably different between Europe and America [34]. Indeed, European paediatric nephrologists are prone to accept lower levels of PTH (i.e. not above two times the upper normal limit), [69] noting that PTH is an independent risk factor for myocardial fibrosis, arteriolar thickening and hypertension both in adults [70] and in children treated with maintenance dialysis [71]; they have reported no negative impact on growth with these values [72]. A consensus on the optimal target for PTH levels depending on the different CKD stages is therefore impossible to determine at the current time; however, optimal growth and normal phosphorus/calcium/25(OH) vitamin D levels should be the primary targets of daily management of CKD–MBD in children.

Current guidelines for managing CKD–MBD in adults consist in decreasing high circulating phosphorus levels maintaining calcium levels, and controlling secondary hyperparathyroidism [65]. Decreased phosphate intake and phosphate binders are used to control serum phosphate and calcium concentrations. Currently, calcium-containing salts are the most widely available and used phosphate

Table 3. PTH serum levels according to the stage of CKD—adapted from the 2009 international KDIGO guidelines[a] [102]

CKD stage	GFR	Target of PTH serum levels	Therapeutic modalities for decreasing PTH serum levels
I	>90	Within the normal levels for the assay.	
II	60–89		
III	30–59	Optimal level not known	If PTH serum levels are above the upper normal limit of the assay, the following therapeutic steps can be proposed:
IV	15–29	If PTH serum levels above the upper	To decrease nutritional phosphorus intake;
V	<15	normal limit of the assay, a screening for hyperphosphataemia, hypocalcaemia and 25(OH) vitamin D deficiency should be performed	To introduce a phosphate binder, calcium supplements and/or native vitamin D If PTH serum levels remain above the target after these corrections, calcitriol or vitamin D analogues should be introduced. If all these measures fail, a parathyroidectomy should be discussed.
V-D	Dialysis	To maintain PTH serum levels in the range of approximately two to nine times the upper normal limit for the assay.	If PTH is above this target, treatment with calcitriol or vitamin D analogues or calcimimetics or a combination of both should be initiated. If all these measures fail, a parathyroidectomy should be considered.

GFR, glomerular filtration rate (mL/min per 1.73 m^2).
In all cases, marked changes in PTH levels in either direction within the range should prompt an initiation or change in therapy to avoid progression to levels outside the target range.
In patients with hypercalcaemia, vitamin D analogues or calcitriol should be decreased or stopped.
[a]Lower PTH targets are suggested by the European Guidelines.

binder in children, although calcium-free, preparations have recently been introduced. Notably, sevelamer hydrochloride has been shown to be a safe and effective phosphate binder, controlling both the skeletal lesions associated with hyperparathyroidism and vascular calcifications. Indeed, fewer episodes of hypercalcaemia have been demonstrated in patients receiving sevelamer [73], thus improving the margin of safety for active vitamin D sterol use in a randomized trial in children undergoing peritoneal dialysis [74]. However, sevelamer hydrochloride has also been associated with a worsening of metabolic acidosis in a dose-dependent manner in a mixed cohort of 44 German children with different stages of CKD and a proportion of them treated with dialysis [75]. More recently, a prospective study has shown that sevelamer carbonate may be a safe and effective phosphate binder and results in less metabolic acidosis in paediatric dialysis patients [76].

25(OH)vitamin D supplementation and active vitamin D analogues are used to decrease PTH circulating levels [65]. Current guidelines suggest that increased PTH levels, in the face of 25(OH)vitamin D insufficiency/deficiency (defined as a value <30 ng/mL) be first treated with 25(OH)vitamin D supplementation. A recent randomized, controlled trial has validated this recommendation, demonstrating a delayed onset of secondary hyperparathyroidism in children with CKD receiving therapy for 25(OH) vitamin D deficiency [27]. Following 25(OH) vitamin D repletion, active vitamin D sterols should be initiated to control serum PTH values. A recent (2010) Cochrane meta-analysis emphasized the paucity of long-term data on the relative safety and efficacy of different active vitamin D sterols for the treatment of secondary hyperparathyroidism in children; however, PTH levels have been shown to decrease similarly with all preparations [73]. Moreover, one randomized, controlled trial demonstrated equivalent suppression of PTH levels and bone turnover with both calcitriol and doxercalciferol, suggesting that both formulations are equivalent for the control of secondary hyperparathyroidism [54]. Although vitamin D sterols are currently the mainstay of therapy for elevated PTH levels, over-suppression of PTH levels in dialysed children may lead to adynamic bone disease which is associated with growth failure and cardiovascular calcifications [77]. Moreover, active vitamin D sterols, particularly calcitriol, may also inhibit the growth plate [78]. Taken together, these data illustrate that active vitamin D sterols exert a positive role in controlling PTH levels and *osteitis fibrosa* but, with excessive use, may result in excessive PTH suppression, adynamic bone disease, growth failure and progressive cardiovascular calcifications. Furthermore, since active vitamin D analogues are potent stimulators of skeletal FGF23 secretion [54, 79], current data implicating FGF23 in the pathogenesis of secondary hyperparathyroidism call into question the wisdom of early active vitamin D sterol therapy. Since there are currently no data demonstrating any differences on the control of secondary hyperparathyroidism or ROD between the various active vitamin D sterols [54] the choice may depend on the geographical localization; for example, French paediatric nephrologists tend to use alfacalcidol while Americans prescribe calcitriol.

Currently, calcimimetics and bone-targeted therapies (i.e. bisphosphonates, teriparatide and raloxifene) are not approved for use in paediatric patients with CKD and long-term data on their effects on bone, growth and biochemical parameters in children are lacking. Thus, further studies are warranted to determine the optimal strategy for controlling secondary hyperparathyroidism in the paediatric CKD population. The new drug, cinacalcet, is highly promising, since it has intriguing benefits when compared with active vitamin D by inducing daily PTH fluctuations [80, 81]; however, paediatric experience is limited to observational data [82]. Of note, the use of this drug in addition to lanthanum carbonate therapy in one child was associated with precocious puberty, calling into question its safety for the paediatric population [83]. Paediatric randomized controlled trials are ongoing and should yield additional paediatric pharmacokinetic, pharmacodynamic and safety data.

rhGH therapy

After correcting all metabolic abnormalities that can worsen growth status such as metabolic acidosis, anaemia, CKD–MBD and malnutrition in paediatric patients with mild-to-moderate renal insufficiency (CKD stages 2–4), the use of supraphysiological doses of recombinant human GH (rhGH) has been proved to be safe and effective in increasing growth and final adult height [30, 84–86], by partly correcting the altered GH–IGF1 axis, by increasing GH and IGF1 serum levels, and by decreasing IGFBP1 and IGFBP5 serum levels simultaneously [8]. The 2005 American K-DOQI guidelines concerning the use of rhGH in CKD children are summarized in Table 4 [87]. Of note, such a therapy is contra-indicated in the case of severe secondary hyperparathyroidism, history of malignancy, hyperglycaemia, hyperinsulinaemia or significant scoliosis [88]. The primary actions of rhGH are on the cartilaginous growth plate and animal models (rats) have demonstrated that secondary hyperparathyroidism influences both the epiphyseal growth plate morphology and the expression of different biomarkers of proliferation and differentiation in this tissue [12]. Although there is little data in humans on the impact of CKD on growth plate, marked chondroclastic erosions and abnormal vascularization were found in the growth plates of autopsy material from children with *osteitis fibrosa* who were treated with maintenance haemodialysis [89]. Several studies have demonstrated a positive effect of rhGH on linear growth but with variable results according to CKD stage: in the NAPRTCS database, catch-up was observed in 27% of children with chronic renal insufficiency and in 25% of transplanted children, but only in 11% of children undergoing renal replacement therapy treated with rhGH therapy [90]. Moreover, the maximal effect of rhGH therapy occurs during the first year of therapy. The waning efficacy of rhGH with a longer therapy duration, may partly be explained by the difficulty of adhering to a daily subcutaneous injection regimen and/or an increasing resistance to the actions rhGH at the level of the growth plate [91].

Independent of its action on the growth plate, the effects of GH on bone quality and bone remodelling are not well known [92]. Nevertheless, rhGH may stimulate osteoblastic proliferation and new bone formation, illustrated in clinical practice by higher osteoblastic activity, bone formation rate and bone mass in patients with acromegaly on the one hand, and by decreased bone mass and osetoblastic activity in patients with GH deficiency on the other. Moreover, GH can promote the proliferation of osteoblasts and increase new bone formation, through the IGF1 pathway [9]. In children receiving long-term corticosteroids, rhGH therapy increases osteoblastic activity, bone formation and probably also bone turnover [93]. Other data also suggest a positive effect of rhGH therapy on BMD [92, 94–97]. Moreover, rhGH therapy may also counteract the negative effect of high-dose calcitriol therapy on bone turnover during childhood CKD [98]. Although several side effects of rhGH therapy have been discussed in the past (e.g. potential increased risk of acute rejection and adverse effect on the preservation of renal function in transplanted children, increased risk of slipped capital femoral epiphysis and benign intracranial hypertension, increased risk of hyperparathyroidism), a Cochrane systematic review performed in 2006 to evaluate the benefits and harms of rhGH therapy in CKD children (15 trials, 629 children) failed to demonstrate a positive effect of rhGH therapy on final adult height since most of the published trials were too short to draw such conclusions. However, a dosage of 28 IU/m^2 per week (or 10 mg/m^2 per week) for 1 year of rhGH resulted in a 3.8 cm/year increase in height velocity in CKD children receiving rhGH therapy in comparison to untreated patients [30].

After initiating rhGH therapy, the physician may observe very different clinical responses that are partly explained by confounding factors such as individual primary renal disease, CKD stage, degree of malnutrition, metabolic disturbances, genetic background, concurrent diseases and therapies and therapeutic compliance [31, 88]. Since there was an inverse relationship between age and rhGH response in a cohort of 270 CKD prepubertal naïve-to-treatment children issued from the NCGS registry, rhGH therapy should be begun early in the course of CKD [31]. It is also important to note that a recent study emphasized the under-prescription of rhGH therapy in paediatric CKD patients since more than half of short CKD children (as defined by a height below the fifth percentile) did not receive rhGH in a retrospective

Table 4. Summary of the 2005 K-DOQI guidelines for using rhGH in CKD children [87]

	Recommendation
1	Children should have hip and wrist bone age X-rays performed prior to initiation of rhGH therapy. Children with active rickets or a slipped capital femoral epiphysis should not begin rhGH therapy until these problems have been resolved.
2	rhGH therapy should not be initiated until the PTH level is no greater than 2× the target upper limit for CKD stages II–IV or 1.5× the target upper limit in CKD stage V-D.
3	rhGH therapy should not be initiated until the phosphorus is no greater than 1.5× the upper limit for age.
4	Children receiving rhGH therapy in stages II–IV CKD should have calcium, phosphorus, PTH and alkaline phosphatase monitored at least every three months during the first year of therapy. Children receiving GH therapy in CKD stage V should have calcium, phosphorus, PTH and alkaline phosphatase monitored at least every month during the first six months of therapy. Thereafter, interval measurements should be made according to CKD stage.
5	Children receiving rhGH therapy should have a wrist bone age performed yearly. Hip X-rays should be performed when clinically indicated.
6	rhGH therapy should be stopped temporarily: In CKD stage II–IV: if the patient has a PTH level above 400 pg/mL; rhGH should not be restarted until the PTH level is equal or below 200 pg/mL; In CKD stage V: if the patient has a PTH level above 900 pg/mL; rhGH should not be restarted until the PTH level is equal or below 450 pg/mL; In all stages of CKD, if the patient develops a slipped capital femoral epiphysis or symptomatic high-turnover ROD.
7	rhGH therapy should be stopped permanently when the epiphyses are closed.

multicentre American study whose main objective was to identify the potential obstacles preventing CKD children to receive rhGH therapy. The most common reasons to explain the absence of rhGH were family refusal, severe secondary hyperparathyroidism and non-compliance; however, in up to 25% of cases, no evident rationale was found. Of note, the need for waiting on insurance company approval induced a significant delay in the initiation of rhGH therapy in 18% of patients [99]. Taken together, these observations confirm that further measures are still needed to optimize growth in children with CKD.

In conclusion, since children with early stages of CKD have a better response to rhGH therapy than dialysis patients on the one hand, and since a young age at the onset of CKD is associated with a greater magnitude of growth retardation on the other hand, rhGH therapy should be introduced as soon as possible in children with CKD (i.e. with a GFR below 75 mL/min per 1.73 m^2) when their SDS for height is more negative than −2 (and −1.88 according some authors) [88]. In the future, newer treatment modalities, targeting preferentially GH resistance (such as recombinant IGF1, recombinant IGFBP3 or IGFBP displacers), are under investigation for the treatment of growth retardation in paediatric patients with CKD [8]. In children below 2 years of age, since growth mainly depends on nutritional parameters, the optimization of nutritional status is a cornerstone in the management of such patients, usually through an enteral nutritional support [100].

Conclusion and perspectives

Since growth failure during CKD has been well demonstrated to be associated with increased hospitalization rates and increased morbidity/mortality [101], and since bone status probably represents only the tip of the iceberg of cardiovascular health and vascular calcifications, large prospective multicentre trials are urgently required in this specific paediatric population to evaluate the impact of rhGH therapy, vitamin D analogues, phosphate-binders and calcimimetics not only on final adult height but also on bone status, fracture risk and global cardiovascular status. In this setting, bone histomorphometry remains an important component of well-designed clinical studies but the role of new non-invasive imaging techniques should also be evaluated.

The evaluation of growth and bone status remains challenging in CKD children even though the recent description of the FGF23 bone/kidney/parathyroid axis highlights new promising and exciting hypotheses to improve diagnosis and clinical management of CKD–MBD. Therefore, at the current time, the daily clinical management of CKD–MBD in children should still focus on three main objectives: (i) to provide an optimal nutritional support to maximize the final height and avoid bone deformations, (ii) to equilibrate calcium/phosphate metabolism so as to provide acceptable bone quality and cardiovascular status and (iii) to correct all metabolic and clinical abnormalities that can worsen both bone and growth (mainly metabolic acidosis, anaemia, malnutrition and 25(OH)vitamin D deficiency).

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References

1. Leonard MB. A structural approach to the assessment of fracture risk in children and adolescents with chronic kidney disease. *Pediatr Nephrol* 2007; 22: 1815–1824
2. Cunningham J. Pathogenesis and prevention of bone loss in patients who have kidney disease and receive long-term immunosuppression. *J Am Soc Nephrol* 2007; 18: 223–234
3. Wesseling K, Bakkaloglu S, Salusky I. Chronic kidney disease mineral and bone disorder in children. *Pediatr Nephrol* 2008; 23: 195–207
4. Hruska KA, Choi ET, Memon I *et al*. Cardiovascular risk in chronic kidney disease (CKD): the CKD-mineral bone disorder (CKD–MBD). *Pediatr Nephrol* [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. 2010; 25: 769–778
5. Groothoff JW, Offringa M, Van Eck-Smit BL *et al*. Severe bone disease and low bone mineral density after juvenile renal failure. *Kidney Int* 2003; 63: 266–275
6. Goodman WG, Goldin J, Kuizon BD *et al*. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000; 342: 1478–1483
7. Yamashita T, Konishi M, Miyake A *et al*. Fibroblast growth factor (FGF)-23 inhibits renal phosphate reabsorption by activation of the mitogen-activated protein kinase pathway. *J Biol Chem* 2002; 277: 28265–28270
8. Mahesh S, Kaskel F. Growth hormone axis in chronic kidney disease. *Pediatr Nephrol* 2008; 23: 41–48
9. Salusky IB, Goodman WG. Growth hormone and calcitriol as modifiers of bone formation in renal osteodystrophy. *Kidney Int* 1995; 48: 657–665
10. Guyton A, Hall J. Pituitary hormones and their control by the hypothalamus. In: Guyton A (ed). *Textbook of Medical Physiology*, 11th edn. Philadelphia: Elsevier Saunders, 2006, pp. 918–929
11. Courtland HW, Sun H, Beth-On M *et al*. Growth hormone mediates pubertal skeletal development independent of hepatic IGF-1 production. *J Bone Miner Res* [Research Support, N.I.H., Extramural] 2011; 26: 761–768
12. Kuizon BD, Salusky IB. Growth retardation in children with chronic renal failure. *J Bone Miner Res* 1999; 14: 1680–1690
13. Wesseling-Perry K, Pereira RC, Tseng CH *et al*. Early skeletal and biochemical alterations in pediatric chronic kidney disease. *Clin J Am Soc Nephrol* 2012; 7: 146–152
14. Ben-Dov IZ, Galitzer H, Lavi-Moshayoff V *et al*. The parathyroid is a target organ for FGF23 in rats. *J Clin Invest* 2007; 117: 4003–4008
15. Danziger J. The bone-renal axis in early chronic kidney disease: an emerging paradigm. *Nephrol Dial Transplant* 2008; 23: 2733–2737
16. Isakova T, Wahl P, Vargas GS *et al*. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int* [Research Support, N.I.H., Extramural] 2011; 79: 1370–1378
17. Shimada T, Urakawa I, Isakova T *et al*. Circulating fibroblast growth factor 23 in patients with end-stage renal disease treated by peritoneal dialysis is intact and biologically active. *J Clin Endocrinol Metab* 2010; 95: 578–585

18. Razzaque MS. FGF23-mediated regulation of systemic phosphate homeostasis: is Klotho an essential player? *Am J Physiol Renal Physiol* 2009; 296: F470–F476
19. Prie D, Urena Torres P, Friedlander G. Latest findings in phosphate homeostasis. *Kidney Int* 2009; 75: 882–889
20. Lafage-Proust MH. Does the downregulation of the FGF23 signaling pathway in hyperplastic parathyroid glands contribute to refractory secondary hyperparathyroidism in CKD patients? *Kidney Int* 2010; 77: 390–392
21. Komaba H, Goto S, Fujii H *et al*. Depressed expression of Klotho and FGF receptor 1 in hyperplastic parathyroid glands from uremic patients. *Kidney Int* 2010; 77: 232–238
22. Galitzer H, Ben-Dov IZ, Silver J *et al*. Parathyroid cell resistance to fibroblast growth factor 23 in secondary hyperparathyroidism of chronic kidney disease. *Kidney Int* 2010; 77:211–218
23. Heidbreder E, Naujoks H, Brosa U *et al*. The calcium-parathyroid hormone regulation in chronic renal failure investigation of its dynamic secretion pattern. *Horm Metab Res* 1997; 29: 70–75
24. Liu PT, Stenger S, Li H *et al*. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006; 311: 1770–1773
25. Priemel M, von Domarus C, Klatte TO *et al*. Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. *J Bone Miner Res* 2009; 25: 305–312
26. Ritter CS, Brown AJ. Direct suppression of Pth gene expression by the vitamin D prohormones doxercalciferol and calcidiol requires the vitamin D receptor. *J Mol Endocrinol* [In Vitro Research Support, Non-U.S. Gov't] 2011; 46: 63–66
27. Shroff R, Wan M, Gullet A *et al*. Ergocalciferol supplementation in children with CKD delays the onset of secondary hyperparathyroidism: a randomized trial. *Clin J Am Soc Nephrol* 2012:doi:10.2215/CJN.04760511.
28. Bacchetta J, Ranchin B, Dubourg L *et al*. Vitamin D revisited: a cornerstone of health? *Arch Pediatr* 2010; 17: 1687–1695
29. NAPRTCS. Annual report, section dialysis 12-12005.
30. Vimalachandra D, Hodson EM, Willis NS *et al*. Growth hormone for children with chronic kidney disease. *Cochrane Database Syst Rev* 2006; 3: CD003264.
31. Mahan JD, Warady BA, Frane J *et al*. First-year response to rhGH therapy in children with CKD: a National Cooperative Growth Study Report. *Pediatr Nephrol* 2010; 25: 1125–1130
32. Harambat J, Cochat P. Growth after renal transplantation. *Pediatr Nephrol* [Review] 2009; 24: 1297–1306
33. Mahan JD, Warady BA. Assessment and treatment of short stature in pediatric patients with chronic kidney disease: a consensus statement. *Pediatr Nephrol* 2006; 21: 917–930
34. Klaus G, Watson A, Edefonti A *et al*. Prevention and treatment of renal osteodystrophy in children on chronic renal failure: European guidelines. *Pediatr Nephrol* 2006; 21: 151–159
35. Tonshoff B, Cronin MJ, Reichert M *et al.* Reduced concentration of serum growth hormone (GH)-binding protein in children with chronic renal failure: correlation with GH insensitivity. The European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. The German Study Group for Growth Hormone Treatment in Chronic Renal Failure. *J Clin Endocrinol Metab* 1997; 82: 1007–1013
36. Tonshoff B, Blum WF, Mehls O. Derangements of the somatotropic hormone axis in chronic renal failure. *Kidney Int Suppl* 1997; 58: S106–S113
37. Powell DR, Liu F, Baker BK *et al*. Insulin-like growth factor-binding protein-6 levels are elevated in serum of children with chronic renal failure: a report of the Southwest Pediatric Nephrology Study Group. *J Clin Endocrinol Metab* 1997; 82: 2978–2984
38. Powell DR, Durham SK, Liu F *et al*. The insulin-like growth factor axis and growth in children with chronic renal failure: a report of the Southwest Pediatric Nephrology Study Group. *J Clin Endocrinol Metab* 1998; 83: 1654–1661
39. Bacchetta J, Boutroy S, Juillard L *et al*. Bone imaging and chronic kidney disease: will high-resolution peripheral tomography improve bone evaluation and therapeutic management? *J Ren Nutr* 2009; 19: 44–49
40. Yamada S, Inaba M, Kurajoh M *et al*. Utility of serum tartrate-resistant acid phosphatase (TRACP5b) as a bone resorption marker in patients with chronic kidney disease: independence from renal dysfunction. *Clin Endocrinol (Oxf)* 2008; 69: 189–196
41. Yang L, Grey V. Pediatric reference intervals for bone markers. *Clin Biochem* 2006; 39: 561–568
42. Bianchi ML, Baim S, Bishop NJ *et al*. Official positions of the International Society for Clinical Densitometry (ISCD) on DXA evaluation in children and adolescents. *Pediatr Nephrol* 2010; 25: 37–47
43. Weber LT, Mehls O. Limitations of dual x-ray absorptiometry in children with chronic kidney disease. *Pediatr Nephrol* 2010; 25: 3–5
44. Soyka LA, Fairfield WP, Klibanski A. Clinical review 117: hormonal determinants and disorders of peak bone mass in children. *J Clin Endocrinol Metab* 2000; 85: 3951–3963
45. Hernandez JD, Wesseling K, Pereira R *et al*. Technical approach to iliac crest biopsy. *Clin J Am Soc Nephrol* 2008; 3 (Suppl 3): S164–S169
46. Miller PD. The role of bone biopsy in patients with chronic renal failure. *Clin J Am Soc Nephrol* 2008; 3 (Suppl 3): S140–S150
47. Wesseling-Perry K, Pereira RC, Tseng CH *et al*. Early skeletal and biochemical alterations in pediatric chronic kidney disease. *Clin J Am Soc Nephrol* 2012; 7: 146–152
48. Salusky IB, Coburn JW, Brill J *et al*. Bone disease in pediatric patients undergoing dialysis with CAPD or CCPD. *Kidney Int* 1988; 33: 975–982
49. Goodman WG, Ramirez JA, Belin TR *et al*. Development of adynamic bone in patients with secondary hyperparathyroidism after intermittent calcitriol therapy. *Kidney Int* 1994; 46: 1160–1166
50. Parfitt AM, Drezner MK, Glorieux FH *et al*. Bone histomorphometry: standardization of nomenclature, symbols, and units. Report of the ASBMR Histomorphometry Nomenclature Committee. *J Bone Miner Res* 1987; 2: 595–610
51. Moe S, Drueke T, Cunningham J *et al*. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006; 69: 1945–1953
52. Bakkaloglu S, Wesseling-Perry K, Pereira R *et al*. Values of the new bone classification system in pediatric renal osteodystrophy. *Clin J Am Soc Nephrol* 2010: Epub, doi;10.2215/CJN.01330210.
53. Kuizon BD, Goodman WG, Juppner H *et al*. Diminished linear growth during intermittent calcitriol therapy in children undergoing CCPD. *Kidney Int* 1998; 53: 205–211
54. Wesseling-Perry K, Pereira RC, Sahney S *et al*. Calcitriol and doxercalciferol are equivalent in controlling bone turnover, suppressing parathyroid hormone, and increasing fibroblast growth factor-23 in secondary hyperparathyroidism. *Kidney Int* [Comparative Study Randomized Controlled Trial Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2011; 79: 112–119
55. Bacchetta J, Boutroy S, Vilayphiou N *et al*. Early impairment of trabecular microarchitecture assessed with HR-pQCT in patients with stage II–IV chronic kidney disease. *J Bone Miner Res* 2010; 25: 849–857
56. Boutroy S, Bouxsein ML, Munoz F *et al*. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. *J Clin Endocrinol Metab* 2005; 90: 6508–6515
57. Lespessailles E, Gadois C, Lemineur G *et al*. Bone texture analysis on direct digital radiographic images: precision study and relationship with bone mineral density at the os calcis. *Calcif Tissue Int* 2007; 80: 97–102
58. Majumdar S. Magnetic resonance imaging for osteoporosis. *Skeletal Radiol* 2008; 37: 95–97
59. Bachrach LK. Measuring bone mass in children: can we really do it? *Horm Res* 2006; 65 (Suppl 2): 11–16
60. Bacchetta J, Fargue S, Boutroy S *et al*. Bone metabolism in oxalosis: a single-center study using new bone imaging techniques and biomarkers. *Pediatr Nephrol* 2010:doi 10.1007/s00467-010-1453x.
61. Lima EM, Goodman WG, Kuizon BD *et al*. Bone density measurements in pediatric patients with renal osteodystrophy. *Pediatr Nephrol* 2003; 18: 554–559

62. Wetzsteon RJ, Kalkwarf HJ, Shults J *et al*. Volumetric bone mineral density and bone structure in childhood chronic kidney disease. *J Bone Miner Res* [Research Support, N.I.H., Extramural]. 2011; 26: 2235–2244
63. Terpstra AM, Kalkwarf HJ, Shults J *et al*. Bone density and cortical structure after pediatric renal transplantation. *J Am Soc Nephrol* 2012.
64. Bacchetta J, Boutroy S, Vilayphiou N *et al*. Bone assessment in children with chronic kidney disease: data from two new bone imaging techniques in a single-center pilot study. *Pediatr Nephrol* [Research Support, Non-U.S. Gov't]. 2011; 26: 587–595
65. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD–MBD). *Kidney Int Suppl* 2009; 113: S1–S130
66. Waller SC, Ridout D, Cantor T *et al*. Parathyroid hormone and growth in children with chronic renal failure. *Kidney Int* 2005; 67: 2338–2345
67. London GM, Marchais SJ, Guerin AP *et al*. Association of bone activity, calcium load, aortic stiffness, and calcifications in ESRD. *J Am Soc Nephrol* [Research Support, Non-U.S. Gov't] 2008; 19: 1827–1835
68. Schmitt CP, Mehls O. Mineral and bone disorders in children with chronic kidney disease. *Nat Rev Nephrol* 2011; 7: 624–634
69. Rees L. What parathyroid hormone levels should we aim for in children with stage 5 chronic kidney disease; what is the evidence? *Pediatr Nephrol* 2008; 23: 179–184
70. Rostand SG, Drueke TB. Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. *Kidney Int* [Research Support, U.S. Gov't, P.H.S. Review] 1999; 56: 383–392
71. Shroff RC, Donald AE, Hiorns MP *et al*. Mineral metabolism and vascular damage in children on dialysis. *J Am Soc Nephrol* [Research Support, Non-U.S. Gov't] 2007; 18: 2996–3003
72. Cansick J, Waller S, Ridout D *et al*. Growth and PTH in prepubertal children on long-term dialysis. *Pediatr Nephrol* 2007; 22: 1349–1354
73. Geary DF, Hodson EM, Craig JC. Interventions for bone disease in children with chronic kidney disease. *Cochrane Database Syst Rev* 2010; CD008327.
74. Salusky IB, Goodman WG, Sahney S *et al*. Sevelamer controls parathyroid hormone-induced bone disease as efficiently as calcium carbonate without increasing serum calcium levels during therapy with active vitamin D sterols. *J Am Soc Nephrol* 2005; 16: 2501–2508
75. Pieper AK, Haffner D, Hoppe B *et al*. A randomized crossover trial comparing sevelamer with calcium acetate in children with CKD. *Am J Kidney Dis* 2006; 47: 625–635
76. Gonzalez E, Schomberg J, Amin N *et al*. Sevelamer carbonate increases serum bicarbonate in pediatric dialysis patients. *Pediatr Nephrol* 2010; 25: 373–375
77. Salusky IB, Goodman WG. Growth hormone and calcitriol as modifiers of bone formation in renal osteodystrophy. *Kidney Int* [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review]. 1995; 48: 657–665
78. Sanchez CP, Salusky IB, Kuizon BD *et al*. Growth of long bones in renal failure: roles of hyperparathyroidism, growth hormone and calcitriol. *Kidney Int* [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.] 1998; 54: 1879–1887
79. Imel EA, DiMeglio LA, Hui SL *et al*. Treatment of X-linked hypophosphatemia with calcitriol and phosphate increases circulating fibroblast growth factor 23 concentrations. *J Clin Endocrinol Metab* [Clinical Trial Research Support, N.I.H., Extramural] 2010; 95: 1846–1850
80. Serra AL, Braun SC, Starke A *et al*. Pharmacokinetics and pharmacodynamics of cinacalcet in patients with hyperparathyroidism after renal transplantation. *Am J Transplant* [Research Support, Non-U.S. Gov't] 2008; 8: 803–810
81. Finch JL, Tokumoto M, Nakamura H *et al*. Effect of paricalcitol and cinacalcet on serum phosphate, FGF-23, and bone in rats with chronic kidney disease. *Am J Physiol Renal Physiol* [Comparative Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] 2010; 298: F1315–F1322
82. Muscheites J, Wigger M, Drueckler E *et al*. Cinacalcet for secondary hyperparathyroidism in children with end-stage renal disease. *Pediatr Nephrol* 2008; 23: 1823–1829
83. Bacchetta J, Plotton I, Ranchin B *et al*. Precocious puberty and unlicensed paediatric drugs for severe hyperparathyroidism. *Nephrol Dialysis, Transplant* 2009; 24: 2595–2598
84. Fine RN, Kohaut EC, Brown D *et al*. Growth after recombinant human growth hormone treatment in children with chronic renal failure: report of a multicenter randomized double-blind placebo-controlled study. Genentech Cooperative Study Group. *J Pediatr* 1994; 124: 374–382
85. Hokken-Koelega AC, Stijnen T, de Muinck Keizer-Schrama SM *et al*. Placebo-controlled, double-blind, cross-over trial of growth hormone treatment in prepubertal children with chronic renal failure. *Lancet* 1991; 338: 585–590
86. Haffner D, Schaefer F, Nissel R *et al*. Effect of growth hormone treatment on the adult height of children with chronic renal failure. German study group for growth hormone treatment in chronic renal failure. *N Engl J Med* 2000; 343: 923–930
87. K/DOQI Clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease. *Am J Kidney Dis* 2005; 46 (Suppl 1): 1–122
88. Fine RN. Etiology and treatment of growth retardation in children with chronic kidney disease and end-stage renal disease: a historical perspective. *Pediatr Nephrol* 2010; 25: 725–732
89. Krempien B, Mehls O, Ritz E. Morphological studies on pathogenesis of epiphyseal slipping in uremic children. *Virchows Arch A Pathol Anat Histol* 1974; 362: 129–143
90. Seikaly MG, Salhab N, Warady BA *et al*. Use of rhGH in children with chronic kidney disease: lessons from NAPRTCS. *Pediatr Nephrol* 2007; 22: 1195–1204
91. Berard E, Andre JL, Guest G *et al*. Long-term results of rhGH treatment in children with renal failure: experience of the French Society of Pediatric Nephrology. *Pediatr Nephrol* 2008; 23: 2031–2038
92. Tritos NA, Biller BM. Growth hormone and bone. *Curr Opin Endocrinol Diabetes Obes* 2009; 16: 415–422
93. Sanchez CP, Goodman WG, Brandli D *et al*. Skeletal response to recombinant human growth hormone (rhGH) in children treated with long-term corticosteroids. *J Bone Miner Res* 1995; 10: 2–6
94. Baroncelli GI, Bertelloni S, Sodini F *et al*. Acquisition of bone mass in normal individuals and in patients with growth hormone deficiency. *J Pediatr Endocrinol Metab* 2003; 16 (Suppl 2): 327–335
95. Murray RD, Adams JE, Shalet SM. Adults with partial growth hormone deficiency have an adverse body composition. *J Clin Endocrinol Metab* 2004; 89: 1586–1591
96. Colao A, Di Somma C, Pivonello R *et al*. Bone loss is correlated to the severity of growth hormone deficiency in adult patients with hypopituitarism. *J Clin Endocrinol Metab* 1999; 84: 1919–1924
97. Baum HB, Biller BM, Finkelstein JS *et al*. Effects of physiologic growth hormone therapy on bone density and body composition in patients with adult-onset growth hormone deficiency. A randomized, placebo-controlled trial. *Ann Intern Med* 1996; 125: 883–890
98. Bacchetta J, Wesseling-Perry K, Kuizon B *et al*. The skeletal consequences of growth hormone therapy in children undergoing peritoneal dialysis. 2011 (submitted).
99. Greenbaum LA, Hidalgo G, Chand D *et al*. Obstacles to the prescribing of growth hormone in children with chronic kidney disease. *Pediatr Nephrol* 2008; 23: 1531–1535
100. KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 update. Executive summary. *Am J Kidney Dis* [Practice Guideline] 2009; 53 (3 Suppl 2): S11–S104
101. Furth SL, Stablein D, Fine RN *et al*. Adverse clinical outcomes associated with short stature at dialysis initiation: a report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatrics* 2002; 109: 909–913
102. Ibrahim S, Rashed L. Serum fibroblast growth factor-23 levels in chronic haemodialysis patients. *Int Urol Nephrol* 2009; 41: 163–169

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